

THE PREVALENCE AND PREDICTION OF PULMONARY FIBROSIS IN AN
ASBESTOS-EXPOSED COHORT

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ABSTRACT

This thesis describes an ancillary project to the *Early Diagnosis of Mesothelioma and Lung Cancer in Prior Asbestos Workers* study and was conducted to determine the effects of asbestos exposure, pulmonary function and cigarette smoking in the prediction of pulmonary fibrosis. 613 workers who were occupationally exposed to asbestos for an average of 25.9 (SD=14.69) years were sampled from Sarnia, Ontario. A structured questionnaire was administered during a face-to-face interview along with a low-dose computed tomography (LDCT) of the thorax. Of them, 65 workers (10.7%, 95%CI 8.12—12.24) had LDCT-detected pulmonary fibrosis. The model predicting fibrosis included the variables age, smoking (dichotomized), post FVC % splines and post-FEV1% splines. This model had a receiver operator characteristic area under the curve of 0.738. The calibration of the model was evaluated with R statistical program and the bootstrap optimism-corrected calibration slope was 0.692. Thus, our model demonstrated moderate predictive performance.

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Peace, Love & Gumption

Marina

TABLE OF CONTENTS

	Page
Abstract	ii
Acknowledgements.....	iii
Table of Contents.....	iv
List of Tables	vi
List of Figures.....	vii
List of Appenices	ix
List of Abbreviations and Definitions	x
CHAPTER I - Introduction	
1.1 Introduction.....	1
1.2 Objective.....	1
1.3 Study Aims	4
CHAPTER II – Literature Review	
2.0 Overview.....	6
2.1 A Global History of Asbestos.....	6
2.2 Asbestos in Canada.....	8
2.3 Impact of Asbestos-Related Diseases.....	9
2.4 Impact of Asbestos-Related Diseases in Canada.....	12
2.5 Types of Asbestos.....	16
2.6 Measuring Asbestos Exposure.....	17
2.7 Pulmonary Function Tests.....	22
2.8 Disease Caused by Asbestos Exposure	25
2.8.1 Pleural Consequences of Asbestos.....	26
2.8.1.1 Pleural Effusion.....	26
2.8.1.2 Pleural Plaques.....	27
2.8.1.3 Diffuse Pleural Thickening.....	28
2.8.1.4 Rounded Atelectasis	29

2.8.2	Parenchymal Consequences of Asbestos Exposure.....	29
2.8.2.1	Asbestosis	29
2.9	Distinguishing between Pleural and Parenchymal Asbestos Disease	30
2.10	Imaging of Asbestos-Exposed Individuals	31
2.10.1	Chest Radiography.....	31
2.10.2	Computed Tomography.....	33
2.11	Radiological-Functional Correlations	38
2.12	Research Questions	45
CHAPTER III - Methodology		
3.1	Introduction	47
3.2	Study Design and Context	47
3.3	Patient Recruitment	47
3.4	Eligibility Criteria	48
3.5	Measurement	48
3.5.1	Consent and Data Collection	48
3.5.2	Occupational History	48
3.5.3	Smoking History Assessment and Other Measurements	49
3.6	Low-Dose Computed Tomography and Follow-up	50
3.7	Pulmonary Function Tests	52
3.8	General Analytic Strategy	53
3.9	Addressing Specific Study Questions	54
CHAPTER IV- Results		
4.1	Outline of Results	57
4.2	Study Population	57
4.3	Assessing the Linearity of Continuous Variable using LOWESS	59
4.4	Predictive Model for Pulmonary Fibrosis	61
4.4.1	Full Predictive Model for Pulmonary Fibrosis	61
4.4.2	Predictive Model Including Smoke*Asbestos Interaction	66
4.4.3	Comparing Predictive Models with and without Variable with $P>0$	69

CHAPTER V- Discussion & Conclusion

5.1	Key Findings	72
	5.1.1. Asbestos Exposure.....	73
	5.1.2 Pulmonary Function	74
	5.1.3 Smoking-Asbestos Interaction	75
5.2	Strengths.....	76
	5.2.1 Study Design	76
	5.2.2 Variables	77
	5.2.3 Low-Dose Computed Tomography	78
5.3	Limitations.....	78
	5.3.1 Asbestos Measurement	78
	5.3.2 Classification of Pulmonary Fibrosis	80
5.4	Unanswered Questions	80
	5.4.1 Descriptive Statistics of Asbestos-Related Disease	80
	5.4.2. Classification of Pulmonary Fibrosis by CT	81
	5.4.3. Investigating Age, Birth and Cohort Effects.....	81
5.5	Association versus Prediction Studies.....	82
5.6	Clinical Utility of the Final Predictive Model.....	83
5.7	Future Directions.....	84
5.8	Conclusion	85
	References	87
	Appendices.....	100

LIST OF TABLES

Table 1 National Mesothelioma Incidence

Table 2 Obstructive and Restrictive Patterns

Table 3 Pulmonary Function Test Variables in Relation to Different Types of Lung Impairment

Table 4 Baseline Characteristics of Asbestos Exposed Cohort Stratified by Presence/Absence of Low-Dose Computed Tomography Found Pulmonary Fibrosis ($N_{\text{total}}=613$)

Table 5: Univariate Models of Pulmonary Function Test Splines- Pre and Post Bronchodilator Predicting LDCT-Found Pulmonary Fibrosis.

Table 6: Full Logistic Regression Model Predicting LDCT Found Pulmonary Fibrosis in a Cohort of Asbestos Workers (n=320)

Table 7: Logistic Regression Model Predicting LDCT Found Pulmonary Fibrosis in a Cohort of Asbestos Workers (n=329) - Investigating Smoke-Asbestos Interaction

Table 8: Logistic Regression Model Predicting LDCT Found Pulmonary Fibrosis in a Cohort of Asbestos Workers Excluding Variables with $P>0.20$ (n=320)

LIST OF FIGURES

Figure 1 Lifetime Probability (risk) of Mesothelioma (pleural + peritoneal) and 95% confidence Intervals Based on a Birth-Cohort and Age Model Estimated from 2003 Surveillance, Epidemiology, and End Results Program data covering 1973-2000

Figure 2 Pneumoconioses Hospitalization Rates (per 100,000), Canada*, 1987-2004 (age-standardized to 1991 Canadian population)

Figure 3 Pneumoconioses Mortality Rates (per 100,000), Canada, 1987-2004 (age- standardized to 1991 Canadian population)

Figure 4 Pneumoconioses and Hypersensitivity Pneumonitis Hospitalization Rates (per 100,000), Canada*, 1987-2004, Aged 35+ Years, (age-standardized to 1991 Canadian population)

Figure 5 Ontario Mesothelioma Incidence Rate, 3 year moving average, by Sex, 1980-2004

Figure 6 Graph of Planned Associations to be Addressed Displaying Potential Predictors of Pulmonary Fibrosis Found by Low-Dose CT of Interest to Hypothesis Testing and Model Adjustments

Figure 7 Low-dose Computed Tomography Follow-up Scheme

Figure 8: Lowess Curve for FVC and Probability of LDCT Found Pulmonary Fibrosis.

Figure 9: Lowess Curve for FEV1 and Probability of LDCT Found Pulmonary Fibrosis.

Figure 10: Calibration Plot of Actual Versus Predicted Pulmonary Fibrosis in Full Predictive Model

Figure 11: Comparison of ROC curves for LDCT Found Pulmonary Fibrosis- Full Predictive Model with *Smoke_Asbestos* Interaction versus Without Interaction. (p=0.2124)

Figure 12: Comparison of ROC Curves for LDCT found Pulmonary Fibrosis- Full Predictive Model versus Model Excluding with Variables $p > 0.2$ (p=0.4300)

Figure 13: Calibration Plot of Actual Versus Predicted Pulmonary Fibrosis in Model Excluding Variables with $p > 0.20$

LIST OF APPENDICES

Appendix A- Patient Consent Forms

Appendix B- Early Diagnosis of Mesothelioma and Lung Cancer in Prior Asbestos
Workers

Questionnaire

Appendix C- Sample of Spirometry Test Results

Appendix D- Lowess Curves for PFT variables

Appendix E- Histograms for PFT variables

Appendix F- Predictive Logistic Model for Asbestosis in a Cohort of Asbestos Workers
Stratified by Smoking Status ($n_{\text{smoke}}=248$; $n_{\text{nosmoke}}= 65$)

Appendix G - R Printout for Calibration Analysis (Modeling and associated graphics)

LIST OF ABBREVIATIONS AND DEFINITIONS (units)

95% CI – 95% confidence interval

ATS – the American Thoracic Society

AUC – area under the curve

DLCO – diffusing capacity of the lung; the capacity of the lungs to transfer carbon monoxide (mL/min/mmHG)

DLCO/VA – the DLCO adjusted for volume (mL/min/mmHg/L)

FEV1 – forced expiratory volume in one second; volume of air forcibly expired from a maximum inspiratory effort in the first second (L)

FEV1/FVC – direct ratio of patient's own FEV1 and FVC

FVC – forced vital capacity; the total volume that can be forcefully expired from a maximum inspiratory effort (L)

ICD – International Classification of Diseases

ILO – International Labor Organization

JEM – job exposure matrices

LDCT – low dose computed tomography

OR – odds ratio

PFT – pulmonary function test

ROC – Receiver Operator Characteristic

TLC – total lung capacity; the total volume of air in the lungs at full inhalation (L)

WHO – World Health Organization

CHAPTER I- INTRODUCTION

1.1 Introduction

Asbestos is the commercial term for a group of silicate minerals with fibrous crystal structures (American Thoracic Society, 2004). The two basic families of asbestos are serpentines and amphiboles. Chrysotile is the only member of the serpentine family, while crocidolite, amosite, actinolite, anthophyllite and tremolite belong to the amphiboles. Inhalation of asbestos fibers is a well-recognized cause of both malignant and non-malignant diseases of the lung parenchyma and pleura. Asbestos has three main effects on health: mesothelioma of the pleura or peritoneum, pulmonary cancer and asbestosis. Asbestos-related diseases have lengthy latent periods ranging from 15-20 years for asbestosis and greater than 40 years for mesothelioma (American Thoracic Society, 2007; The Spanish Society of Pulmonology, 2005; Cugell & Kamp, 2004; Bartrip, 2004). Today, even with stringent regulation of asbestos use and the disappearance of almost all asbestos-containing products from the market in the developed world, asbestos-related disease remains a concern for older workers exposed to asbestos. The long latency between initial exposure to asbestos and subsequent biological consequence means that new cases of asbestos-related disease will continue to be present as a result of previous exposures. All types of asbestos are associated with these diseases. Chrysotile fibers are thought to be less harmful than the amphiboles because they are more readily broken down and removed by the lung (Cugell & Kamp, 2004).

The focus of this study was pulmonary fibrosis, also known as asbestosis. According to the American Thoracic Society (ATS), asbestosis is simply diffuse interstitial pulmonary fibrosis due to the inhalation of asbestos fibers (American Thoracic

Society, 2004). For asbestosis to develop, the process requires the inhalation of considerable numbers of asbestos fibers, and usually over a long period of time. The most recent ATS guidelines require evidence of causation as demonstrated by one or more of the following criteria: 1) occupational and environmental exposure with plausible latency, 2) markers of exposure such as pleural plaques and 3) recovery of asbestos from tissue. The ATS recognizes both chest x-ray and computed tomography as useful in the diagnosis of asbestos-related diseases. Currently, evidence of functional impairment is not required for the diagnosis of asbestosis, though it is considered an important part of overall evaluation. Evidence of functional impairment includes symptoms and signs such as crackling, change in ventilatory function (restrictive pattern), impaired gas exchange (DLCO), and detection of inflammation (American Thoracic Society, 2004).

Though the incidence of asbestos-related diseases in the general population is low, their impact in exposed populations, mainly through occupation, is severe. The incidence of mesothelioma of the pleura in Canada (excluding Quebec) between 1984 and 1996 was 11.3 cases per million population in men and 1.64 cases per million in women (Sub-Committee on the Epidemiology of Asbestos Related Diseases, 2004). The incidence in Quebec is significantly higher due to the presence of numerous asbestos mining regions within the province. The incidence for Quebec was 15.3 cases per million population (Sub-Committee on the Epidemiology of Asbestos Related Diseases, 2004).

Determining the incidence or prevalence of asbestosis has varied and been difficult to establish due to difference in duration, intensity and type of exposure to asbestos. Among miners exposed to chrysotile in Quebec, there was a 5% prevalence of small patchy opacities after exposure to 20 fiber-years, in which exposure was calculated

individually for each participant on the basis of work history and industrial hygiene measurements (The Spanish Society of Pulmonology, 2005).

Imaging, whether chest radiography or computed tomography, contributes to the evaluation of asbestos-related disease on many levels: in diagnosis (American Thoracic Society, 2004), for the quantification of disease extent (American Thoracic Society, 2004; The Spanish Society of Pulmonology, 2005), as part of medico-legal claims evidence (Copley, Gary Lee, Hansell, Sivakumaran, Rubens, Taylor, Rudd, Musk & Wells, 2007), to screen high-risk individuals for cancer and for distinguishing other (non asbestos-related) causes of pulmonary dysfunction (Copley et al., 2007). Though radiological evaluations of asbestos-exposed individuals are relatively sensitive and reproducible for these purposes, frequent use is questionable owing to the radiation burden and high economic cost (Xaubet, Agusti, Luburich, Roca, Monton, Ayuso, Barbera, & Robriguez-Roicin, 1998). It has been reported that pulmonary dysfunction precedes chest x-ray findings of pneumoconiosis (occupational lung disease), suggesting the importance of pulmonary function tests in screening for early disease and prediction of subsequent disease (Tonori, Nitsuya, Sato, Sugiura, Miyake, & Aizawa, 2005). A second potential contribution of pulmonary function tests in asbestos-exposed individuals is in quantifying the extent of disease (Xaubet et al., 1998). According to various studies, pulmonary function tests can offer significant information about the extent of abnormalities, and thus, indicate that it is possibly not necessary to perform tests of high radiation burden routinely for quantification of disease severity (Neri, Boraschi, Antonelli, Falaschi, & Baschiere; Sette, Neder, Nery, Kavakama, Rodrigues, Terra-Filho, Guimaraes, Bagatin, & Muller). Correlation studies between radiological findings and

pulmonary functions tests have also been used to determine the proportion of pulmonary deficit attributable to specific disorders such as fibrosis, diffuse pleural thickening and emphysema (Copley, Wells, Rubens, Chabat, Sheehan, Musk, & Hansell).

With the advent of low-dose CT techniques and single breath-hold scanning capabilities, there has been interest in the use of CT as a mass screening method for patients with high risk for developing lung cancer, including asbestos-exposed populations. Though several studies have correlated chest x-ray and high resolution computed tomography with pulmonary function, no work to date has been done to correlate *low-dose* computed tomography changes with pulmonary function tests in asbestos-exposed individuals.

The interaction between smoking and asbestos is a very important issue in a number of lung diseases, most notably lung cancer. Some data suggests synergy between asbestos and smoking in the development of pulmonary fibrosis however current data is preliminary and inclusive (Alfonso et al., 2004; Neri et al., 1996; Wang et al., 2006). For this reason further exploration is needed including a comprehensive interaction analysis, which has not been performed to date.

1.2 Study Aims

This study has several aims. The first is to determine the prevalence of pulmonary fibrosis in a well described asbestos-exposed occupational cohort from Sarnia, Ontario, Canada. The second is to assess multiple predictors of pulmonary fibrosis found by low-dose CT in a prediction model, specifically past asbestos exposure, pulmonary function indices (FVC, FEV1, FEV1/FVC, TLC, and DLCO) and smoking status. The third aim is

to determine if there is an interaction between asbestos exposure and smoking that affects the risk of pulmonary fibrosis.

CHAPTER II- REVIEW OF THE LITERATURE

2.0 Overview

This chapter provides the background and rationale for this study. The chapter begins with a modern history of asbestos, the impact of asbestos-related disease and an overview of the properties of asbestos fibers. Particular attention is given to asbestos-induced fibrotic disease involving both the pleura and pulmonary interstitium. A brief explanation of the most common imaging techniques used for asbestos-exposed persons including chest radiography and computed tomography is given. Lastly, a review of radiological-functional correlation studies in asbestos exposed individuals is presented.

2.1 A Global History of Asbestos

In 1907, the first well documented fatal case of an asbestos-related disease, pneumoconiosis, an inflammation of the lung characterized by fibrosis and reduction of lung function caused by inhalation of asbestos fibers, was described by Dr. Montague Murray in the United Kingdom (The Spanish Society of Pulmonology, 2005; Cugell & Kamp, 2004). The term for this condition, asbestosis, was not coined until 1925 by Thomas Oliver (Bartrip, 2004). In 1930, Merewether and Price published an article in which one fourth of 363 factory workers in England had signs of asbestosis (Merewether & Price, 1930). More importantly, Merewether believed the disease was preventable and anticipated dust control would increase the length of time before developing fibrosis. He hypothesized if asbestos exposure was eliminated there would be a total disappearance of the disease (Bartrip, 2004). The result of the Merewether Report was the first dust-control regulations for Great Britain in 1931 (Cugell & Kamp, 2004;

Parkes, 1974). Similar regulations were not imposed in the United States until 1971 (Cugell & Kamp, 2004).

The first indication that asbestos could also be a human carcinogen was in 1935 when there was a reported association between asbestosis and lung cancer (Bartrip, 2004). In 1955, Doll established enough information that most informed observers believed a causal association between asbestos exposure and lung cancer (Bartrip, 2004; Doll, 1960). However, Doll believed that the Asbestos Industry Regulations had greatly reduced the risk of lung cancer for those who worked in Britain's asbestos factories, and an asbestos ban was not necessary (Bartrip, 2004).

In the 1960's a third asbestos-related disease was reported, mesothelioma (Wagner, Sleggs, & Marchand, 1960; Niklinki, Niklinska, Chyczewska, Laudanski, Naumnik, Chyczewski, & Pluygers, 2004). A paper by Wagner et al. established a possible association between the development of mesothelioma of the pleura and exposure to asbestos dust in people living in the Cape asbestos fields of South Africa (Bartrip, 2004; Wagner et al., 1960). Evidence revealed that hazards of asbestos were not confined to the exposed asbestos workers but also other users of asbestos products and those who lived near asbestos factories (Bartrip, 2004; Selikoff, Hammond, & Churg, 1964; Selikoff, Hammond, & Churg, 1965). These events led to a revisiting of the 1931 dust-control regulations in Britain resulting in the Asbestos Regulation of 1969. This allowed the continued use of asbestos only if maximum allowable concentrations of asbestos dust were not exceeded and other precautions were observed. Asbestos dust was defined as dust containing asbestos to such an extent as is likely to cause danger to the health of employed persons, implying a quantitative threshold. Occupational exposure to

crocidolite should not exceed 0.2 fibers/ml of sampled air when measured over any 10 minute period and for other asbestos 2 fibers/ml measured over a four hour period. This amount of allowable crocidolite was so low its use was eliminated. Finally, in July 1999 the European Commission announced a European Union ban on all remaining chrysotile use which was implemented in October 1999.

2.2 Asbestos in Canada

Industrial consumption of asbestos in Western Europe, Scandinavia, North America and Australia peaked in the 1970's when the gradual recognition that this "magic mineral" was associated with the occurrence of several serious health consequences led to a strict curtailment of asbestos' industrial use (Niklinki et al., 2004; Tossavainen, 2004). The worldwide production of asbestos products in 1975 exceeded five million tons while currently the level is approximately two million tons, of which 90% is chrysotile (Tossavainen, 2004).

Canada exported approximately 300,000 tons of asbestos in 2000 (Brophy, Keith, Schieman, 2007). According to the International Labor Organization, between 1983 and 2006, national asbestos bans, with minor exceptions, have been successfully implemented in thirty-nine countries worldwide in accordance with measures of health protection in international trade agreements (Tossavainen, 2004; Brophy et al., 2007). The Canadian government challenged these regulations at the World Trade Organization (WHO) (Tossavainen, 2004; Brophy et al., 2007, World Trade Organization, 2001). Despite an overwhelming consensus from major health organizations such as the International Agency for Research on Cancer (IARC) and the WHO, that all forms of asbestos are human carcinogens and have no safe threshold at which there is no increased risk of

cancer, the Canadian federal government continues to advocate the controlled use of chrysotile (Brophy et al., 2007).

In Canada, occupational health and safety regulations fall under provincial jurisdiction, with each province setting its own standards. In Ontario, the all type asbestos exposure standard is 0.1 fibers /ml (Brophy, 2007; World Trade Organization, 2006).

2.3 The Impact of Asbestos-Related Disease

In 1987 the U.S. National Institute of Health estimated that approximately eleven million individuals had been exposed to asbestos in the United States since 1940 (Manning, Vallyathan, & Mossman, 2002; NIH Research Findings, 1978). The overall incidence of mesothelioma in the general population was extremely low. According to the data from the Surveillance, Epidemiology and End Results Program (SEER), the incidence of mesothelioma in the United States is 14 to 15 cases per million population of men (Price & Ware, 2004). This amounts to 1750 males diagnosed with mesothelioma each year in the U.S. The incidence in women is about two cases per million population, which is, approximately 250 new cases of mesothelioma each year (Price & Ware, 2004). The incidence of mesothelioma shows an *age* effect, meaning the incidence increases with age (Price & Ware, 2004). Mesothelioma incidence also shows a birth-cohort effect. Figure 1 shows the lifetime risk for males is a maximum of 2.1×10^{-3} for the 1925-1929 birth cohort and then declines sharply for subsequent cohorts (Price & Ware, 2004). Male members from this cohort would have been at work during the years 1930-1960, a period of increasing and maximum asbestos consumption in the United States. Table 1 shows the results of a recent study which estimated the incidence of mesothelioma based on the global use of asbestos.



Figure 1: Lifetime Probability (risk) of Mesothelioma (Pleural + Peritoneal) and 95% Confidence Intervals Based on a Birth-Cohort and Age Model Estimated from 2003 Surveillance, Epidemiology, and End Results Program data covering 1973-2000 (Price & Ware, 2004)

In a study comparing the incidence rates of mesothelioma of the pleura in Quebec compared to those in the rest of Canada between 1984 and 1996, the incidence rate (adjusted for age and year) of mesothelioma of the pleura in men was 11.3 cases per million population in Canada outside of Quebec. The incidence rate for Quebec was 1.35 (95% CI = 1.20 – 1.46) times higher than those of Canadians in all other provinces combined at 15.3 cases per million population. The incidence rate of mesothelioma of the pleura in women was 1.64 cases per million in Canada, excluding Quebec and 3.14 cases per million in Quebec (Sharpe & Hardt, 2006).

Based on the Canadian Agricultural Injury Surveillance Program asbestos-related deaths accounted for 61% of death from occupational diseases and 31% of all workplace fatalities in Canada in 2005 (Sharpe & Hardt, 2006). The fatality rate from asbestos is up

from 0.4 per 100,000 workers in 1996 to 2.1 per 100,000 in 2005 (Sharpe & Hardt, 2006). The number of Canadian men who receive a diagnosis of mesothelioma each year has been steadily increasing over the past twenty years, from 153 cases in 1984 to 344 cases in 2003 (Statistics Canada, 2008). The number of new cases of pleural mesothelioma in Ontario males rose from 20 in 1982 to 72 in 2002 (Cancer Care Ontario, 2004).

In the United Kingdom, France, and Australia, the mesothelioma incidence is not expected to peak until the 2010-2020 period (Tossavainen, 2004). In Canada, where the production and use of asbestos is not banned, the number of deaths related to occupational asbestos exposure is not expected to peak until after 2010-2020 due to the lengthy latent period of asbestos-related diseases (Tossavainen, 2004).

Table 1. National Mesothelioma Incidence
(Tossavainen, 2004; Sub-Committee on the Epidemiology of Asbestos-Related Disease, 2004)

Country	Mesothelioma Incidence	
	Cases (year)	Cases/million/year
Australia	465 (1997)	35
Finland	74 (1999)	18
France	750 (1996)	16
Germany	1007 (1997)	15
Great Britain	1595 (1999)	33
Italy	930 (1995)	19
Netherlands	377 (1997)	30
New Zealand	50 (1996)	18
Norway	48 (1995)	14
Sweden	105 (1996)	15
United States	2800 (2000)	14
Canada (excluding Quebec)	N/A (1996)	11.3
Quebec	N/A (1996)	15.3

The incidence of asbestosis in Canada has not been clearly established. The majority of studies undertaken are not free of bias or have not followed a sufficiently

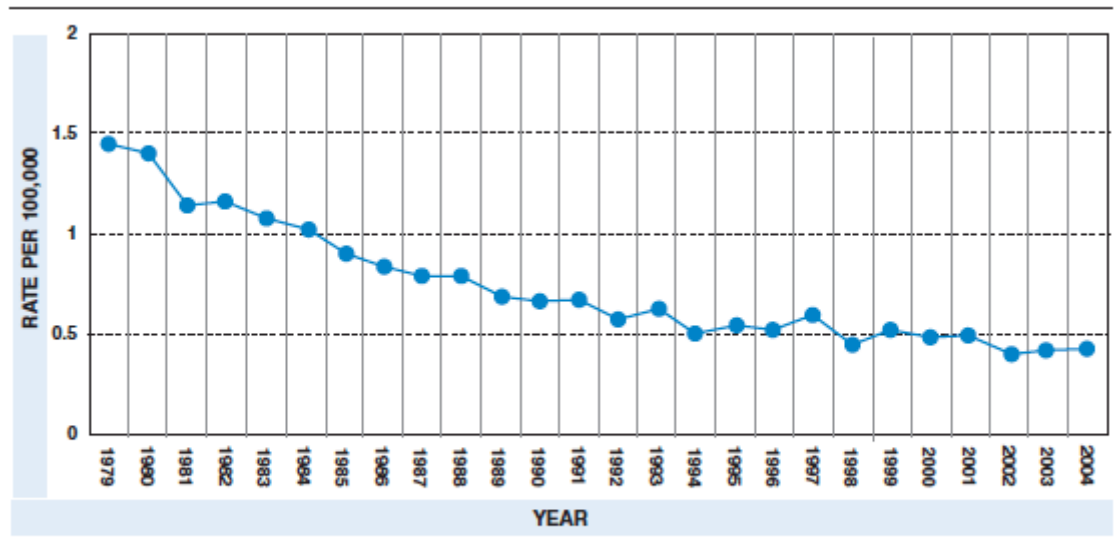
large cohort over a long enough period of time. The most realistic estimate of the prevalence of asbestosis is between 1% and 5% of asbestos-exposed workers (The Spanish Society of Pulmonology, 2005). The prevalence of radiologically documented asbestosis varies considerably in studies of asbestos-exposed workers. This inconsistency may be due to differences in duration, intensity and type of asbestos exposure between workplaces. However, even when exposure is calculated individually for each member of a cohort based on work history and industrial hygiene measurements, there are still considerable differences in observed associations due to fiber type and the industrial process (Liddell & McDonald, 1980; Lilis, Miller, Godbold, Chan, Benkert, & Selikoff, 1991). In a recent study modeling the prevalence and incidence of fibrosis and pleural plaques in asbestos-exposed populations for screening found 6% of subjects had interstitial changes compatible with asbestosis on CT-scan (Paris, Martin, Letouneux, & Wild, 2008). In a study of former crocidolite asbestos workers in Western Australia the prevalence of radiographic asbestosis was as high as 17.6% (Alfonso, Fritschi, de Klerk, Olsen, Sleith, & Musk, 2004). A screening study for lung cancer found 85 cases of asbestosis out of 2857 persons with asbestos-related occupational disease (Tiitola, Kivisaari, Huuskonen, Mattson, Koskinen, Lehtola, Zitting, & Vehmas, 2002)

2.4 The Impact of Asbestos-Related Diseases in Canada

In Canada there have been significant changes in the prevalence of occupational respiratory disease over the past thirty years. Though Canada is rich in minerals and mining continues to be common in many parts of the country, pneumoconiosis has declined as a cause of mortality and hospital admission (Figures 2 and 3). Yearly hospital admission rates due to pneumoconioses have been only 1 or 2 per 100,000 population

since the early 1990s, with mortality rates below 0.25 per 100,000 population, and less than 0.5 per 100,000 population among those 35 years of age and older. These trends are similar to those reported in the United States and may reflect improved occupational hygiene conditions in mines, better dust control, and better use of respiratory protective measures.

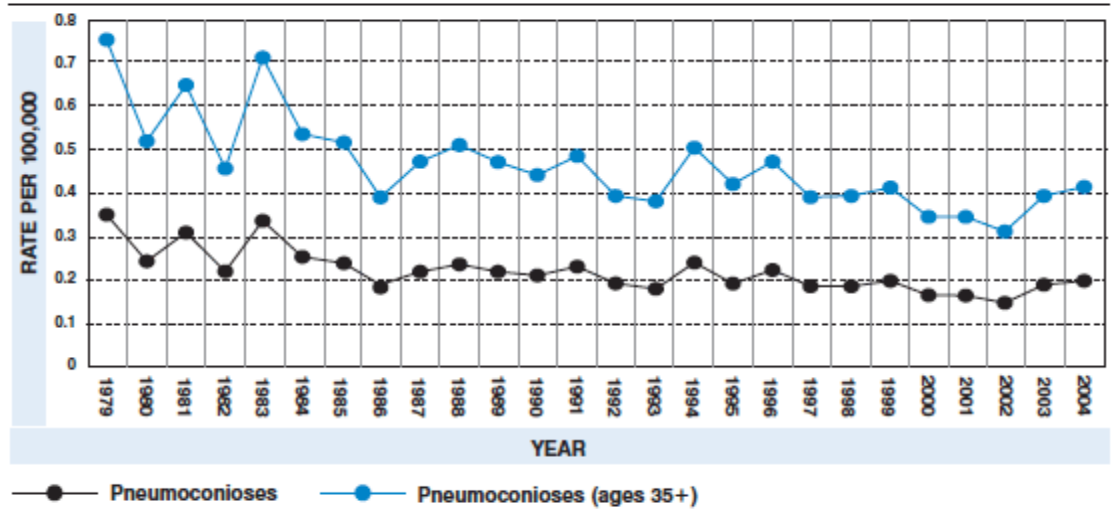
However, this decline in admission rates for all pneumoconiosis is not occurring for asbestosis over time. This would be expected if better preventive measures at work which involves asbestos exposure were being implemented.



* Data for territories unavailable prior to 1993 and data for Nunavut not available for 2002.

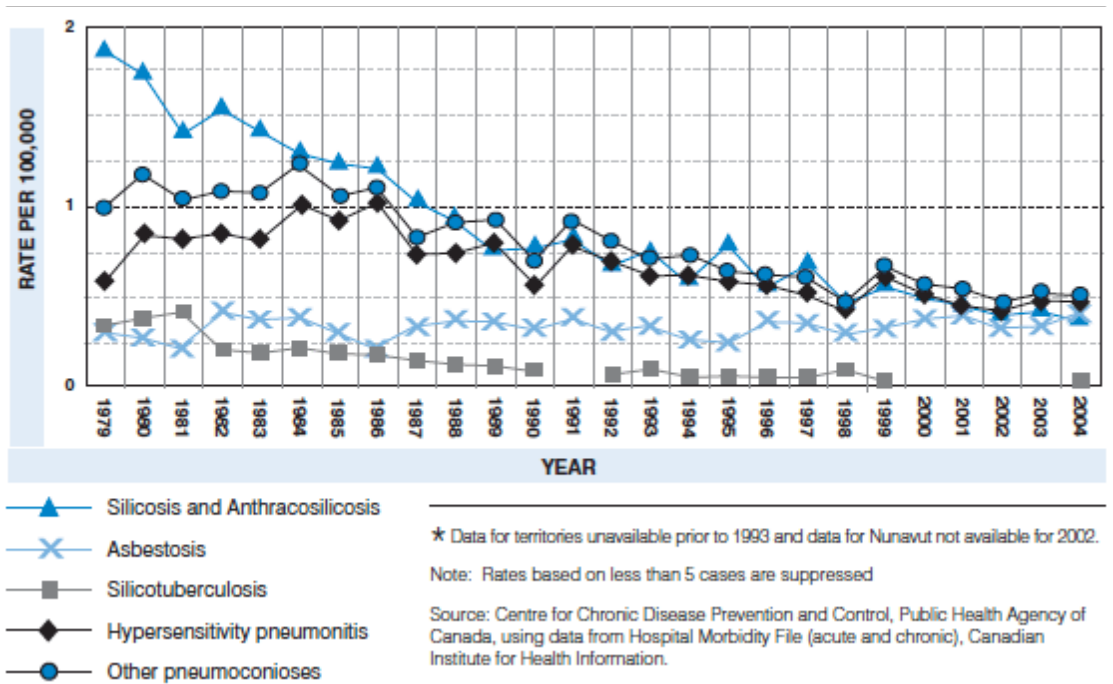
Source: Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada, using data from Hospital Morbidity File (acute and chronic), Canadian Institute for Health Information.

Figure 2: Pneumoconioses Hospitalization Rates (per 100,000), Canada*, 1987-2004 (Age-Standardized to 1991 Canadian Population) (Life and Breath: Respiratory Disease in Canada, 2007)



Source: Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada, using Statistics Canada annual mortality data.

Figure 3: Pneumoconioses Mortality Rates (per 100,000), Canada, 1987-2004 (Age- Standardized to 1991 Canadian population) (Life and Breath: Respiratory Disease in Canada, 2007)



* Data for territories unavailable prior to 1993 and data for Nunavut not available for 2002.

Note: Rates based on less than 5 cases are suppressed

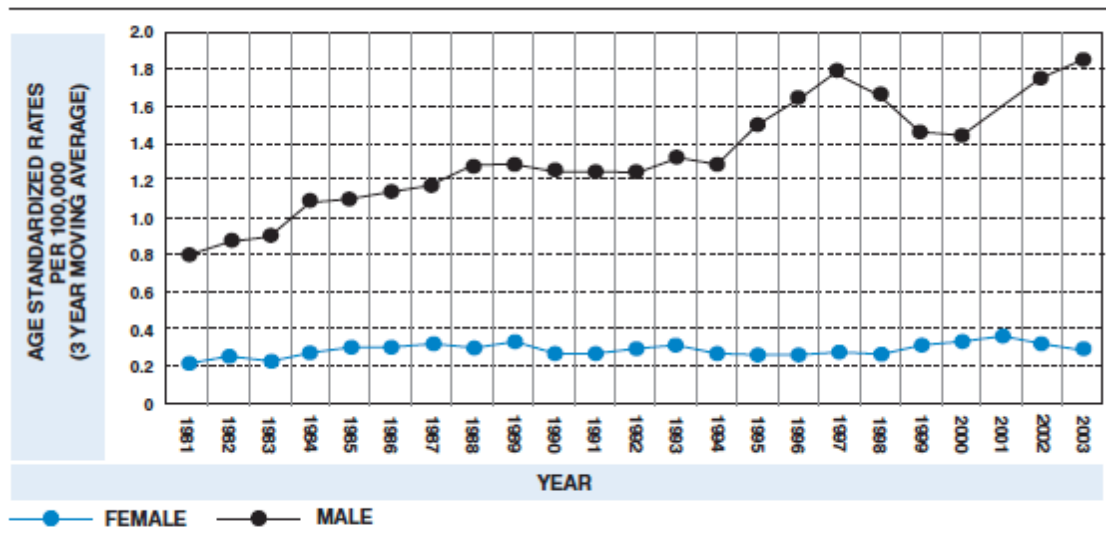
Source: Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada, using data from Hospital Morbidity File (acute and chronic), Canadian Institute for Health Information.

Figure 4: Pneumoconioses and Hypersensitivity Pneumonitis Hospitalization Rates (per 100,000), Canada*, 1987-2004, aged 35+ years, (Age-Standardized to 1991 Canadian population) (Life and Breath: Respiratory Disease in Canada, 2007)

Given the long latency of asbestosis and reduced exposure in the past twenty years, a further decline in hospitalizations would be expected. What other explanations are there for this finding? The answer to this is yet to be found.

Mesothelioma is a malignant tumor affecting the lining of the chest or abdomen caused by asbestos exposure. Figures were not available for mesothelioma under the ICD coding system until the introduction of ICD 10 codes in 2001, and there are no current national estimates for this complication of asbestos exposure, as ICD 10 codes were not implemented in all provinces until 2006. However, the numbers of (pleural) mesothelioma cases reported by Cancer Care Ontario (Figure 5) have demonstrated the marked rise associated with asbestos exposure decades earlier.

Figure 4-4 Ontario Mesothelioma Incidence Rate, 3 year moving average, by Sex, 1980-2004



Source: Cancer Care Ontario (Ontario Cancer Registry 2006). Age-standardized to Canada 1991

Figure 5: Ontario Mesothelioma Incidence Rate, 3 Year Moving Average, by Sex, 1980-2004 (Life and Breath: Respiratory Disease in Canada, 2007)

A study by Teschke et al., investigated whether there were previously unrecognized sources of asbestos exposure in British Columbia, Canada using incident cases of mesothelioma (n=51) and population-based controls (n=154). The subjects were interviewed about occupational histories and asbestos-specific exposures. When excluding subjects who worked in occupations which were *a priori* at risk for mesothelioma, three groups remained of interest: non-asbestos miners (OR=9.6, 95%CI=1.8-53), bricklayers (OR=5.4, 95%CI=1.0-28) and construction laborers (OR=2.8, 95%CI=0.7-10.5). The wide confidence intervals suggest cause for concern, however considering that sample size when excluding those *a priori* at risk was as small as 19, the trend toward significant is impressive. Teschke et al. point out that despite this problem the major occupations at risk for mesothelioma were easily detected in their study (Teschke, Morgan, Checkoway, Granklin, Spinelli, Belle, & Weiss, 1997).

2.5 Types of Asbestos

Asbestos is a naturally occurring group of hydrated silicate fibrous minerals. Asbestos is traditionally subdivided into two groups: serpentines (curly fibers) and amphiboles (straight, needle-like fibers). Chrysotile is the only commercially used serpentine and has many industrial applications. It is long, curly, pliable and heat resistant; however it is damaged in acidic environments (American Thoracic Society, 2004; The Spanish Society of Pulmonology, 2004; Manning et al., 2002). Chrysotile fibers are made of fibrils with a layered silicate structure formed of cylindrical tubes. Due to its physical and chemical properties, this serpentine form of asbestos is most suitable for making fabrics and other flexible products. It is estimated that 90 – 95% of all past commercially used asbestos in North America has been chrysotile with most of

this being derived from Canadian and Russian mines (American Thoracic Society, 2004; Manning et al., 2002).

The second group of asbestos fibers is amphiboles. Amphibole fibers include amosite (brown asbestos), crocidolite (blue asbestos), tremolite, actinolite, and anthophyllite. They are characterized by their short straight needle-like appearance, lack of pliability and relative resistance to acid. The basic subunit of amphiboles is a silicon dioxide tetrahedron arranged in parallel chains and linked laterally by cations. Among the five amphiboles, the most commonly used are amosite and crocidolite. Amphiboles have superior chemical and physical stability and have been used in the production of asbestos-cement pipe, floor tiles and when mixed with chrysotile a vast array of friction products, gaskets, roofing, insulation, and fire-proofing material (American Thoracic Society, 2004; Manning et al. , 2002).

Amphiboles and chrysotile are different from each other in terms of their chemical and physical composition, shapes, sizes, durability and pulmonary penetration abilities, and thus their potency to increase health risk differ. Chrysotile fibers are less harmful than amphiboles, partly because they are more readily broken down and removed from the lung (Cugell & Kamp, 2004). Of those fibers which remain in the lung, some become coated with ferritin and then form asbestos bodies (Roach, Davies, Attanoos, Crane, Adam, Wilson, Dee, & Hansell, 2000).

2.6 Measuring Asbestos Exposure

The accuracy of exposure assessment is a major determinant of the informativeness of a study and the validity of risk estimates drawn from it. The retrospective assessment of occupational asbestos exposure has several important aspects

to consider. The pulmonary response to asbestos is thought to be proportional to the amount and duration of exposure that contributes to the retention of fibers in the distal airspace. Therefore there are three major considerations for asbestos exposure assessment: 1. exposure intensity (concentration of asbestos fibers), 2. latency period (time since first exposure), and 3. duration of exposure. A recent study by Paris et al., 2008 found that time since first exposure and exposure intensity were predictive of asbestosis and pleural plaques, but not duration of exposure (Paris et al., 2008).

The type of asbestos involved in exposure (chrysotile, crocidolite, amosite, etc.), if known, should be considered given that chrysotile fibers are potentially less harmful than the amphiboles (Cugell & Kamp, 2004). Also, measures taken to protect workers are important to include in analysis when attempting predictions of risk or studying etiology.

In occupational epidemiology, retrospective exposure assessment offers certain advantages, but also poses several major challenges. In the case of asbestos exposure, exposed individuals are mainly scattered in specific worksites therefore, a study centered in a geographical area where workers reside is logistically simpler than assembling a prospective cohort study. The retrospective case-control also allows the evaluation of multiple exposures, including occupational and residential exposures, and lifestyle factors which may confound or interact with exposure-disease associations.

The main challenge of asbestos exposure measurement is the method by which data is gathered. There is rarely a quantitative measurement of asbestos exposure on record therefore, retrospectively collected detailed occupational histories, job tasks or specific recall to asbestos exposures are used. There are several potential sources of error

in the collection of occupational exposures such as misclassification, incomplete data on concentrations or work time, poor sources of data (e.g. statement of usual occupation of death certificates) and recall bias. Information on level of exposure is only available on rare occasions because dust levels in the workplace were not measured until the late 1980's. Owing to the lengthy latent period, incident asbestos-related disease is often associated with exposure that occurred before such levels were monitored (American Thoracic Society, 2004). Due to the lack of documentation of actual exposure in the past, the use of crude exposure classifications is often necessary. The most common retrospective exposure assessment methods are: use of occupational history to infer exposure, known as job exposure matrices (JEMs); self reported exposures; and expert assessment of exposures. Each exposure assessment method has strengths and limitations.

JEMs combine information across occupation and industry in an attempt to provide greater accuracy as to exposure status. JEMs attempt to relate specific jobs to exposure presence, intensity, frequency and/or probability, assigning an exposure category based on standardized occupational and industrial codes. In 1991 this approach was taken in developing the National Occupational Hazard Survey Job Exposure Matrix (NOHS-JEM). The NOHS was carried out between 1972 and 1974 in the United States, collecting information at the work site on chemical and physical agents in a wide range of occupations and industries. The major drawback of using the NOHS-JEM is that it is based on exposure conditions in 1972-1974, and these may differ from periods before and after this time interval (Sieber, Sundin, Frazier, & Robinson, 1991). It was found that expert assessment identified more asbestos exposure than the NOHS-JEM, which the

NOHS-JEM did not classify many occupation-industry couplets, and no assessment of intensity was made (Cicioni, London, Garabrant, Berstein, Phillips, & Peters, 1991). A major limitation of JEMs is their inability to account for variability in exposures within jobs or across time (Teschke, Olshan, Daniels, De Roos, Parks, Schulz, & Vaughan, 2002). Therefore JEMs are vulnerable to non-differential misclassification due to these with-in job variations in exposure (Benke, Sim, Fritschi, Aldred, Forbes, & Kauppinen, 2001). These limitations have decreased enthusiasm for generic JEMs and promotes the use of study specific JEMs (Teschke et al., 2002). A new JEM has been developed to provide a link between job title or activity reported in a work history, the type and length of asbestos fibers, and intensity of exposure which may be all useful in exposure reconstruction in the future (Rice & Heineman, 2003).

The use of occupational hygienists is thought to be the gold standard of exposure assessment. An occupational hygienist (or panel), with no prior knowledge of disease status, reviews work information provided from questionnaires administered to study participants. Hygienists evaluate completeness of work histories and assign relative exposure intensity for any job where there was a probability of exposure to asbestos (Nam, Rice, & Gail, 2005; Benke et al., 2001). High cost considerations for hygiene panels prevent many asbestos-related studies from their use in ascertaining exposure status (Benke et al., 2001). Experts do have an advantage over self reported exposures by subjects due to training, understanding the mechanisms of occupational exposures, and knowledge on where to find data. The major limitation of experts is that they rely heavily on a detailed occupational history because they are unlikely to be aware of specific work conditions for individual subjects (Teschke et al., 2002).

Questionnaires are commonly used to ask about subject's occupational history, use of specific agents, trade name products or specific type of asbestos. Though studies that assess exposure with direct questions to participants, such as "Were you ever exposed to asbestos?", are prone to recall bias and may be vulnerable to widely varied interpretations among participants of what constitutes exposure, data derived in this crude fashion can still yield useful information (Teschke et al. , 2002). A study comparing next-of-kin assessment, expert assessment and the use of the NOHS-JEM found that disease-exposure odds ratios based on next-kin respondents are inflated by recall-bias, whereas those from the NOHS-JEM are attenuated. Also NOHS-JEM exposure categorization based on next-of-kin data predicted asbestos levels that matched expert assessment better than only NOHS-JEM (Nam et al., 2005). Though information from proxy respondents is regarded as inferior to self-reports for occupational exposures, for rapidly fatal diseases such as mesothelioma, next-of-kin respondents may be an important and only source of data.

In summary, among the asbestos exposure assessment methods in use today, expert assessment is the best approach, however it can also have low validity and reliability if there is not proper training of the expert, and if not enough information is provided in the detailed occupational history of subjects. However, all exposure assessment methods, whether by experts or self-report have limitations and can have low validity and reliability.

2.7 Pulmonary Function Tests

A brief description of pulmonary function tests and their relevance in asbestos-exposed individuals is presented and is followed by a description of known functional deficits in specific asbestos-related diseases.

Pulmonary function tests provide objective and quantifiable measures of lung function. They are used to evaluate and monitor diseases that affect the lung and heart, to monitor the effects of environmental, occupational and drug exposures, to assess risks of surgery, and to assist in evaluations performed before employment or for insurance purposes. According to the 2004 American Thoracic Society (ATS) guidelines, demonstration of functional impairment is not required for the diagnosis of a nonmalignant asbestos-related disease, but where present should be documented as part of a complete evaluation (American Thoracic Society, 2004).

It has been reported that pulmonary dysfunction precedes chest x-ray findings of pneumoconiosis (occupational lung disease), suggesting the importance of pulmonary function tests in screening for early disease (Tonori et al., 2005). A second potential contribution of pulmonary function tests in asbestos-exposed individuals is in quantifying the extent of disease (Xaubet et al., 1998), and to assess the progression of lung disease (Al-Ashkar, Mehra, & Mazzone, 2003). Though radiological evaluations of asbestos-exposed individuals are relatively sensitive and reproducible for determining the extent of disease, their frequent repetition is questionable owing to the radiation burden and their high economic cost (Xaubet et al., 1998). According to various studies, pulmonary function tests can offer significant information about the extent of abnormalities, and thus, indicate that it is possibly not necessary to perform tests of high radiation burden

routinely for quantification of disease severity (Neri et al., 1996, Sette et al., 2004). This will be discussed in further detail in Section 2.11 Radiological-Functional Correlation.

Evaluation of subjects with suspected asbestos-related disease should include a panel of tests including spirometry, measurements of lung volume and diffusion capacity for carbon monoxide (DLCO) (American Thoracic Society, 2004). Spirometry measures changes in lung volume over time during forced breathing maneuvers. The patient is instructed to take a full inspiration and then exhales as forcefully as possible for as long as possible. The total volume of air expired is the forced vital capacity (FVC). The air expired in the first second of forced expiration is FEV1. FVC and FEV1 are expressed as both absolute volumes and percent predicted values, with predicted values based on healthy volunteer data which are matched to the patient's age, height, sex and race. The FEV1/FVC is a direct ratio of the patient's own values.

The DLCO measures the ability of the alveolar capillary membrane to diffuse gases. The patient inhales a harmless composite gas (10% helium, 0.3% carbon monoxide) and is instructed to hold their breath for 10 seconds. The exhaled breath is then analyzed for dilution of helium and CO. There are three major pulmonary disorders which may cause a decreased in DLCO, obstructive airway disease (i.e. emphysema, cystic fibrosis), interstitial lung disease (i.e. pulmonary fibrosis), and pulmonary vascular disease (Al-Ashkar et al., 2003). DLCO can also be adjusted for alveolar volume and is called DLCO/VA.

Lastly, total lung capacity (TLC) can be obtained by four methods: nitrogen washout, helium dilution, body plethysmography (the gold standard TLC measurement,

although it is complex and expensive), and rough estimation using chest x-ray during maximal expiration.

Obstructive lung disease is characterized by decreased airflow during expiration. Some classic examples of obstructive lung disease are asthma, chronic bronchitis, and emphysema. Obstruction is defined as having an FEV1 less than 70-80 % of the predicted value. FVC may be normal or decreased, but to a lesser degree than FEV1. An FEV1/FVC of less than 70% is also characteristic of obstruction. DLCO generally does not decrease in most obstructive lung diseases with the exception of emphysema. A DLCO of less than 74% predicted is mild impairment and less than 40% predicted severe impairment.

Restrictive lung disease is characterized by a decreased lung volume, defined as having a TLC less than 80% predicted. There are extrinsic and intrinsic causes of restrictive lung disease. Extrinsic causes of restrictive lung disease are decreased chest wall compliance, which occurs in obesity, and weakening of respiratory muscles due to neuromuscular disorders. Intrinsic causes are those which occur within the lung tissue such as interstitial lung disease or congestive heart failure. FEV1 and FVC are both reduced in restriction; however FEV1/FVC remains normal or increased. A decreased DLCO is seen in significant interstitial lung disease (e.g. pulmonary fibrosis), but remains normal when there are other causes of decreased lung volumes (such as obesity, pleural scarring, neuromuscular disease). See Table 2 and Table 3 for a summary of pulmonary function test variables and their relation to pulmonary disorders.

Table 2. Obstructive and restrictive patterns
(Adapted from Al-Ashkar et al., 2003)

Measurement	Obstructive Pattern	Restrictive Pattern
Forced vital capacity (FVC)	Decreased or normal	Decreased
Forced expiratory volume in 1 second (FEV1)	Decreased	Decreased or normal
FEV1/FVC ratio	Decreased	Normal or increased
Total lung capacity (TLC)	Normal or increased	Decreased

2.8 Diseases Caused By Asbestos Exposure

Epidemiologic and animal studies have indicated several well-recognized benign and malignant diseases of the lung parenchyma and pleura associated with inhaled asbestos exposure. Asbestos fibers have a natural, unexplained predilection to the pleura, the outer covering of the lungs (visceral pleura) and the inner covering of the chest cage (parietal pleura). It is at the pleural surface where the effect of asbestos exposure often occurs. There are four distinct benign pleural reactions to asbestos: (1) pleural effusion, (2) pleural plaques (fibrosis of the parietal pleura), (3) diffuse pleural fibrosis (typically affects visceral pleura which can extend to parietal), and (4) rounded atelectasis (an area of visceral pleural fibrosis extending to the parenchyma rendering the underlying lung tissue airless) (American Thoracic Society, 2004; Cugell & Kamp, 2004; Chapman et al., 2003). The primary malignancy of the pleura is mesothelioma (Cugell, 2004). The parenchymal consequences of asbestos exposure are asbestosis (fibrosis of the pulmonary interstitium) and bronchogenic lung cancer (American Thoracic Society, 2004; Cugell & Kamp, 2004).

2.8.1 Pleural Consequences of Asbestos Exposure

Brief explanations of the benign pleural consequences of asbestos exposure are described below. The four types of benign asbestos-related pleural disease are important because they are common in asbestos-exposed workers and may result in abnormal lung function and symptoms.

2.8.1.1 Pleural Effusion

Benign pleural effusion attributed to asbestos-exposure is an early manifestation of pleural asbestos disease and usually appears within twenty years of first exposure (American Thoracic Society, 2004; The Spanish Society of Pulmonology, 2005; Chapman, Cookson, Musk, & Lee, 2003). The latency period can be as short as ten years (American Thoracic Society, 2004; The Spanish Society of Pulmonology, 2005). The exact prevalence of pleural effusions is unknown because many cases are subclinical, but could be estimated in a population screening study using computed tomography, the most sensitive imaging modality for visualizing pleural fluid (Cugell, 2004; Roach, Davies, Attanoos, Crane, Adam, & Phillips, 2002). Pleural effusions, accumulation of fluid in the pleural cavity, are exudative and often hemorrhagic with mixed cellularity and usually do not contain asbestos bodies (Roach et al., 2002).

The presentation can vary from completely asymptomatic with total resolution, to an active, inflammatory pleuritis with pain, fever, and dyspnea (American Thoracic Society, 2004; The Spanish Society of Pulmonology, 2005, Chapman et al., 2003). The symptoms of asbestos-related pleural effusion do not differ from other forms of acute pleuritis and therefore can only be attributed to asbestos after two to three years of observation, when there is a history of asbestos exposure and all other causes, particularly

malignancy, have been excluded (Cugell & Kamp, 2004). Asbestos pleural effusions have no prognostic implications with respect to subsequent development of other asbestos pleural diseases or pulmonary functional complications.

2.8.1.2 Pleural Plaques

Pleural plaques are circumscribed and discrete areas of hyaline or calcified fibrosis, which are localized on the parietal pleura of the lateral chest wall, the diaphragm, or the mediastinum (Chapman et al., 2003; Genenois, de Maertelaer, & Madani, 1998). They are clearly the most common manifestation of the inhalation, retention and biologic effect of asbestos (American Thoracic Society, 2004). Their prevalence is most directly related to time since first exposure and they rarely occur within less than 20 years of first exposure (American Thoracic Society, 2004). Pleural plaques consistent with asbestos exposure appear in the chest radiography of 2.3% of U.S. males (Rogan, Gladen, Ragan, & Anderson, 1987). Approximately 85% of heavily exposed asbestos workers showed pleural plaques on chest radiography with more than 40 years since first exposure (Sison, Hruban, Moore, Kuhlman, Wheeler, & Hutchins, 1989).

Assessments of pulmonary function of patients with pleural plaques has yielded conflicting results, with studies complicated by variations in degrees of exposure, the presence of other asbestos-related diseases, and confounding factors such as smoking. Some studies have demonstrated no significant association between pleural plaques and abnormal lung function (Oliver, Eisen, Green, & Sprince, 1988; Ohlson, Rydman, Sundell, Bodin, & Hogstedet, 1984).

This led to the notion that pleural plaques were inconsequential markers of asbestos exposure; however several large cohort studies have shown a significant reduction in lung function attributable to plaques. Taking into account the degree of interstitial fibrosis, smoking and duration of asbestos exposure, pleural plaques were associated with decreased vital capacity. (Schwartz, Fuortes, Galvin, Burmeister, Schmidt, Leistikow, LaMarte, & Merchant, 1990). This has not been a consistent finding, and is possibly related to early subclinical fibrosis not detectable by plain chest radiograph, or residual confounding (Schwartz et al., 1990).

2.8.1.3 Diffuse Pleural Thickening

Diffuse pleural thickening is extensive fibrosis of the visceral pleura with areas of adhesion to the parietal pleura, and ill-defined margins often involving the costophrenic angles, apices and interlobular fissures (American Thoracic Society, 2004; Chapman et al., 2003). Diffuse pleural thickening, unlike circumscribed pleural plaques can cause significant restrictive pulmonary function impairment, especially with blunting of the costophrenic angle (Cugell & Kamp, 2004). A reduction of 270 ml of FVC has been associated with diffuse pleural thickening (Schwartz et al., 1990; Kee, Gamsu, & Blanc, 1996). Workers with diffuse pleural thickening have a significantly greater decrease in FVC (two times) compared to those with circumscribed pleural plaques (Schwartz et al., 1990). Copley et al. found an inverse relationship with FVC and diffuse pleural thickening along with a reduction in carbon monoxide diffusing capacity, suggesting that reductions in lung volumes was not solely due to pleural fibrosis but also parenchymal fibrosis (Copley et al., 2001).

2.8.1.4 Rounded Atelectasis

Rounded atelectasis (RA), also known as shrinking pleuritis, folded lung, or Blesovsky syndrome, is the least common of all benign asbestos-induced pleural and parenchymal changes (Cugell & Kamp, 2004; Stathopoulos, Karamessini, Sotiriadi, & Pastromas, 2005). RA is found in areas adjacent to pleural fibrosis and consists of collapsed pulmonary parenchyma surrounded by thickened and invaginated pleura (Stathopoulos et al., 2005; Terra-Filho, Kavakama, Bagatin, Capelozzi, Nery, & Tavares, 2003). RA appears on CT-scans as a rounded peripheral mass abutting thickened pleura with a diameter between 3.5-7-cm (Cugell & Kamp, 2004). The classic “comet tail” is pathognomonic and is more readily seen on high resolution computed tomography (HRCT) than on plain chest radiographs (American Thoracic Society, 2004). A solitary RA causes no significant functional impairment unless it is accompanied by other pleural or parenchymal sequelae of asbestos exposure, especially diffuse pleural thickening (Kee et al., 1996).

2.8.2 Benign Parenchymal Consequences of Asbestos Exposure

2.8.2.1 Asbestosis

The development of diffuse interstitial pulmonary fibrosis due to inhalation of asbestos fibers is known as asbestosis (American Thoracic Society, 2004; The Spanish Society of Pulmonology, 2005; Cugell & Kamp, 2004). A latency period of 15 and 20 years between first exposure and appearance of fibrosis has been estimated; however no consensus has been reached on the subject (The Spanish Society of Pulmonology, 2005).

The most common clinical symptom of asbestosis is dyspnea on exertion which becomes progressively more severe and present at rest (Copley et al., 2001). Over time this will lead to restrictive impairment and decreased diffusing capacity characterized by a reduction in FVC, TLC and DLCO (American Thoracic Society, 2004; Manning et al., 2002; Ross, 2003).

Though the classic finding in asbestosis is a restrictive impairment, mixed restrictive and obstructive impairments are frequently seen. However, isolated obstructive impairment is rare and unusual (American Thoracic Society, 2004). Low diffusing capacity for carbon monoxide has been reported as the most sensitive indicator of early asbestosis, though the finding is also relatively non-specific (The Spanish Society of Pulmonology, 2005). This is because diffuse interstitial pulmonary fibrosis first and most extensively affects the smallest airways, alveolar ducts, alveoli and microcirculation where gas exchange occurs (Ross, 2003). However many additional factors can lead to a low DLCO therefore it is not highly specific for asbestosis (Ross, 2003).

2.9 Distinguishing Between Pleural and Parenchymal Asbestos Disease

The diagnosis of asbestosis has important medicolegal implications and the distinction between asbestos-related parenchymal and pleural disease is important as the magnitude of compensation may be much greater with asbestos-induced interstitial fibrosis (Copley et al., 2001). Pleural changes are often present in cases of asbestosis. It has been reported that 80% of patients with asbestosis have coexistent pleural disease at chest radiography (Dee, 2000) and the percentage rises to 100% with the use of high-resolution CT (Aberle, Gamsu, Ray & Fauerstein, 1988). Parenchymal bands are defined

as linear opacities, several millimeters wide and up to 5-cm long which extend to the pleura (Peacock, Copley, & Hansell, 2000; Genenois et al., 1998). This feature is due to adjacent visceral pleural thickening and is not regarded as a defining feature of asbestosis (Genenois et al., 1998). Because pleural disease can cause distortion of adjacent lung parenchyma, parenchymal features in areas unrelated to pleural disease are more diagnostically convincing for asbestosis (Genenois et al., 1998; Kipen, Lilis, & Suzuki, 1987).

2.10 Imaging of Asbestos-Exposed Individuals

Imaging has several implications in the evaluation of asbestos-related disease: in diagnosis, for the quantification of disease extent, as part of medicolegal claims evidence, to potentially screen high-risk individuals for cancer and for distinguishing other (non asbestos-related) causes of pulmonary disability.

2.10.1 Chest Radiography

Imaging findings are pivotal in the diagnosis of asbestos-related diseases. The American Thoracic Society (ATS) guidelines published in 2004 advocated caution in diagnosing asbestosis if radiographic changes were not present.

Since 1980 the International Labor Organization (ILO) Classification of Radiographs for the Pneumoconioses has been the gold standard for recording chest radiographic abnormalities of the lung and pleura related to asbestos exposure (International Labour Office, 2000; Huuskonen, Kivisaari, Zitting, Taskinen, Tossavainen, & Vehmas, 2001). The purpose was to improve workers' health surveillance by facilitating international epidemiologic comparisons through coding of radiographic abnormalities in a simple reproducible manner by means of comparison

with a standard set of radiographs to reduce inter-observer variability (Roach et al., 2002). In contrast to most tests, it was designed primarily for population epidemiology rather than individual diagnoses. The system describes changes on a posteroanterior chest radiograph. Small opacities, which may differ in shape, size and profusion, are seen in early disease and are denoted by the symbols *s*, *t*, and *u* for irregular opacities, and *p*, *q* and *r* for rounded or nodular opacities (International Labour Office, 2000). Large opacities are those greater than 1-cm in diameter and are graded A, B or C based on the combined dimensions of all large opacities present (Roach et al., 2002). Profusion of the small opacities is classified into four categories (0 – 3) in comparison to the standard films, category 0 being no excess of small opacities above normal. For example, 1/0 indicates the appearance most closely resembles category 1 but the reader has also considered category 0 (International Labour Office, 2000).

The initial radiographic presentation of asbestosis is ground-glass opacification and bilateral, small, irregular parenchymal opacities in the lower lobes (American Thoracic Society, 2004). In more advanced stages of the disease the fine reticular pattern becomes coarser and results in honeycombing (Roach et al., 2002). However, honeycombing is only present in 7 – 17 % of cases (Aberle et al., 1998). If radiographically found fibrosis is predominantly in the upper or mid zone distribution, asbestosis is less likely than other causes (American Thoracic Society, 2004). Though asbestosis characteristically appears earliest in the lower lung lobes, there is a rare but well-characterized syndrome of massive bilateral upper lobe fibrosis, in the absence of tuberculosis or lung cancer (Hillerdal, 1990).

A disadvantage of the chest radiograph is that the radiograph may be normal in individuals with asbestosis (Kipen et al., 1987). Although chest radiograph findings are usually abnormal in patients with asbestosis, approximately 10-15% appear normal, yielding a sensitivity of 85-90% (Friedman, Fiel, Fisher, Radecki, Lev-Toaff, & Caroline, 1988). Furthermore, many factors other than asbestos exposure can lead to a mildly abnormal chest radiograph finding, affecting specificity. Such factors are differing radiographic technique, aging, obesity, smoking, presence of chronic obstructive pulmonary disease, and exposure to other fibrogenic and non-fibrogenic dusts (American Thoracic Society, 2004; Roach et al., 2002). Lastly, the chest radiograph and the International Labor Organization (ILO) system have significant inter- and intraobserver variability for both pleural and parenchymal diseases (Bourbeau & Ernst, 1988).

Chest radiography remains an important epidemiological and diagnostic tool because of limited access to CT and because it is relatively specific in individuals with advanced parenchymal disease and appropriate asbestos exposure history. However, in individuals with early parenchymal changes due to asbestos-exposure and extensive pleural disease which obscures the lung parenchyma, the need for thin-section CT is evident.

2.10.2 Computed Tomography

Several studies and most recently the 2004 ATS guidelines recognize computed tomography (CT) as having increased sensitivity, greater inter-observer agreement and more diagnostic accuracy for structural pulmonary change (American Thoracic Society, 2004; Grenier, Valeyre, & Cluzel, 1991; Mathieson, Mayo, & Staples, 1989). The ATS

guidelines recommend that CT sections should be obtained with at least 2-mm intervals for the most accurate assessment of pleuropulmonary abnormalities (American Thoracic Society, 2004). However, early studies demonstrated that even conventional thick slice CT was more sensitive for diffuse pleural thickening and early asbestosis than chest radiography due to the lack of superimposed structures (Katz & Kreel, 1979).

There are several high-resolution (HR)-CT features of asbestosis which have been extensively described. In early disease, subpleural branching is seen. As the disease becomes more advanced the subpleural branching becomes more confluent producing pleural based nodular irregularities. Other features of fibrosis on CT scans include subpleural curvilinear areas (linear densities usually within 1-cm of the pleura and parallel to the chest wall), ground glass opacity (increased attenuation of the lung without obstruction of the underlying bronchovascular margins), parenchymal bands (linear non-tapering densities 2-5 cm in length, extending through the lung to contact the pleural surface), thickened interlobular (septal) and intralobular (core) lines (when numerous appear as fine reticular pattern), and later honeycombing (cystic air spaces with well-defined walls) (Gamsu, Salmon, Warnock, & Blanc, 1995; Lynch, Gamsu, & Aberle, 1989).

Subpleural curvilinear lines which represent fibrosing bronchioloalveolitis was initially thought to be characteristic of asbestosis (Yoshimura, Hatakeyama, & Otsuji, 1986), however after being found in patients without asbestos exposure is no longer thought to be pathognomonic.

Gamsu et al. found the most common HR-CT abnormalities of asbestosis were interstitial lines (defined as thickened interlobular septa and centrilobular core structures),

which were found in 84% of cases (Gamsu et al., 1995). This was followed by parenchymal bands in 76% of cases and distortion of secondary pulmonary lobules (56% of cases). Features such as subpleural lines and honeycombing were less frequent.

However, all of the above listed CT features are non-specific, since they can also be observed in pulmonary fibrosis from other causes, especially idiopathic pulmonary fibrosis (IPF) (Lynch et al., 1989). Asbestosis is not characterized by an individual CT feature, rather a constellation of the features listed above which are bilateral and multifocal with a coexisting occupational history (Gamsu et al., 1995). Often the presence or absence of pleural plaques or diffuse pleural thickening and/or coexisting appropriate occupational history is relied on to discriminate between asbestosis and IPF. Differences in prognosis and eligibility for compensation highlight the need for accurate differentiation. The lack of a standardized interpretation of CT, such as the ILO for chest radiographs is a limitation for using CT in the diagnosis of asbestos-related diseases.

Despite an absence of an internationally accepted classification tool for asbestosis determined by CT, Huuskonen et al. recorded several specific HR-CT parenchymal abnormalities and found good inter- and intraobserver agreement. The parenchymal abnormalities were: (i) subpleural dependent opacity, (ii) subpleural curvilinear opacities, (iii) subpleural perpendicular lines (septal lines), (iv) parenchymal bands, (v) small irregular parenchymal opacities, and (vi) honeycombing. The severity of each abnormality was recorded from mild to profuse. Receiver-operating characteristic (ROC) area under the curve was significantly greater for HR-CT fibrosis score (0.89) than for the ILO radiographic classification (0.76) ($P < 0.0001$) (Huuskonen et al., 2001). It has been suggested that this type of semi-quantitative HRCT scoring system could be of use

when an international HR-CT classification is designed for occupational lung disease (American Thoracic Society, 2004).

Multidetector CT (MDCT) is the newest design of CT technology which differs from its predecessors in the design of the detector array. By replacing a single detector row by 4-, 6- or 64- detector rows, the simultaneous collection of data from different slice locations can occur during a single rotation of the x-ray source. This allows for rapid scanning and anatomic coverage. The raw data can then be reconstructed to provide thin 1.25-mm and 5-mm sections (Prokop, 2003). Therefore a single scan by the MDCT can be given to patients who potentially have combined focal and diffuse lung disease. This also provides the opportunity to screen individuals at high risk for lung cancer or mesothelioma due to smoking or asbestos-exposure while evaluating potential asbestosis.

The International Commission of Radiological Protection has suggested the principle of ALARA (as low as reasonably achievable). This concept has become more relevant with the growing use of CT for diagnostic, interventional and screening purposes (Zhu, Yu, & Huang, 2004). The low-dose CT has been primarily used for lung cancer screening studies and in pediatric patients because of the potential risk associated with repeated annual screening (Roberts, Patsios, Paul, McGregor, Weisbrod, Chung, Herman, Boerner, Waddell, Keshavjee, Darling, Pereira, Kale, Bayanati, Sitartchouk, Tsao, & Shepard, 2007; Zhu et al., 2004). Radiation dose is proportional to the tube current at a fixed voltage, scanning time, and slice width therefore lowering tube current or X-ray flux can lower radiation dose received by patients. A milliamper-second (mAs) corresponds to the rate at which electrons leave the cathode in the X-ray tube and is directly proportional to the radiation dose. Therefore a reduced mAs is a practical means

of lowering radiation dosage. There has been investigation of optimal low-dose imaging protocols which results in a minimal reduction in image quality. A study by Zhu et al. attempted to minimize patient exposure to ionizing radiation from MDCT scans while maintaining sufficient image quality to detect pulmonary diseases (Zhu et al., 2004). A low-dose (40 or 25 mAs) MDCT produced satisfactory image quality while maximally protecting patients from radiation exposure.

The combination of MDCT and low-dose techniques stimulated interest in using CT as a first-line imaging modality for the diagnosis of asbestos-related disease. A study comparing the use of low dose multidetector helical CT with contiguous 5-mm reconstructions as opposed to thin interspaced sections for the detection of asbestos-related pleura-parenchymal disease found no apparent loss of diagnostic accuracy (Remy-Jardin, Sobaszek, Duhamel, Mastora, Zanetti, & Remy, 2004). The study included eighty-three male workers with a mean duration of occupational exposure to asbestos of eighteen years who underwent CT as part of a medicolegal investigation. Interpretations of the low-dose and thin-section CT images were interpreted several weeks apart by two radiologists simultaneously. Two main groups of abnormalities were assessed: (a) pleural abnormalities including pleural plaques and diffuse pleural thickening, and (b) CT features of asbestosis which included four major abnormalities, thickened interstitial short lines, curvilinear subpleural lines, ground glass opacities, and honeycombing. The only significant difference observed was the depiction of fissural pleural plaques, which were seen more frequently in low-dose CT images. There was no significant difference in the depiction of CT features compatible with the presence of lung parenchymal asbestosis (Remy-Jardin et al., 2004).

2.11 Radiological-Functional Correlation

The traditional radiological evaluation in asbestos-exposed individuals has historically been chest radiography and various studies have correlated radiographic features with physiological indices such as exercise data and pulmonary function tests, with conflicting results (Becklake, Fournier-Massey, & McDonald, 1970; Lee, Singh, & Pang, 2003; Miller, Lilis, & Godbold, 1992; Wang, Yano, Wang, Wang & Christiani, 2006; Ohar, Sterling, Bleecker, & Donohue, 2004; Kilburn & Warshaw, 1994). Although abnormal pulmonary function induced by exposure to asbestos is thought to be characterized by a restrictive pattern, and reduced lung volumes and gas transfer, it has remained a controversial issue whether asbestos exposure is also associated with substantial airway obstruction. Several studies have suggested an association between asbestos and airway obstruction (Begin, Cantin, Berthiaume, Boileau, Peloquin, & Masse, 1983; Kilburn & Warshaw, 1994; Ohar et al., 2004) while others did not (Alfonso et al., 2004; Wang et al., 2006). This discrepancy between studies may be due to variations in occupational conditions, exposure intensity, smoking habits or other differences in the selected study subjects. Another reason for the inconsistency between studies may be due to different analytic methods.

Ohar et al. attempted to assess patterns of asbestos-induced lung disease from the Selikoff Registry. A total of 3383 asbestos-exposed workers were referred for independent medical evaluation and received a chest radiograph, pulmonary function test, and an extensive questionnaire. Entry criteria for a medical evaluation included documented workplace asbestos exposure, a latency of greater than ten years since exposure, and an abnormal chest radiography pattern consistent with asbestos exposure. In a regression model, latency corrected for age, percentage of predicted FEV1 and

smoking history in pack-years predicted ILO score, but not FEV1/FVC or percentage of predicted FVC. When patients were classified according to disease state, restrictive pulmonary function was found mainly in subjects with mesothelioma, and an obstructive pattern was the major finding in subjects with bronchogenic cancer and subjects with both high and low ILO scores. In this study the mean latency of subjects was 41.4 (SD=10.1) years, the mean age was 65.1 (SD=9.9) years, and the frequency of current smokers was 19%. The conclusion that asbestos-induced lung disease is characterized by normal or obstructive pulmonary function abnormalities was based on descriptive statistics, as regression results were not done, and therefore may not be appropriate (Ohar et al., 2004).

Several studies have also shown that asbestos is not involved in the development of obstructive lung disease. Alfonso et al. conducted a prospective cohort of former workers of Western Australia, a unique well documented cohort which has been almost exclusively exposed to documented levels of crocidolite asbestos (Alfonso et al., 2004). Cumulative exposure was determined by the product of estimated or measured fiber concentration and the length of time at the job, for each job. Each subject had a plain chest radiograph classified according to ILO criteria at study entry and at least one spirometric test. The data was modeled by general linear mixed effects model. To assess the effects of asbestos exposure and tobacco smoking on the levels and rates of decline of lung function, the dependent variables (FEV1, FVC and FEV1/FVC) were regressed on time controlled for sex, age and height. The study found that higher cumulative exposure to asbestos or subjects with radiographic asbestosis had significantly lower levels of FEV1 and FVC. FEV1/FVC was not associated with asbestosis. These findings suggest

asbestosis is associated with restrictive respiratory defect, not obstructive. The study also found no significant interaction of smoking status on the relationship between asbestos exposure and lung function. Wang et al. conducted a cross-sectional study involving 468 chrysotile asbestos workers in Chongqing, China, and 282 electronic equipment manufacturing workers as a control group. Occupational history ascertained from face-to-face interview and factory records determined cumulative exposure year as a surrogate of personal exposure level since data on individual exposure levels was not available. Posteroanterior chest radiograph was used to diagnose asbestosis. Multivariate regression analysis indicated that exposure to asbestos was significantly associated with decreased FVC and DLCO. Radiographic asbestosis was strongly associated with a decreased FVC, and elevated FEV1/FVC. There were no significant interactions observed (Wang et al., 2006).

The aforementioned studies among others used chest radiography to ascertain morphological changes due to asbestos exposure. However, chest radiography has been shown to be an insensitive means of correlating morphology with pulmonary function in other causes of diffuse interstitial lung disease (Carrington, 1976; Gaensler, Carrington, & Coutu, 1972). According to the American Thoracic Society CT-scan is now without contest the reference tool for diagnosis of asbestos-related diseases as this technique is both more sensitive and specific than radiographic systems based on the ILO classification system (American Thoracic Society, 2004). An international consensus conference has recommended the use of CT-scan in exposed populations for clinical individual evaluation or research purposes with respect to pleura plaques and asbestosis (Consensus Report, 1997).

In addition, individuals with asbestosis may have other co-existing histopathological processes also contributing to functional deficits, such as emphysema, small airways disease or diffuse pleural thickening. Cigarette smoking is common among workers exposed to asbestos, and emphysema frequently complicates the interpretation of physiologic impairment in patients with asbestosis (Copley et al., 2007). It has been suggested that concurrent emphysema with interstitial lung disease may be impossible to properly detect radiographically, therefore it is a major confounder of previous pulmonary function indices, with a paradoxical preservation of lung volumes and disproportionate reduction in DLCO (Wells, King, & Rubens, 1997). Also, additional conditions may be distributed separately from the predominantly lower zone interstitial fibrosis, such as upper zone centrilobular emphysema. Therefore CT may give a more detailed description of the relative proportions of morphologic changes in the lungs and pleura such as interstitial fibrosis, emphysema, and diffuse pleural thickening. In asbestos-exposed individuals, the definition of the functional consequences of asbestos, as opposed to those caused by smoking, has significant medicolegal implications because emphysema is not generally compensatable (Copley et al., 2007).

Accordingly it became of interest to know whether this higher sensitivity of thin-section CT, as compared to conventional radiography, would translate into an enhanced prediction of physiologic parameters. Several studies have correlated physiological indices with CT morphology in asbestos-exposed individuals (Aberle, Gamsu, & Ray, 1988; Staples, Gamsu, & Ray, 1988; Neri et al., 1996; Sette et al., 2004). The first group to correlate thin-section CT morphology with lung function in asbestos-exposed individuals was Aberle et al. in 1988. They found significant inverse correlations between

probability scores for asbestosis and percent predicted FVC and single-breath diffusing capacity (Aberle et al., 1988). The probability scores were derived from the combinations of thin-section CT features such as parenchymal bands, interstitial thickening and honeycombing. The study did have several limitations in that no attempt to correlate CT-found pleural disease with pulmonary function. No attempt was made to identify the presence of emphysema.

Staples et al. attempted to correlate HRCT findings with lung function in their study of asbestos workers with normal chest radiograph. When comparing asbestos-exposed workers with a normal or near-normal HRCT to workers with abnormal and suggestive for asbestosis HRCT the groups did not differ significantly in their duration of asbestos exposure, latency, smoking history, or measures of airflow obstruction (FEV1%, FEV1/FVC). The subjects with parenchymal abnormalities did show significantly different values of FVC% (-7.2) and DLCO% (-8.9) in comparison to subjects with apparently normal parenchyma suggesting reduced lung function indicative of restrictive lung disease. This work investigated the prevalence of lesions related to asbestos-exposure in persons already affected with clinical symptoms or for whom a suspicion of asbestosis had already been formulated (Staples et al., 1988). Neri et al. evaluated the presence of asbestos-related pleural and parenchymal abnormalities in asymptomatic workers with normal chest radiographs and their correlation with pulmonary function and smoking habits (Neri et al., 1996). Asbestos-exposed asymptomatic workers received a HRCT scan, CO-diffusing capacity, pulmonary function tests and face-to-face interviews to determine occupational, smoking and health history. There was no non-asbestos exposed control group. The study found that early parenchymal abnormalities found by

HRCT were correlated with function impairment. HRCT parenchymal abnormalities were associated with decreased FVC in nonsmoking asbestos workers, and with a reduction in obstructive indices among smoking colleagues, without any clinical evidence of disease (Neri et al., 1996). The interaction between packs/years smoked and duration of asbestos exposure was not significant. This study also failed to account for co-existing conditions, particularly emphysema.

Sette et al. (2004) explored the relationship between thin-section CT interstitial abnormalities and indices of pulmonary gas exchange impairment at rest and during moderate exercise in workers exposed to asbestos, using a scoring system based on a combination of semi-quantitative and severity score and a qualitative score based on individual CT features (Sette et al., 2004). Using this system to classify CT findings, CT was found to be useful in assessing the likelihood of gas exchange impairment at rest and during exercise. Specifically, the results of the logistic regression analysis, which was used to consider all abnormalities, including pleural plaques, indicated that only parenchymal bands and subpleural nodules were significantly associated with impairment in gas exchange. However, once again the effects of coexisting diffuse pleural thickening and emphysema were not evaluated. Also notable is that there was no association between CT abnormalities and any clinical variables including smoking history, years of asbestos exposure or individual spirometric values such as FEV1 or FVC (Sette et al., 2004).

Most recently, Copley et al. (2007) retrospectively correlated the extent of individual disease seen at thin-section CT with pulmonary function in a group of patients with asbestos-related parenchymal disease (asbestosis) (Copley et al., 2007). The results

demonstrated that CT substantially increased the precision with which the results of pulmonary function tests can be interpreted in patients exposed to asbestos. By using multiple regression analysis, Copley et al. identified a combination of CT features most closely linked to individual pulmonary function indexes. Thus, for a given reduction in TLC or DLCO, the proportion of pulmonary deficit that can be ascribed to fibrosis, diffuse pleural thickening and emphysema could be preliminarily estimated. The derived multiple regression analyses were validated by their accurate prediction of pulmonary function indexes in a subsequent study group.

2.12 Research Questions

The previous literature review suggests several study questions. We evaluated the following questions in a cohort of asbestos-exposed workers from the Sarnia, Ontario, Canada:

- 1) What is the prevalence of pulmonary fibrosis in a well described asbestos-exposed cohort of workers in Sarnia, Ontario, Canada as determined by low-dose computed tomography?
- 2) To develop a predictive model which assesses multiple predictors of pulmonary fibrosis found by low-dose CT, specifically past asbestos exposure, pulmonary function indices (FVC, FEV1, FEV1/FVC, TLC, and DLCO) and smoking.
- 3) Based on this model, is there an interaction between asbestos exposure and smoking that affects risk of pulmonary fibrosis?

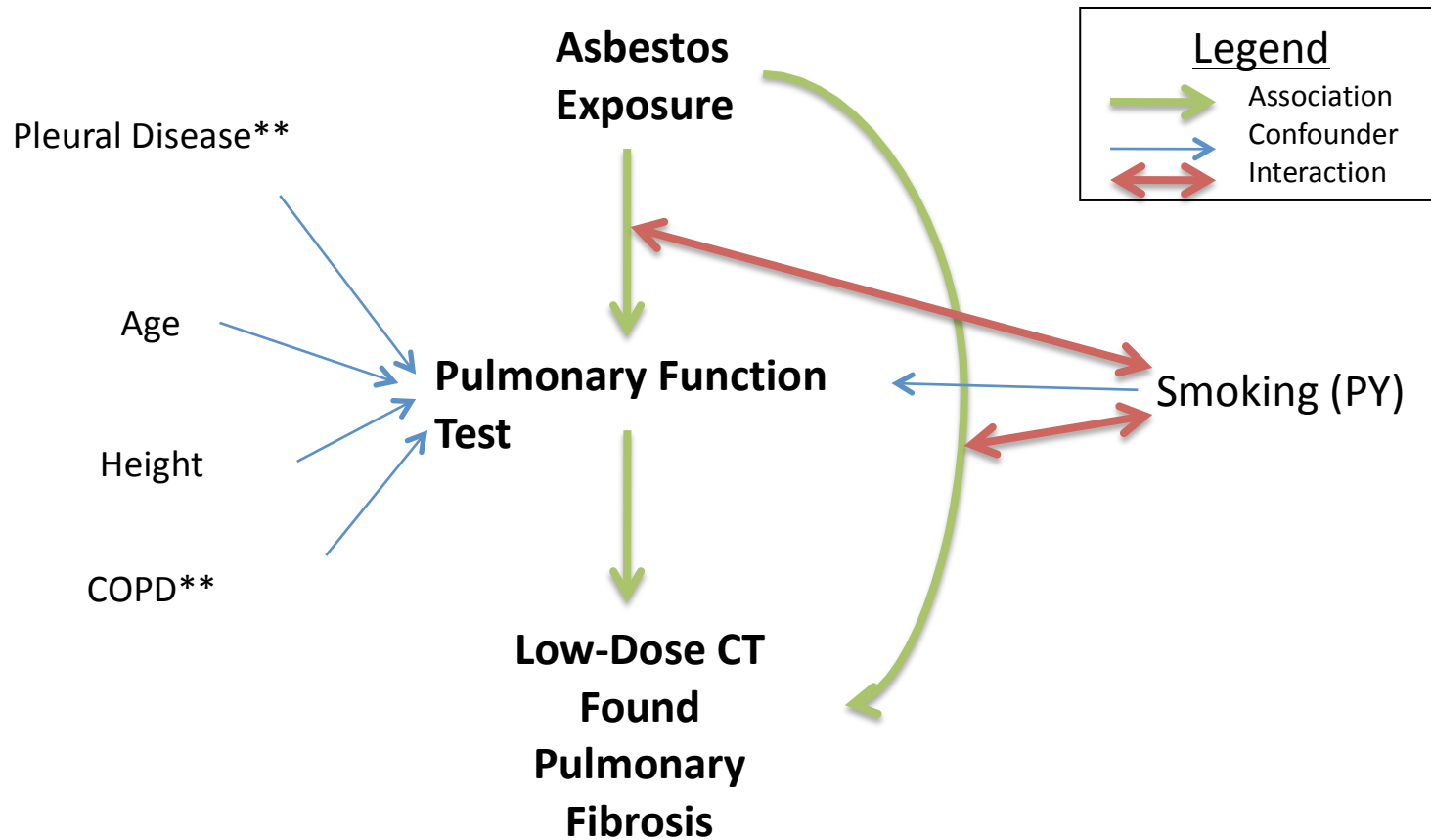


Figure 6: Graph of Planned Associations to be Addressed Displaying Potential Predictors of Pulmonary Fibrosis Found by Low-Dose CT of Interest to Hypothesis Testing and Model Adjustment

*COPD= Chronic Obstructive Pulmonary Disease

** Found by low dose computed tomography at baseline scan

CHAPTER III- METHODS

3.1 Introduction

This chapter describes the study design and methods. The methods of patient recruitment and consent, data collection, imaging techniques, and specific measurements are outlined. The chapter concludes with a description of the analytic strategies that will be used within the study to address the specific research questions presented in the previous chapter 2.

3.2 Study Design and Context

The current project is an ancillary study attached to a longitudinal occupational cohort that is being conducted at Princess Margaret Hospital. The study is led by researchers at the Toronto University Health Network, and the Occupational Health Clinic for Ontario Workers (OHCOW) in Sarnia-Lambton, Ontario. The cohort is the *Early Diagnosis of Mesothelioma and Lung Cancer in Prior Asbestos Workers*. The original study was designed to evaluate lung cancer and mesothelioma at an early stage by screening high-risk individuals, defined by their prior occupational asbestos exposure and/or presence of pleural plaques, with low-dose computed tomography.

3.3 Patient Recruitment

Patient accrual began in March, 2005 and is still in progress. For the purpose of this study, data collected between March, 2005 and November, 2008 are used. The majority of patients have been referred to the study from the Sarnia-Lambton, OHCOW. Sarnia-Lambton is situated along the St. Clair River and contains a large petrochemical complex, which produces approximately 40% of Canada's chemicals, using companies such as Imperial, Dow, Bayer, Shell and Suncor (Brophy et al., 2007). The majority of

the chemical industries in Sarnia-Lambton have a history of extensive asbestos use. Consequently, many workers in Sarnia-Lambton are at elevated-risk for developing asbestos-related diseases.

3.4 Eligibility Criteria

To be eligible for entrance into the original study subjects were required to meet the following criteria:

- 1) ≥ 30 years of age
- 2) Asbestos exposure at least 20 years ago and/or documented pleural plaques
- 3) Presumable good health
- 4) Have no prior cancer (with the exception of non-melanotic skin cancer)

3.5 Measurements

3.5.1 Consent and Data Collection

Eligible individuals were asked to read a consent form and sign it. Once consent was obtained individuals were administered a questionnaire in a face-to-face interview with the clinical research coordinator or clinical research assistant. Appended is a copy of the consent form and questionnaire. The questionnaire includes questions regarding patient address, contact information, date of birth, date of entry to study, occupational history, medical history and smoking habits.

3.5.2 Occupational History

The baseline questionnaire included detailed questions regarding occupational history. Questions included:

- *Name of employer*

- *Occupation (construction, ship construction, mining, building maintenance, demolition, repair, chemical industry, other)*
- *Start and end year of exposure (and corresponding age)*
- *How often was the exposure? (everyday, once a month, once a week, other)*
- *Did you work directly with asbestos? (If yes, describe your activities i.e. spraying, applying, cutting, removing)*
- *Which type of asbestos were you in contact with? (serpentine/ chrysotile/white, amphiboles/brown/off-white, crocidolite/blue, unknown)*
- *Did you wear any personal protective equipment?*
- *Did you work in areas where other workers were generating asbestos dust? (indirect exposure)*

3.5.3 Smoking History Assessment and Other Measurements

Smoking history was obtained from the face-to-face questionnaire. Information on smoking status (never smoker, former smoker, current smoker), type of tobacco used/smoked (cigarettes, marijuana, cigars, pipes, smokeless tobacco), age when smoking cigarettes began, packs of cigarettes smoked per day (for current and former smokers) and how many years did you smoke this amount of packs per day, were obtained.

Other data collected were sex, race, height (self-reported), weight (self-reported), has a health professional ever told that he/she had any of these medical conditions (asthma, asbestosis, pleural plaques, emphysema, chronic bronchitis, hypertension, heart attack, stroke, heart failure, liver disease, renal disease, connective tissue disease, other), respiratory symptoms in the past year, family history (lung disease, asbestosis, mesothelioma), and general health.

3.6 Low-Dose Computed Tomography and Follow-up

The baseline CT scan consists of a low-dose, thin-slice acquisition, which is performed on one of the several scanners within the Department of Medical Imaging at University Health Network, acquired from various manufacturers (General Electric Medical System, Toshiba Medical Systems, and Siemens Medical Solutions) and having different numbers of channels (4 to 64) all using a low-dose regimen (40 to 60 mA, 120 kV, 1 to 1.25-mm axial reconstructions).

All participants were given a low-dose CT (LDCT) examination of the entire thorax. The results from the CT scan were summarized into a *Research CT Evaluation Report* (Appendix C) by the study radiologists. The report includes descriptions of nodules, plaques, asbestos-related findings and other chest abnormalities. The Research CT Evaluation Report was abstracted for information regarding date of scan, presence of chronic obstructive pulmonary disorder (emphysema, chronic bronchitis, and bronchiectasis), atelectasis (non-obstructive, round) and fibrosis of the lung parenchyma. All of the above abnormalities were coded as 0=not present, 1=mild, 2=moderate, 3=severe, and 8=present with severity not marked. As noted previously, there have been attempts to describe several specific CT parenchymal abnormalities of asbestosis including (i) subpleural dependent opacity, (ii) subpleural curvilinear opacities, (iii) subpleural perpendicular lines (septal lines), (iv) parenchymal bands, (v) small irregular parenchymal opacities, and (vi) honeycombing (Huuskonen et al., 2001). These CT scan found abnormalities had a ROC-AUC of 0.89 and performed better in classification of pulmonary fibrosis than ILO radiographic classification (ROC-AUC=0.76). However, the primary goal of the *Early Diagnosis of Mesothelioma and Lung Cancer in Prior Asbestos Workers* was not for classification of pulmonary fibrosis, therefore an in-depth

classification was not performed. Pulmonary fibrosis will be examined dichotomously, present or absent as noted by the study radiologist. The study radiologist took into consideration to following CT features when classifying a person as having pulmonary fibrosis: subpleural curvilinear lines, interlobular septa thickening, intra-(core lines), subpleural ground glass opacity, honeycombing, and parenchyma bands.

Structural findings from the baseline low-dose CT scan determines the time of follow-up CT scan. Figure 7 graphically depicts the follow-up algorithm. All participants received an annual follow-up scan. Other possible follow-up dates are 3 or 6 month as well as 3 month post-annual, and biennial.

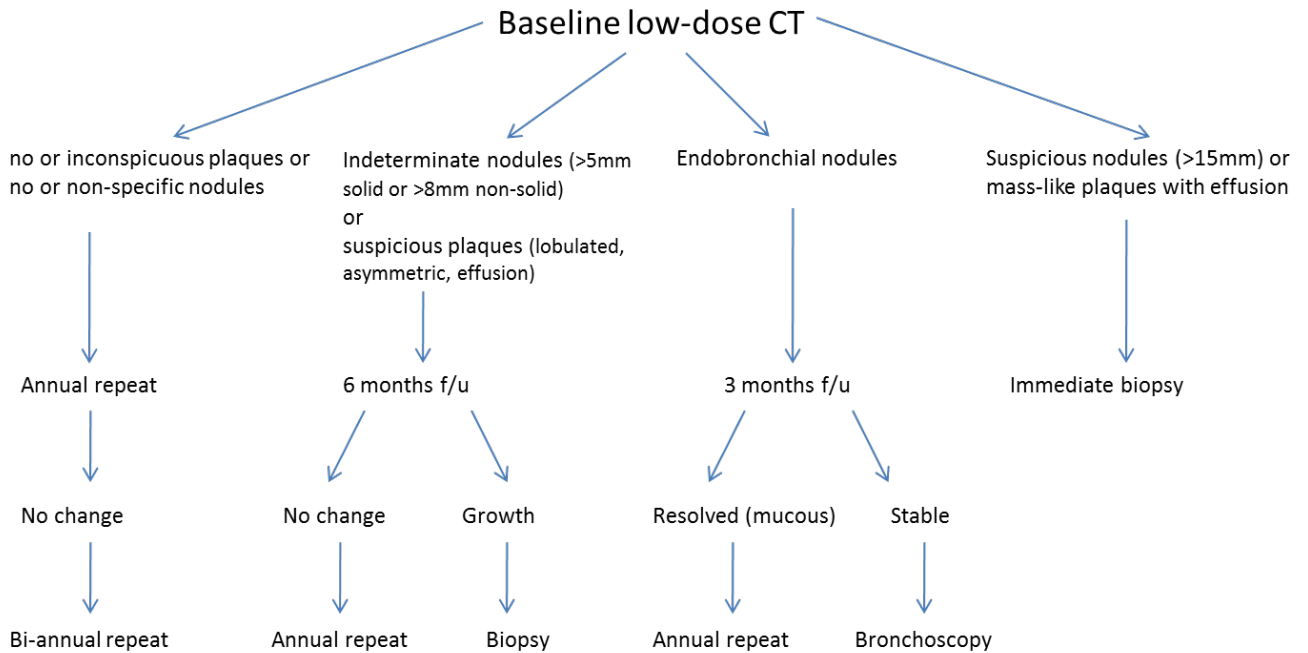


Figure 7: Low-dose Computed Tomography Follow-Up Scheme

3.7 Pulmonary Function Tests

The hardcopy medical records of subjects were abstracted at Toronto General Hospital to obtain all pulmonary function tests which had been performed. Variables abstracted include date of PFT, spirometry measures (FVC, FEV1, and FEV1/FVC), measurements of lung volume (TLC) and diffusion capacity for carbon monoxide (DLCO, DLCO/VA). These functional variables are expressed as absolute liters (L) and as a percentage of the predicted value (%) according to a course of reference values based on healthy volunteer data and which are matched to the patient's age, height, sex, and race. The timing of PFTs in relation to date of the LDCT varied for subjects, but in the current dataset only PFTs that preceded the LDCT were included.

Table 3: Pulmonary Function Test Variables in Relation to Different Types of Lung Impairment

Variable	Pre or Post Bronchodilator	Unit	Lung Impairment Measure and Important Notes
Forced Vital Capacity (FVC)	Pre and post	Absolute Liters (L) and percentage of predicted (%)	Decreased in restrictive lung impairment
Forced Expiratory Volume in First Second of Expiration (FEV1)	Pre and post	Absolute Liters (L) and percentage of predicted (%)	Decreased in obstructive lung impairment <70-80% predicted
FEV1/FVC	Pre and post	Direct ratio of patient's values (%)	1) < 70% characteristic of obstruction 2) > 70% characteristic of restriction
Total Lung Capacity (TLC)	N/A	Absolute Liters (L) and percent of predicted (%)	Restrictive lung impairment defined as TLC < 80% predicted
Diffusion capacity/ Carbon Monoxide Diffusion	N/A	Percent predicted (%)	1) Decreased in obstruction with alveolar destruction 2) Decreased in intrinsic restrictive lung impairment

3.8 General Analytic Strategy

Statistical analyses were performed using STATA® software (STATA11; STATAcorp, College Park, TX, USA). Excel files were converted to STATA files using STAT/TRANSFER (Circle Systems; Seattle, WA, USA). Standard data cleaning procedures were undertaken.

To explore bivariate associations between continuous variables (i.e. cumulative asbestos exposure and FEV1) prior to multivariate regression analysis, the STATA command lowess was used to graphically assess the linearity of variables. Lowess carries out a locally weighted regression, which draws a smooth (but not necessarily straight) line. The STATA command mkspline created variables containing a restricted cubic splines of any non-linear continuous variables with five knots. The use of restricted cubic splines provides a powerful and more biologically plausible method for identifying nonlinear relationships.

Considering the primary purpose of this study was the prediction of pulmonary fibrosis, to eliminate predictor variables we used a $P < 0.20$. R statistical program was used to create calibration plots to evaluate calibration of the prediction models.

3.9 Addressing Specific Study Questions

Study Aim 1: What is the prevalence of pulmonary fibrosis in a well described asbestos-exposed occupational cohort as determined by low-dose computed tomography?

The number of cases of disease (pulmonary fibrosis) in the defined population during the given time will determine the prevalence.

Study Aim 2: To assess multiple predictors of pulmonary fibrosis found by low-dose CT, specifically past asbestos exposure, pulmonary function indices (FVC, FEV1, FEV1/FVC, TLC, and DLCO), and smoking.

Logistic regression odds ratios (ORs) and 95% confidence intervals were used to evaluate associations between predictors and the dichotomous outcome pulmonary fibrosis. Modeling was determined by *a priori* reasoning to determine which factors predicted CT-detected fibrosis. Exposure to asbestos (age at first exposure, cumulative exposure), parameters of lung function (post FEV1, FVC, FEV1/FVC, TLC, DLCO), and smoking (ever versus never) will be predictor variables. All continuous variables (PFT variables) were kept in this format (not categorized). Only PFT's that were performed prior to the CT-scan were used in the analysis. To assess the contribution of predictors, especially pulmonary function test variables, to the model, the likelihood ratio statistic assessing the difference in likelihoods from the nested model was used.

The model's ability to discriminate was assessed using the concordance or c-statistic and/or its equivalent, the receiver operator characteristic area under the curve (ROC AUC). Model calibration (does the predicted probability match the observed probability) was assessed by evaluating how much the slope of the calibration line

(plotting the predicted probability versus the observed probability) deviated from the ideal of 1. The mean absolute error and 90th percentile absolute error in calibration were used to appraise calibration. The Hosmer-Lemeshow goodness-of-fit test was also used to assess calibration of the model. To assess the fit of the model a significant Hosmer-Lemeshow goodness-of-fit test indicates lack of fit.

Logistic Post-Estimation Diagnostics

Overall model performance was evaluated with the R^2 statistic.

Study Aim 3: Is there an interaction between asbestos exposure and smoking that affects risk of pulmonary fibrosis?

To assess the question of whether there is an interaction between asbestos exposure and smoking that affects pulmonary function in exposed workers, several steps were completed. In order to test for interactions, new variables were created by multiplying variables of interest together to create interaction terms (Smoking Ever versus Never*Asbestos Exposure Duration Dichotomous). Asbestos exposure was dichotomized at greater than 29 years of exposure.

Next, the term was entered in to the multivariable models along with the main effects terms used to create the new term to examine level of significant. The likelihood ratio test was examined to indicate a significant multiplicative interaction.

Final Predictive Model

After analyzing Aims 2 and 3, a final predictive model will be developed. To determine which variables were retained in the final predictive model (and whether the smoking*asbestos interaction should be included), we kept all variables which had a p

value for the likelihood ratio test of <0.20 . This was done to create a more clinically usable model.

CHAPTER IV- RESULTS

4.1 Outline of Results

The results below will follow a specific sequence: 1) baseline characteristics, 2) lowess curves and restricted cubic splines for assessing non-linearity of predictor variables (mainly PFTS), 3) univariate models investigating splines, 4) full predictive model using logistic regression and all *a priori* explanatory variables, 5) model including an interaction term between smoking and asbestos exposure, which will be evaluated using the likelihood ratio test, and 6) the final model excluding all variables with a $p > 0.20$.

4.2 Study Population and Prevalence of Pulmonary Fibrosis (Aim 1)

The following tables show the important baseline characteristics (Table 4). The mean age for the total population was 61.17 (SD=9.46) years of age. Age was significantly different between those with and without fibrosis. Participants with fibrosis were on average 65.14 (SD=8.99) years of age, while those without fibrosis had a mean age of 60.64 (SD=9.41) ($p=0.0003$). There was no significant difference in exposure to asbestos parameters between those with pulmonary fibrosis and those without. There was a higher frequency of current smokers in those with pulmonary fibrosis. Pack-years was not different between the two groups. The prevalence of pulmonary fibrosis was found to be 10.7% 95%CI (8.12—12.24).

Table 4: Baseline Characteristics of Asbestos Exposed Cohort Stratified by Presence/Absence of Low-Dose Computed Tomography Found Pulmonary Fibrosis (N = 613)

	Total Population	Pulmonary Fibrosis	No Pulmonary Fibrosis	p Value
Mean age, years	61.12	65.14	60.64	<0.001
Sex, (%)				
Male	594 (97.38)	65 (100.00)	529 (97.06)	0.399
Female	16 (2.62)	0 (0.00)	16 (2.94)	
BMI, kg/m ²	28.51	29.04	28.44	0.337
Smoking (%)				
Never	151 (24.59)	12 (18.46)	137 (25.14)	0.047
Former	116 (18.89)	7 (10.77)	108 (19.82)	
Current	347 (56.51)	46 (70.77)	300 (55.05)	
Mean Pack-years smoking	17.70	20.21	17.40	0.283
Asbestos Parameters				
Mean age at first exposure, y	21.69	21.76	21.79	0.928
Mean duration of exposure, y	25.91	26.76	25.81	0.620
Time since first exposure, y	42.21	43.80	42.02	0.905
COPD*† (%)	87 (14.26)	16 (24.62)	71 (13.03)	0.020
Pleural Plaques† (%)	285 (46.72)	37 (56.92)	248 (45.50)	0.090
Pulmonary fibrosis %	N/A	65 (10.66)95%CI(8.12- 12.24)	545 (89.34)	N/A
<u>Sarnia Cohort n= 320</u>				
Post FVC (mean % predicted)	103.49	97.82	104.35	0.024
Post FEV1/FVC (mean)	74.35	75.66	74.16	0.353
TLC (mean)	99.66	93.69	100.50	0.009
DLCO (mean)	89.61	84.70	90.32	0.110
DLCO/ VA (mean)	100.34	97.67	100.73	0.414
*COPD= chronic obstructive pulmonary disorder				
†Low-dose computed tomography found (LDCT) pulmonary fibrosis, pleural disease and COPD at baseline				
‡P-values were computed for age, body mass index, pack-years, asbestos latency, FEV1(L), FVC(L), TLC(L), DLCO, and DLCO/VA using the <i>t</i> test; for dichotomous variables; male, female, LDCT found pulmonary fibrosis, COPD, pleural plaques the Fisher exact test was used				

4.3 Assessing Linearity of Continuous Variables using Lowess

The lowess technique draws a smooth line representing the average value of the variable on the y-axis as a function of the variable on the x-axis. In the case of binary outcome (presence/absence of LDCT found pulmonary fibrosis), these average the outcome proportions over groups whose size was specified by the bandwidth of the selected smoothing method. Lowess curves were generated for all predictor continuous variables (i.e., age, height, FEV1, FVC, FEV1/FVC, DLCO, and TLC etc.). See Appendix D for all lowess curve. Below are the lowess curves for FVC and FEV1 both showing a non-linear relationship with probability of LDCT found pulmonary fibrosis. Restricted cubic splines with five knots were created for all variables which were visibly non-linear when examining the lowess curves. These variables were: FVC, FEV1, FEV1/FVC, TLC, and DLCO. All variables were percent predicted and post-bronchodilator due to higher accuracy, since pre-bronchodilator lowess curves appeared visually similar and when put into a preliminary model, no absolute measure significantly predicted pulmonary fibrosis. The lowess curve for post-FVC (Figure 8) shows a downward relationship with fibrosis to approximately 110% and then an upward relationship to 160%. The lowess curve for post-FEV1 (Figure 9) is flat, then goes downward to approximately 110% and then upward to 150%.

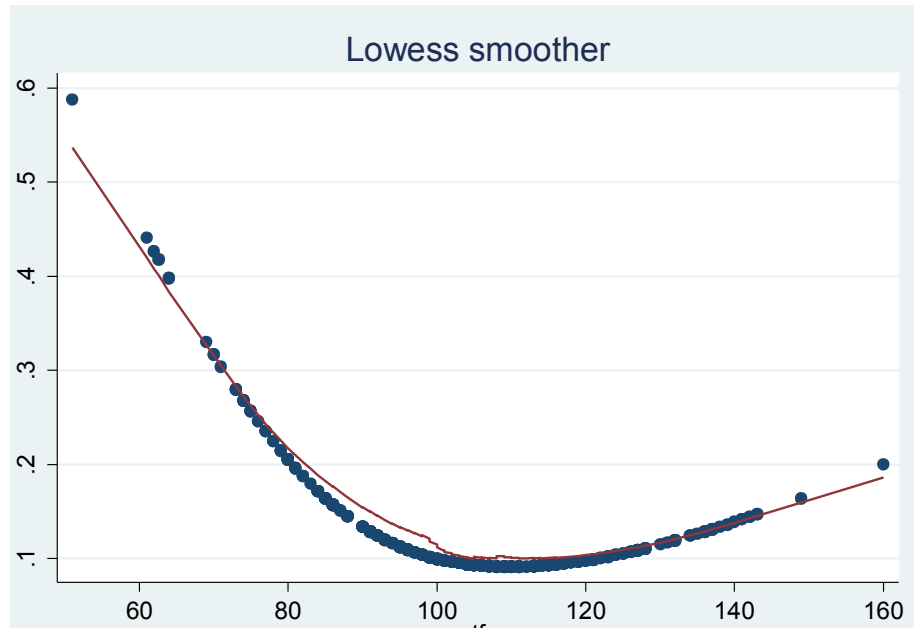


Figure 8: Lowess Curve for FVC and Probability of LDCT Found Pulmonary Fibrosis. X-axis is the Post-Bronchodilator Forced Vital Capacity (FVC). Y-axis is the Probability of Fibrosis.

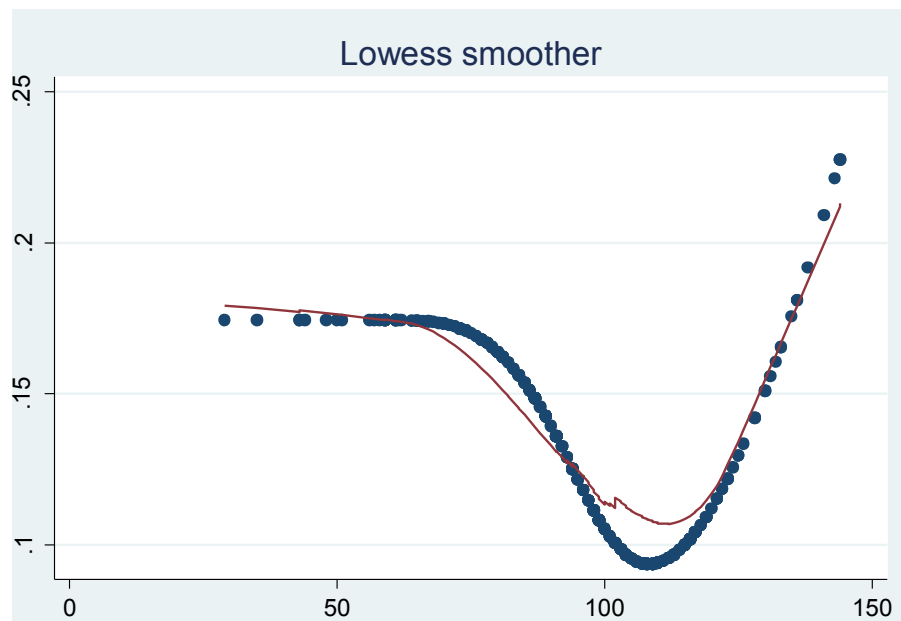


Figure 9: Lowess Curve for FEV1 and Probability of LDCT Found Pulmonary Fibrosis. X-axis is the Post-Bronchodilator Forced Expiratory Volume (FEV1). Y-axis is the Probability of Fibrosis.

4.4 Predictive Models for Pulmonary Fibrosis (Aim 2)

Presented in Table 5 are the univariate models investigating splines of pre- and post-bronchodilator PFT variables including FVC, FEV1, FEV1/FVC, TLC and DLCO. Both pre- and post-bronchodilator FVC and FEV1 reached statistical significance based on p-values and 95%CI (the post FEV1 had a trend towards significance). The proper evaluation of splines should be as a group using the likelihood ratio test.

4.4.1 Full Predictive Model for Pulmonary Fibrosis

The full predictive model using logistic regression including all *a priori* variables based on well-established predictors from the literature is shown in Table 6. Table 6 also contains the likelihood ratio tests for each variable listed, assessing the variables contribution to the model. Age contributed to the model with a LRT of 0.1218. Both the post-FVC and post-FEV1 splines were included in the predictive model with LRT's of 0.0012 and 0.0240. Dichotomous (ever versus never) smoker variable had an effect estimate of 2.62 and contributed to the model with a LRT of 0.0538. Though age at first asbestos exposure, dyspnea and pleural plaques did not reach a p value of < 0.20 they were retained in the model due to *a priori* reasoning based on past literature and expert opinion. The ROC AUC, which indicates an overall measure of classification accuracy, of the predictive model was 0.7493. The goodness of fit test yielded a value of 0.2461, indicating a fit for the model. Calibration and the calibration plot was accomplished using 200 repetition bootstrapping. The slope of the apparent calibration line deviates from 1 by 0.3319.

Additional analyses that included the main clinical and radiologic variables described in Table 4 (e.g., BMI, radiologic evidence of COPD or plaques) found that none of these contributed to the predictive model (LRT $p > 0.20$ for each variable).

The predictive model was stratified by smoking status (Appendix F). Due to small numbers of smokers ($n=65$), confidence intervals were extremely wide and not included in the body of the results.

Table 5: Univariate Models of Pulmonary Function Test Splines- Pre and Post Bronchodilator Predicting LDCT-Found Pulmonary Fibrosis.

Restricted Cubic Splines	OR (95%CI)	p-value
Pre-FVC%1	0.94 (0.90-0.99)	0.03
Pre-FVC%2	1.05 (0.88-1.25)	0.55
Pre-FVC%3	0.98 (0.48-1.96)	0.96
Post-FVC%1	0.94 (0.89-0.99)	0.03
Post-FVC%2	1.07 (0.90-1.28)	0.43
Post-FVC%3	0.89 (0.41-1.94)	0.77
Pre-FEV1%1	0.95 (0.92-0.99)	0.03
Pre-FEV1%2	1.05 (0.95-1.17)	0.28
Pre-FEV1%3	0.84 (0.46-1.57)	0.60
Post-FEV1%1	0.96 (0.92-1.00)	0.09
Post-FEV1%2	1.03 (0.92-1.15)	0.59
Post-FEV1%3	0.99 (0.52-1.91)	0.99
Pre-FEV1_FVC1	0.94 (0.89-1.00)	0.07
Pre-FEV1_FVC2	1.12 (0.98-1.29)	0.09
Pre-FEV1_FVC3	0.43 (0.12-1.57)	0.20
Post-FEV1_FVC1	0.97 (0.91-1.03)	0.32
Post-FEV1_FVC2	1.05 (0.91-1.21)	0.53
Post-FEV1_FVC3	1.16 (0.31-4.32)	0.83
TLC1	0.96 (0.91-1.02)	0.25
TLC2	1.02 (0.86-1.19)	0.83
TLC3	0.95 (0.36-2.47)	0.91
DLCO1	0.97 (0.93-1.02)	0.25
DLCO2	1.03 (0.86-1.22)	0.74
DLCO3	0.95 (0.47-1.88)	0.88

Table 6: Full Logistic Regression Model Predicting LDCT Found Pulmonary Fibrosis in a Cohort of Asbestos Workers (n=320)

	Odds Ratio (95%CI)	P Value	Likelihood Ratio Test P Value
VARIABLES			
Age (per 10 years)	1.03 (0.99-1.07)	0.124	0.122
Age at first asbestos exposure (years)	0.98 (0.93-1.03)	0.382	0.369
Dyspnea	1.59 (0.74-3.36)	0.214	0.218
Smoking (Ever vs. Never)	2.62 (0.91-7.54)	0.074	0.054
Post FVC Splines (%)	0.93 (0.86-0.99)	0.049	0.001
	1.25 (0.75-2.08)	0.396	
	0.09 (0.00-2.11)	0.136	
	132 (0.93-1887)	0.053	
Post FEV1 Splines (%)	1.01 (0.94-1.07)	0.839	0.024
	0.92 (0.69-1.24)	0.604	
	8.49 (0.62-115)	0.109	
	0.01 (0.00-0.87)	0.044	
Pleural Plaques	1.58 (0.74-3.36)	0.324	0.225
MODEL PERFORMANCE			
R-square Stata	0.133		
Hosmer Lemeshow goodness-of-fit	p=0.246		
C-statistic	0.749		
Calibration			
Calibration slope	0.668		
Mean absolute error	0.022		
90 th percentile absolute error	0.046		
*Variables were included into the predictive logistic model by <i>a priori</i> reasoning based on literature review and expert opinion (pulmonologist)			
† Dichotomized smoking variable as Ever versus Never smoker			

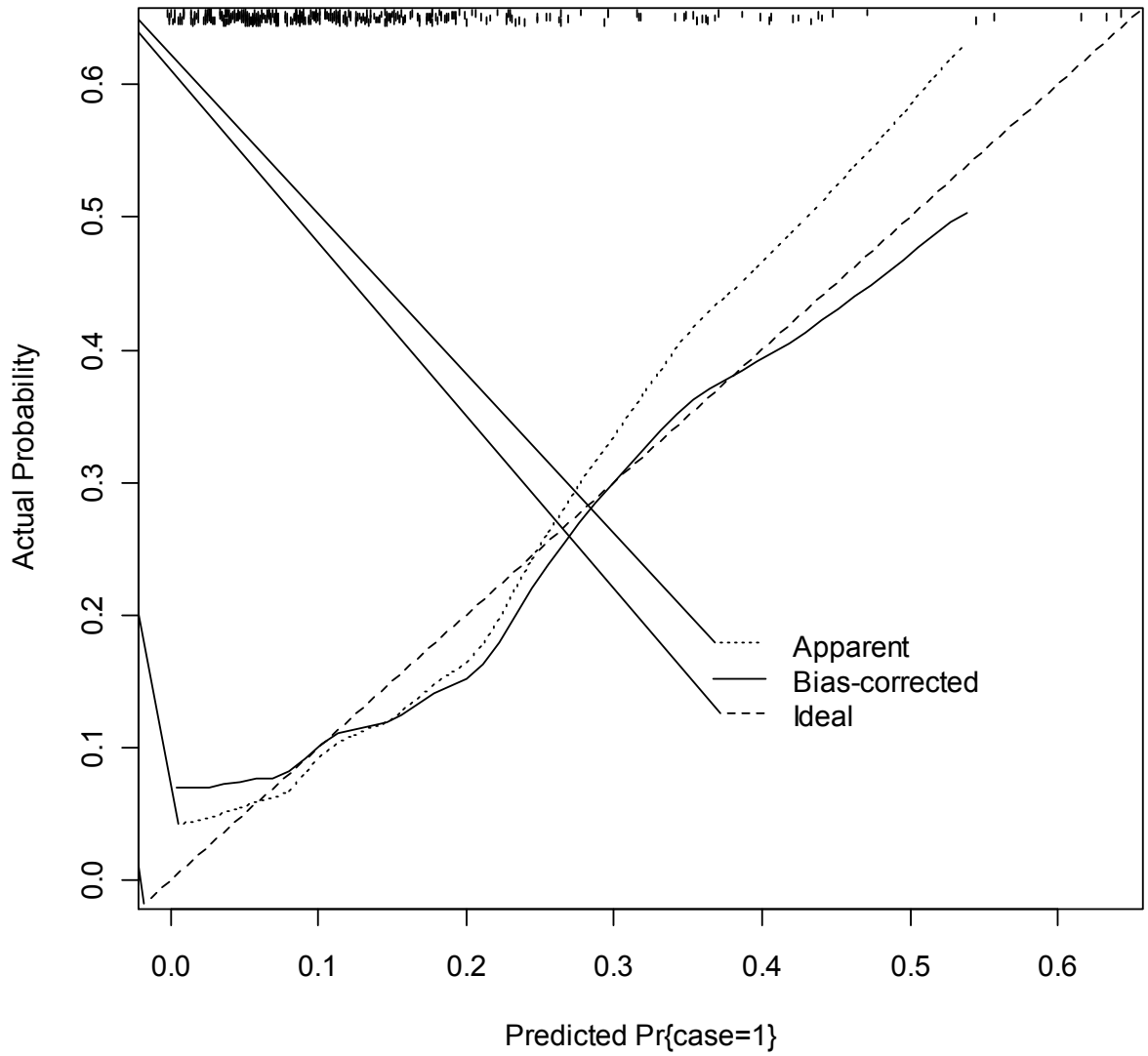


Figure 10: Calibration Plot of Actual Versus Predicted Pulmonary Fibrosis in Full Predictive Model. Calibration Used 200 Boot-Strap Repetitions on 329 Participants to Generate Curves. The Mean Absolute Error was 0.022.

4.4.2 Predictive Model Including Smoking*Asbestos Interaction (Aim 3)

Table 7 presents the predictive model including the main effect terms of smoking dichotomized (ever versus never), asbestos exposure duration dichotomized and the interaction term between these two variables. The likelihood ratio test shows that the interaction does not independently predict pulmonary fibrosis with a value of 0.225. Though the C-statistic does increase to 0.760 when comparing the models with and without the interaction term using roccomp, there is not a significant difference ($p=0.212$). Roccomp is a test of equality for ROC areas.

Table 7: Logistic Regression Model Predicting LDCT Found Pulmonary Fibrosis in a Cohort of Asbestos Workers (n=329) - Investigating Smoke-Asbestos Interaction

	Odds Ratio (95%CI)	P Value	Likelihood Ratio Test P Value
VARIABLES			
Age (per 10 years)	1.03 (0.99-1.08)	0.111	
Age at first asbestos exposure (years)	0.97 (0.92-1.03)	0.340	
Dyspnea	1.60 (0.77-3.31)	0.210	
Post FVC Splines (%)	0.92 (0.85-0.99)	0.044	
	1.25 (0.74-2.10)	0.402	
	0.09 (0.00-2.30)	0.149	
	116.14 (0.78-17360.45)	0.063	
Post FEV1 Splines (%)	1.01 (0.95-1.07)	0.838	
	0.93 (0.69-1.25)	0.629	
	7.78 (0.57-106.44)	0.124	
	0.00 (0.00-1.06)	0.053	
Pleural Plaques	1.67 (0.77-3.58)	0.189	
Smoke Dichotomous	6.43 (0.79-52.51)	0.083	
Asbestos Duration Dichotomous	2.82 (0.28-28.80)	0.381	
Smoke*Asbestos Interaction	0.25 (0.02-2.80)	0.260	0.225
MODEL PERFORMANCE			
R-square Stata	0.140		
Hosmer Lemeshow goodness-of-fit	p=0.142		
C-statistic	0.760		
*Variables were included into the predictive logistic model by <i>a priori</i> reasoning based on literature review and expert opinion (pulmonologist) with backward selection			

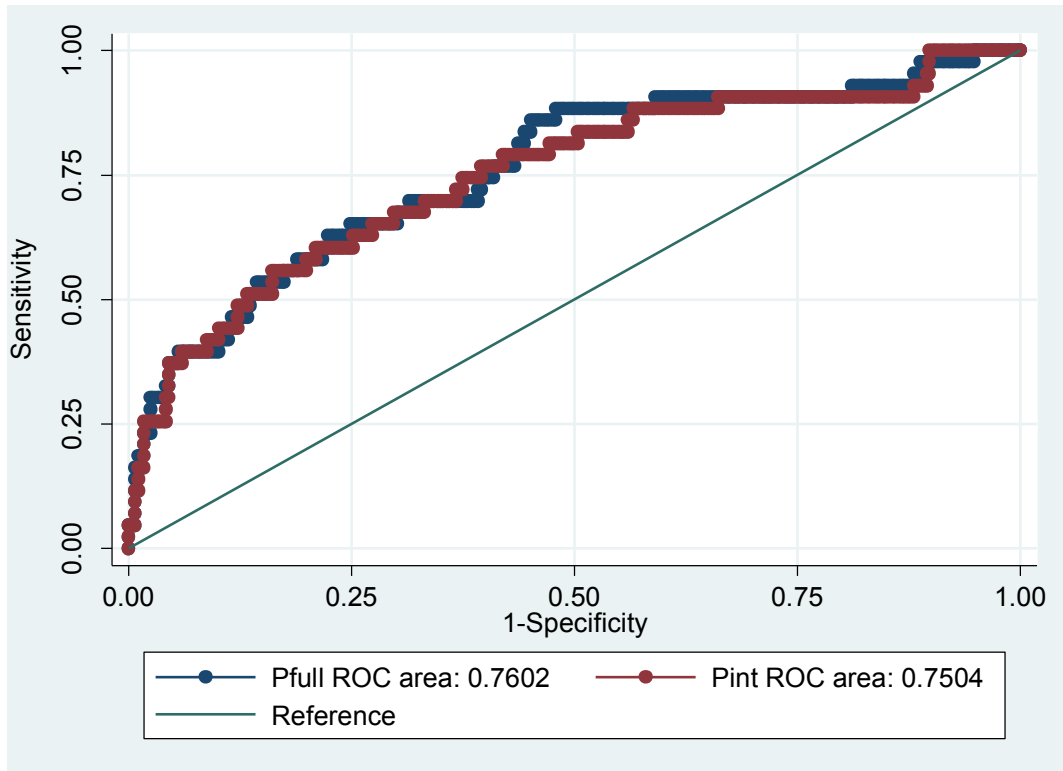


Figure 11: Comparison of ROC curves for LDCT Found Pulmonary Fibrosis- Full Predictive Model with *Smoke_Abestos* Interaction versus Without Interaction. (p=0.212)

4.4.3 Development of a Final Predictive Model: Comparing Predictive Models With and Without Variables with $P > 0.20$

Table 8 presents our predictive model excluding variables with a p-value of >0.20 including age at first asbestos exposure, dyspnea and pleural plaques. Without these variables the R-square decreases from 0.133 to 0.118, the C-statistic decreases from 0.749 to 0.738 (Figure 12) and the measures of calibration, including mean absolute error (0.022 to 0.023) and 90th percentile absolute error (0.046 to 0.054) become less significant shown in Figure 13. However, the fit of the model increases from 0.246 to 0.428 when excluding these variables.

Table 8: Logistic Regression Model Predicting LDCT Found Pulmonary Fibrosis in a Cohort of Asbestos Workers Excluding Variables with $P > 0.20$ (n=320)

	Odds Ratio (95%CI)	P Value
VARIABLES		
Age (per 10 years)	1.03 (0.99-1.07)	0.111
Smoking Dichotomized	2.91 (1.02-8.24)	0.045
Post FVC Splines (%)	0.92 (0.86-1.00)	0.054
	1.25 (0.75-2.08)	0.389
	0.09 (0.00-2.03)	0.131
	133.64 (0.98-18209)	0.051
Post FEV1 Splines (%)	1.01 (0.95-1.07)	0.693
	0.91 (0.68-1.21)	0.502
	9.54 (0.72-127)	0.088
	0.01 (0.00-0.72)	0.037
MODEL PERFORMANCE		
R-square Stata	0.118	
Hosmer Lemeshow goodness-of-fit	p=0.428	
C-statistic	0.738	
Roccomp test	p=0.430	
Calibration		
Calibration slope	0.692	
Mean absolute error	0.023	
90 th percentile absolute error	0.054	

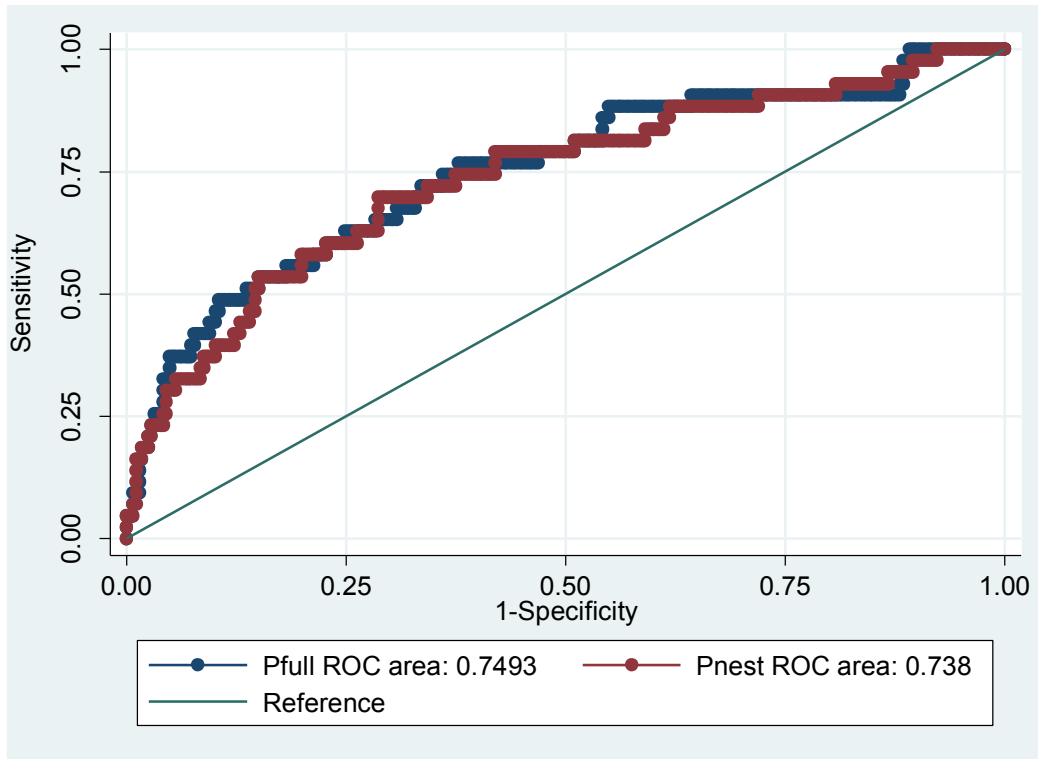


Figure 12: Comparison of ROC curves for LDCT Found Pulmonary Fibrosis- Full Predictive Model versus Model Excluding with Variables $p > 0.2$ ($p=0.430$)

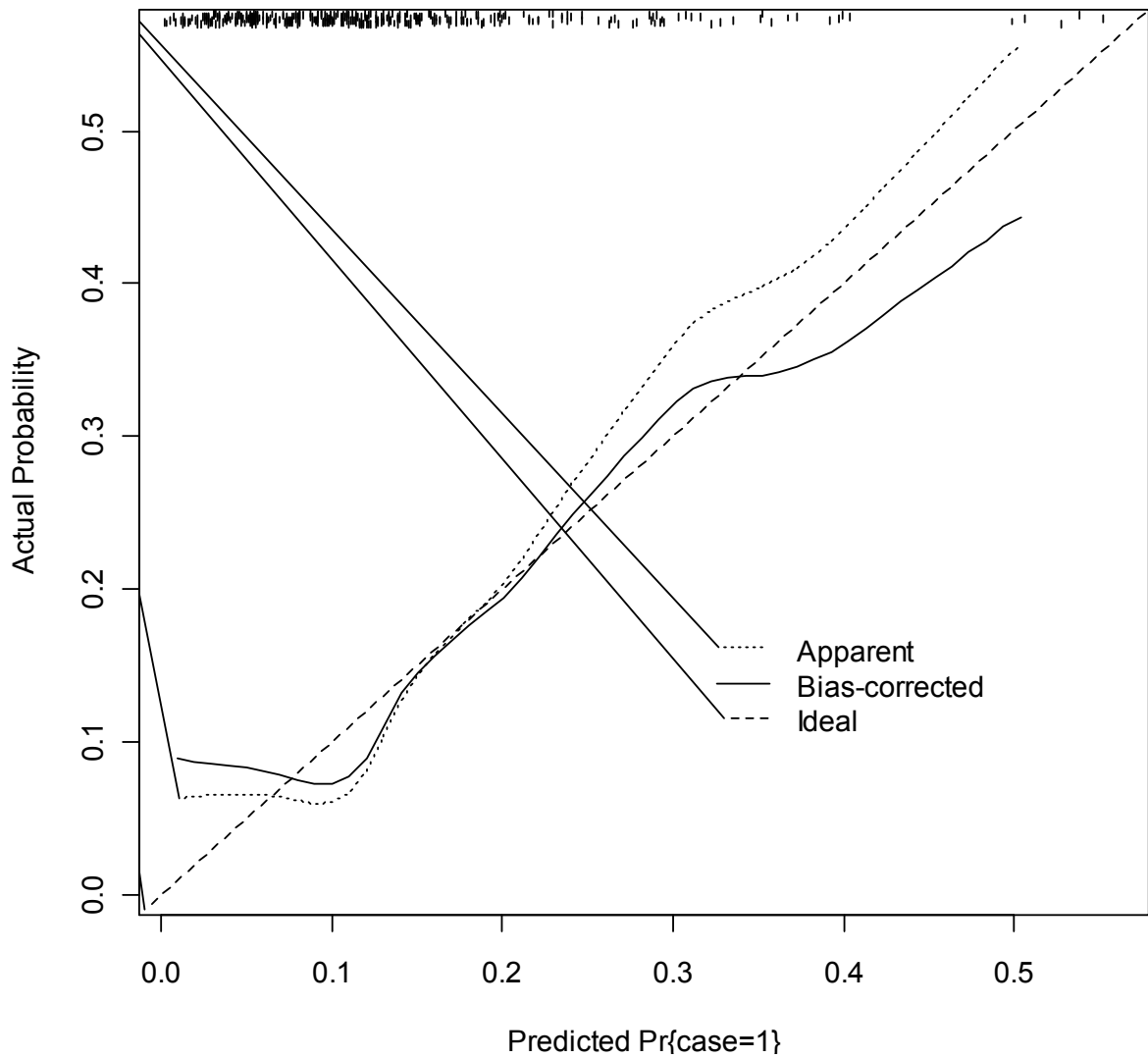


Figure 13: Calibration Plot of Actual Versus Predicted Pulmonary Fibrosis in Model Excluding Variables with $p > 0.20$. Calibration Used 200 Boot-Strap Repetitions on 338 participants to Generate Curves. The Mean Absolute Error was 0.023.

CHAPTER V- DISCUSSION & CONCLUSIONS

5.1 Key Findings

Our study found the prevalence of pulmonary fibrosis in this asbestos exposed cohort to be 10.7% (Aim 1). Previous studies investigating the association between exposure to asbestos, smoking, abnormal lung function and pulmonary fibrosis have focused on predicting pulmonary function, or having pulmonary function indices as the dependent outcome variable (Alfonso et al., 2004; Begin et al., 1983; Kilburn & Warshaw, 1994; Ohar et al., 2004; Wang et al., 2006). However, it has been reported that pulmonary dysfunction precedes chest x-ray and CT findings of pneumoconiosis, suggesting the importance of pulmonary function tests in screening for early disease and prediction of subsequent disease, such as pulmonary fibrosis, in those exposed to asbestos (Tonori et al., 2005). To our knowledge the current study is the second (Paris et al., 2008) to predict pulmonary fibrosis in those exposed to asbestos and the first to investigate other predictive variables beyond simply asbestos exposure. Our final predictive model for prediction of LDCT-found pulmonary fibrosis, included the following predictive variables: age, smoking dichotomized, post FVC(%) splines, and post FEV1(%) splines. This model had an ROC-AUC of 0.738 and a calibration slope 0.692. These measures of predictive performance suggest moderately good predictive ability (Aim 2). Our study did not find a significant interaction between smoking, asbestos exposure and pulmonary fibrosis (Aim 3).

The following discussion will first review the main predictors in our final model (A), including current results compared to past literature, starting with a discussion of

asbestos exposure. This will be followed by a discussion of strengths and limitations of the study design and analysis (B). Finally, there will be a discussion of the clinical utility and future directions of this research (C).

5A. PREDICTORS OF FINAL MODEL

5.1.1 Asbestos Exposure

All subjects underwent a face-to-face interview in order to obtain occupational histories. Therefore our measure of asbestos exposure was self-report. Several parameters were calculated including time since first exposure, duration and age at first exposure to asbestos. All asbestos exposure indices were not different when comparing those with and without pulmonary fibrosis diagnosed by LDCT (Table 4) and none significantly predicted pulmonary fibrosis in our model as tested by the likelihood ratio test (Table 6). There are three major considerations for asbestos exposure assessment: 1. exposure intensity (concentration of asbestos fibers), 2. latency period (time since first exposure), and 3. duration of exposure. A recent study by Paris et al. (2008) found that time since first exposure and exposure intensity were predictive of asbestosis and pleural plaques, but not duration of exposure. The authors suggested these two parameters; time since first exposure and dose, must be included in the definition of high risk populations suitable for screening of these diseases (pleural plaques and asbestosis). In our predictive model only age at first exposure to asbestos was included as a predictor of LDCT-found pulmonary fibrosis (OR=0.98, 95%CI: 0.93-1.03) (Table 6). The discrepancy between the current study and Paris et al. may be due to different analytic techniques or error in the measurement of asbestos exposure. The current study ascertained asbestos exposure

through a self-reported face-to-face questionnaire, which was not previously validated and administered by a research coordinator. Also, our assessment of asbestos exposure lacked systematic measurements of dust or fiber concentrations. We used exposure duration, latency and age since first exposure as surrogates of personal exposure, which might have led to exposure misclassification. Also, since all participants were found to have some exposure, differences or dose-responses were difficult to investigate. In the study by Paris et al. more precise assessments of asbestos exposure were obtained by occupational hygiene measurements and a job-exposure matrix. A quantitative assessment of occupational exposure was obtained using a specific job-exposure matrix elaborated from actual airborne measurements collected in the plant. However, a study by Wang et al. (2006) used a more crude estimate of asbestos exposure obtained from a face-to-face interview and still found that exposure to asbestos (yes versus no) and cumulative exposure years, without any measurement of fiber concentrations, was associated with reduced FVC, FEV1 and DLCO in cross-sectional study of factory workers. However, we did not evaluate PFT variables as an outcome. Similar results were found from a cohort study conducted in Western Australia with regard to the relationship among asbestos exposure and changes in lung function in which asbestos fiber concentration was estimated from the results of a survey carried out at worksites in 1966 where particle counts were performed (Alfonso et al., 2004).

5.1.2 Pulmonary Function

Currently, PFTs are a widely accepted tool in the medical surveillance of those exposed to asbestos, both for worker's compensation and monitoring of disease

progression. Moreover, PFT's can play a role in early detection, diagnosis and prevention of disease (Wang et al., 2006). Our study found that FEV1 and FVC restricted cubic splines significantly predicted LDCT found pulmonary fibrosis. Our findings were similar to Wang et al. 2006, in which workers with asbestosis had the lowest FVC followed by asbestos workers without asbestosis. Decreased FVC would be the optimal index to reflect the severity of parenchymal abnormalities. DLCO was simultaneously lower in asbestos workers, regardless of chest x-ray found asbestosis (Wang et al., 2006). The authors suggest this indicates that reduced diffusing capacity may be a sensitive index to reflect the earliest physiological changes due to asbestos exposure. Diffusing capacity is a measure of the ability of the lung to transfer gas. Diffusion of the lungs is most efficient when the surface area for gas exchange is high and the blood is readily able to accept the gas being exchanged. DLCO is decreased when: 1) conditions that minimize the ability of blood to accept and bind to the gas that is diffusing (anemia), 2) conditions that decrease the surface area of the alveolar-capillary membrane (emphysema, pulmonary embolism), and 3) conditions that alter the membrane or increase its thickness (pulmonary fibrosis). Wang et al., 2006 hypothesized that it was likely that DLCO changes would correlate well with high resolution CT scanning changes and pathologic findings at early stages. Our study is the first to correlate LDCT with PFT measures and did not find that reduced diffusing capacity predicted LDCT pulmonary fibrosis (Table 6).

5.1.3 Smoking-Asbestos Interaction

Previous studies generally agree that asbestos exposure is associated with restrictive lung impairment along with reduced diffusing capacity. It is well established

that obstructive lung impairment is also associated with asbestos exposure, cigarette smoke, or if there is an interaction between asbestos and smoking. Some of the controversy may be due to variations of occupational conditions, type of asbestos exposure, differing analytic strategies, difference in intensity of exposure, severity of pathological changes, and age. Previous reports have suggested that cigarette smoking enhances the development of interstitial fibrosis in workers exposed to asbestos. No interaction or joint effects were observed between asbestos exposure and smoking in our study. Results from a previous studies suggests that smoking and asbestos exposure act independently (additively) rather than synergistically (multiplicative) on the level and rate of decline in lung function in the cohort (Alfonso et al., 2004; Wang et al., 2006).

5B. STRENGTHS AND LIMITATIONS

5.2 Strengths

5.2.1 Study Design

This study has several strengths. The current study yielded similar results to those of Alfonso et al., 2004, a cohort conducted in Western Australia with subjects solely exposed to crocidolite asbestos, with regard to the relationships among asbestos exposure, smoking and the changes in lung function. It is interesting to note that although subjects were sampled based on exposure (not outcome status) this study is technically a cohort. However, no new cases of pulmonary fibrosis were found beyond the initial LDCT scan after four years of follow-up, therefore the study is cross-sectional in nature and thus does not allow us to determine a clear exposure-response relationship. This also

means there is no true ‘time-to-event’. A longer follow-up period, such as ten years, may yield new cases of pulmonary fibrosis. The study by Wang et al., 2006, was a cross-sectional design and they acknowledged that they were inherently limited to determining clear causal effects of exposure to asbestos and smoking. Yet, similar results such as those from the Western Australian cohort and the present cohort were also found.

5.2.2 Variables

This study made the best use of the continuous predictor PFT variables, by keeping them continuous and not categorizing them. Categorizing would have led to serious statistical inference problems including bias, and loss of power. Merely excluding subjects with incomplete data from analysis is a mistake. The amount of missing data at baseline should be carefully documented, including the proportion of missing values for each variable being analyzed and a description of the types of subjects which have missing variables. In the current study, 41.4 % of subjects were missing a pulmonary function test. This was dealt with by only including those from the Sarnia cohort, which had complete pulmonary function test information. There was no missing data for the main outcome variable of LDCT-pulmonary fibrosis because every subject had at least the baseline scan where they were categorized as 1= pulmonary fibrosis, 0=no pulmonary fibrosis or 8=bilateral apical fibrosis. Category 8 was not included as a case of pulmonary fibrosis. Isolated bilateral fibrosis is not typically associated with asbestosis. Apical fibrosis would only be seen in asbestosis if there was extensive fibrotic disease throughout the lung.

5.2.3 Low-Dose Computed Tomography

Another major strength of this study was how the outcome was ascertained by LDCT. There have been many previous radiological-functional correlation studies in asbestos exposed populations either with chest x-ray (Alfonso et al., 2004; Ohar et al., 2004; Wang et al., 2006) or computed tomography (Aberle, Gamsu, & Ray, 1988; Staples, Gamsu, & Ray, 1988; Neri et al., 1996; Sette et al., 2004). However, this is the first study correlating pulmonary function indices with LDCT found pulmonary fibrosis. Though high resolution computed tomography does have increased sensitivity and specificity in comparison to chest x-ray, its use for screening and diagnosis is questionable owing to the increased radiation burden and high economic cost (Xaubet et al., 1998). Therefore using LDCT is attractive due to the reduced radiation burden in those already at high risk for many conditions.

5.3 Limitations

5.3.1 Asbestos Measurement

This study is also vulnerable to non-differential misclassification bias (biasing the risk estimates toward the null). Non-differential misclassification bias occurs when the degree of misclassification of exposure is independent of case-control status (fibrosis vs. no fibrosis), or vice-versa (Szklo & Nieto, 2006).

The manner in which asbestos exposure was measured, by self-report is a limitation. The superior method of asbestos exposure ascertainment would be the use of systematic measurements of dust or fiber concentrations along with the aid of an industrial hygienist (Teschke et al., 2002). Wang et al., 2006 used exposure duration as a

surrogate of personal exposure, which also may have lead to exposure misclassification. In a study of former crocidolite workers in Western Australia, job histories were obtained from employment records. Fiber concentration for all job categories was estimated from results of a survey of airborne respiratory fibers crocidolite in 1966. Each subject's cumulative exposure was calculated by adding over all their different jobs the product of estimated or measured fiber concentration and the length of time in that job (Alfonso et al., 2004).

In our study questionnaires were used to ask about subject's occupational history, use of specific agents, trade name products or specific type of asbestos in a face-to-face interview. Though studies that assess exposure with direct questions to participants, such as "Were you ever exposed to asbestos?", are prone to incorrect measurement and may be vulnerable to widely varied interpretations among participants of what constitutes exposure, but data derived in this crude fashion can still yield useful information. A study comparing next-of-kin assessment, expert assessment and the use of a job exposure matrix found that disease-exposure odds ratios based on next-kin respondents are inflated by recall-bias, whereas those from the job exposure matrix are attenuated. Also job exposure matrix exposure categorization based on next-of-kin data predicted asbestos levels that matched expert assessment better than only the JEM (Nam, 2005). Therefore among the asbestos exposure assessment methods in use today, expert assessment is the best approach, however it can also have low validity and reliability if there is not proper training of the expert, and if not enough information is provided in the detailed occupational history of subjects. All exposure assessment methods, whether by experts or self-report have limitations and can have low validity and reliability.

5.3.2 Classification of Pulmonary Fibrosis

Classification of pulmonary fibrosis (dichotomous present/not present) may be inappropriate. Despite an absence of an internationally accepted classification tool for pulmonary fibrosis as determined by CT, Huuskonen et al. recorded several specific HR-CT parenchymal abnormalities and found good inter- and intraobserver agreement. The parenchymal abnormalities were: (i) subpleural dependent opacity, (ii) subpleural curvilinear opacities, (iii) subpleural perpendicular lines (septal lines), (iv) parenchymal bands, (v) small irregular parenchymal opacities, and (vi) honeycombing. The severity of each abnormality was recorded from mild to profuse. Receiver-operating characteristic (ROC) curve area under the curve was significantly greater for HR-CT fibrosis score (0.89) than for the ILO radiographic classification (0.76) ($P < 0.0001$) (Huuskonen et al., 2005). It has been suggested that this type of semi-quantitative HRCT scoring system could be of use when an international HR-CT classification is designed for occupational lung disease (American Thoracic Society, 2004). It would be interesting to apply the criteria of Huuskonen to our dataset in the future however the crude dichotomous classification was sufficient for the purpose of this study. Note that screening for mesothelioma was the primary aim of this cohort; therefore detailed fibrosis data was simply not available.

5.4 Unanswered questions

5.4.1 Descriptive Statistics of Asbestos-Related Diseases

There is a clear lack of descriptive statistics regarding asbestos related disease in Ontario, including mesothelioma and asbestosis. This study describes the prevalence of pulmonary fibrosis in a well described asbestos-exposed cohort of workers in Ontario as determined by LDCT, to be 10.7%.

5.4.2 Classification of Pulmonary Fibrosis by CT

As previously noted, there have been attempts to describe several specific CT parenchymal abnormalities of asbestosis including: (i) subpleural dependent opacity, (ii) subpleural curvilinear opacities, (iii) subpleural perpendicular lines (septal lines), (iv) parenchymal bands, (v) small irregular parenchymal opacities, and (vi) honeycombing (45). Proper quantification of pulmonary fibrosis (not a simple present/absent) based on Huuskonen et al. is necessary. Copley et al. used multivariate regression and found a combination of CT features most closely linked to individual pulmonary function indices has been identified and tested in separate groups. Thus, for a given reduction in TLC or DLCO, the proportion of the deficit ascribable to fibrosis, diffuse pleural thickening and emphysema can be preliminarily quantified (Copley et al., 2001). Validating this approach to CT-found pulmonary fibrosis quantification could be accomplished using the current dataset.

5.4.3 Investigating Age, Birth and Cohort Effects

Age is a strong risk factor for many health outcomes and frequently associated with various risk factors. Therefore even if investigating the effect of age on an outcome is not the primary study aim, it is important to assess its relationship with outcomes and

exposures (given the potential confounding effect) (Szklo & Nieto, 2006). *Age effect* occurs when there is a change in the rate of a condition according to age, irrespective of birth cohort and calendar time. For many diseases, exposures have a cumulative effect that is expressed over long periods of time. Long latency periods and cumulative effects characterize, for example, numerous exposure/disease associations, such as smoking/lung cancer, radiation/thyroid cancer, and in our case asbestosis or mesothelioma/asbestos (Szklo & Nieto, 2006). *Cohort effect* is a change in the rate of a condition according to the year of birth. In addition to age and cohort effects, *period effect* occurs when there is a change in the rate of a condition affecting an entire population at some point in time (e.g. date of asbestos ban in Canada, Hiroshima, war, new treatment etc.). The term “period effect” is frequently used to describe a global shift or change in trend that affects the rates across birth cohort and age groups (Szklo & Nieto, 2006). With true longitudinal follow-up, it would be interesting to use our data to estimate the parameters of a birth-cohort and age effect to determine patterns of mesothelioma and asbestosis in the Sarnia-Lambton, Ontario population. Unfortunately we do not have the data to do this.

5C. CLINICAL UTILITY AND FUTURE DIRECTIONS

5.5 Association versus Prediction Studies

Most previous studies have focused on associations between various clinical and radiological parameters and pulmonary fibrosis. One exception to this is a study by Paris et al., 2008, however this study only examined various parameters of asbestos exposure, and ignored other key clinical variable. No one has previously looked at PFTs in a

predictive model. Therefore, the current analysis is unique because it is a predictive model of pulmonary fibrosis which looks at PFT variable and multiple other clinical variables. It should also be made clear that variables which are associated may not be useful as a predictor. One clear example in the current study is of chronic obstructive pulmonary disease. Although COPD is univariately significantly associated with pulmonary fibrosis (Table 4), COPD did not contribute in the predictive model.

5.6 Clinical Utility of the Final Predictive Model

There are several potential uses of this predictive model. First this model could be used for risk stratification to determine which asbestos exposed individuals should undergo CT screening for pulmonary fibrosis. Currently there are no guidelines as to who should actually go for CT screening. If all asbestos exposed individuals were to have CT scans it would be expensive and people might be receiving radiation which is not necessary. Further, the original Princess Margaret Hospital screening program has not provided much evidence to support screening of everyone with asbestos exposure (i.e., though a number of cases

of lung cancer and mesothelioma were diagnosed during the course of screening, the majority of cases were identified in between screening scans). Therefore, it is unlikely we would ever utilize CT screening for everyone so if we want to identify fibrosis we could use this prediction model to identify who are the highest risk individuals. In these people CT screening may be feasible. Currently, most research has been focused on using biomarkers to identify individuals with mesothelioma (e.g. soluble mesothelin related peptide) (Pass et al., 2008). In the future there may be potential biomarkers for

pulmonary fibrosis (particularly biomarkers within the inflammatory pathway). Developing a baseline predictive model would be highly useful when determining whether the addition of a biomarker would improve the model (e.g. tested by the likelihood ratio test). There are also several ways in which clinical implementation could happen with a predictive model. One is plugging values into software of the model or to develop a visual nomogram which then deliver the risk of having pulmonary fibrosis by a specific individual. The level of risk would help guide clinicians to proceed with additional testing (or not). Having identified the prevalence in this study this can be used as a baseline value to input into the nomogram. A second method would be to develop an actual scoring system based on the predictive model which is simplified for clinicians to use, however this may prove difficult with the inclusion of restricted cubic spline for pulmonary function test variables. However, it is important to note that though the present model did have moderately good predictive ability, it is not ready for clinical implementation.

5.7 Future Directions

There are several things that should be done before this predictive model could be ready for clinical implementation. First the model should be validated in a larger and independent set of participants. As stated before, it would be interesting to use this model as a baseline to test the benefit of various potential biomarkers. And lastly it would be useful to get a better definition of pulmonary fibrosis (possibly multiple levels of severity) for a better predictive model.

5.8 Conclusion

This study has several important contributions. The description of the prevalence of pulmonary fibrosis in this cohort in Ontario is new data. The need for descriptive statistics for asbestos-exposed workers in Ontario is very important. Also this is only the second study to create a predictive model for pulmonary fibrosis in asbestos-exposed individuals beyond simply asbestos exposure.

This study describes the prevalence of pulmonary fibrosis in a well described asbestos-exposed cohort of workers in Ontario at 10.7%. Because of the clear lack of descriptive statistics regarding asbestos related disease in Ontario, including mesothelioma and asbestosis, this finding is important. Our final predictive model for prediction of LDCT-found pulmonary fibrosis, included the following predictive variables: age, smoking dichotomized, post FVC(%) splines, and post FEV1(%) splines. This model had an ROC-AUC of 0.738 and a calibration slope 0.692. These measures of predictive performance suggest moderately good predictive ability. Our study did not find a significant interaction between smoking, asbestos exposure and pulmonary fibrosis.

Though chest radiography has its advantages (cost and availability), CT is increasingly useful in the context of investigation of asbestos-exposed individuals. The limitations of chest radiography, and its inferiority compared to CT is becoming accepted worldwide. CT plays an important and central role in the clinical and medico-legal assessment of individuals with suspected asbestos-induced parenchymal lung disease. Though radiological evaluations of asbestos-exposed individuals are relatively sensitive and reproducible for these purposes, their frequent use is questionable owing to the radiation burden and their high economic cost. The current study provides the first much needed evaluation of the prediction of low dose computed tomography found pulmonary

fibrosis. The current prediction model could be developed further to improve the predictive ability (through larger, better annotated samples or through the addition of biomarkers) to decipher who is at highest risk for pulmonary fibrosis. These variables can also be used to stratify high-risk populations suitable for screening of pulmonary fibrosis.

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**APPENDIX A- Sample Consent Form for Subjects Involved in the Early
Diagnosis of Mesothelioma and Lung Cancer in Prior Asbestos Workers Study**



University Health Network

Toronto General Hospital | Toronto Western Hospital | Princess Margaret Hospital

CONSENT FORM

**TITLE : Low-dose Computed Tomography for the Early
Diagnosis of Mesothelioma and Lung Cancer in
Prior Asbestos Workers**

**INVESTIGATOR: Dr. Demetris Patsios MD, Telephone Number 416- 586-4200
extension 5598**

You have been asked to take part in a research study. This study is designed to detect mesothelioma and lung cancer in an early stage. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure that all your questions have been answered to your satisfaction before signing this document.

Background and Purpose

Asbestos exposure may result in several different diseases to the lung and to the lining of the lung, the so-called *pleura*. Mostly they are benign, but there are two common malignant diseases in people with prior asbestos exposure, the so-called *mesothelioma* – which originates from the pleura - and cancer of the lung. Symptoms of any of these malignant diseases generally do not appear for 10-35 years after the first asbestos exposure, and include shortness of breath, chronic or new cough, coughing of blood, chest pain or weight loss. Unfortunately, these symptoms are most often caused by very

advanced diseases, when patients can no longer be cured. Currently there is no accepted tool for the early diagnosis of mesothelioma or lung cancer in asbestos-exposed subjects available. Standard of care includes regular chest radiographs, which are not sufficient to show mesothelioma or lung cancer in an early stage.

In the last decade, **computed tomography (CAT-scan, CT)** has been successfully developed for the early detection of lung cancer in smokers, both worldwide and in Toronto, under the leadership of Dr. Roberts. Physicians of the University Health Network hope to prove that using CT will enhance the possibility of early detection of mesothelioma in high-risk people with prior asbestos exposure. We are conducting this study in people who have been exposed to asbestos at least 20 years ago, and/or do have pleural plaques, a population at high risk of mesothelioma and lung cancer. You have been invited to participate in this study because of your asbestos history.

Secondly, there is evidence in other types of cancers such as cancers of the prostate and ovary, that **analysis of blood** may reveal protein markers that indicate the presence of cancer in the body. A companion blood analysis study is being undertaken in an effort to discover such markers for lung cancer and mesothelioma, so that the accuracy of CT-scan diagnosis for lung cancer may be further improved.

Thirdly, **Pulmonary Function Testing (PFT)** has been suggested as useful tools to follow people who have been exposed to asbestos.

PFT's (breathing test) will be combined with CT-scan (blood and sputum) information to study ways to improve our screening process.

Additionally, there is evidence that the **analysis of sputum** using a new test - called LungAlert™, developed by the company International Medical Innovations, Inc. - also can reliably detect lung cancer. This part of the study will examine if this test can distinguish cancer from other lung diseases and from healthy lungs, in a screening population. In a pilot study the LungAlert™ test was able to detect over 80% of lung cancers.

This analysis of your blood and sputum is compared to the results of the CT scan. The purpose of this study is to assess whether the results from the blood or sputum analysis are in agreement with, or complementary to the CT results, and whether they help reducing the false positive results from the screening CT. Long-term goal would be to develop a non-invasive, and inexpensive screening tool which does not require complex technology and special visits to health centres.

Procedures

If you decide to take part in the screening study, you will be asked to answer a questionnaire about your occupational and smoking history, as well as basic demographic information. The completion of the consent and the questionnaire might take 5 – 30 mins, depending on the questions you may have. The sampling of blood and serum will take no longer than 10-15 mins, the same amount of time might be needed for the CT study itself.

The PFT (breathing test) will take approximately 10 minutes.

Including waiting times, you should allocate up to 2 hours in the hospital, however, most likely it will be faster than that. Your participation in the research study begins at the time of your signature.

A screening **CT examination**, also called **CAT scan**, of the lungs will be performed without intravenous contrast. The CT examination as such is not an experimental procedure, CAT scans are performed routinely since decades. However, in your particular case, this albeit standard examination is performed for the purposes of research only, it is not part of standard of care. The screening CT examination of the lungs takes less than 10-20 minutes to perform. You will be asked to remove your upper body garments and wear a gown that would be left on during the procedure. You will not be required to have any injections, take any medications by mouth or apply any to your body.

If **no abnormalities** are found on the initial examinations, you will be examined with one **repeat screening CT of the chest after one year**.

If **pleural plaques** or a **nodule** in the lungs is seen on your baseline CT, this will lead to further testing. Quite likely (approximately 1 in 3 chance), you will be invited for a **follow-up CT 3 or 6 months**. Further investigations will be chosen according to standard of care and will be explained to you at the time. These will be coordinated by your physician with Dr. Marc de Perrot, Department of Thoracic Surgery.

Both at the time of your baseline screening CT and at your annual follow-up screening CT, you will be asked to provide 5 ml (approximately 2 teaspoons full) **blood sample** through a needle stick. A blood-taking technician employed by the University Health Network or a certified nurse will carry out this procedure. Purpose of this study is to search in the blood for so-called “markers”, substances in the blood which indicate that there is a cancer in the lungs or pleura. Most of these markers are still in development, thus your blood will be stored and analyzed at a future date.

You will also be asked to provide a **sputum sample** to the study nurse by coughing up sputum / phlegm into a cup. Most likely you will be able to produce sputum spontaneously. If you cannot voluntarily produce sputum, no further measures are taken. There are no dietary restrictions or other preparations required prior to the test. The sputum sample will then be sent to a laboratory to be tested for the presence of a sugar molecule that is believed to be associated with lung cancer. Purpose of this study is to see whether these sugars can indicate the presence of a cancer in the lungs or pleura.

You will be asked to have a **PFT (breathing test)**. You will take deep breathes and blow into a mouthpiece connected to a machine known as a **spirometer**. The machine measures how forceful and how much air you can blow in each breath.

Spirometry will be conducted using a flow-sensitive spirometer (Presto Flash Portable Spirometer Version 1.2) To estimate lung function, we will use both forced expiratory volume in 1 second (FEV) and forced vital capacity (FVC).

Risks

The risk associated with the screening CT scan is attributable to radiation. The screening study is using CAT scans with recent technology that allows for a significant reduction in radiation dose. This brings the radiation dose from the CAT scan down to a level that is significantly less than standard chest CT and closer to two views of the chest, as you might have for a chest x-ray. For the screening CT, the radiation dose of the CT scan is less than 2 rads. Annual radiation from environment is 100-200 mrad. The radiation dose of the repeat screening CT scan is the same as the first CT scan.

Screening may lead to a cascade of further evaluations and potential complications. Since a CT scan is a more sensitive test for pleura and lung abnormalities, more abnormalities will be detected than on a chest x-ray. Many of these may be benign, that is, not malignant (i.e. not cancer).

Given all the different tests that may have to be performed after your initial screening study, it may take a few months to finally determine whether the plaque or nodule is benign, or whether you really have cancer or mesothelioma. This time period following the initial positive screening result will be full of anxiety, insecurity and fear, which might be difficult to deal with. If you feel anxious at any time during your participation in the study, please contact the study staff or the investigator involved in this study, at any time, to discuss your concerns and feelings.

CT is an unproven technology for screening for mesothelioma and lung cancer. It is therefore possible that you could have a negative CT screening study and still develop mesothelioma or lung cancer and die from it. Furthermore, despite best efforts, small carcinomas may be missed. Finally, given the nature of CT, lung cancer screening with CT targets small cancers in the periphery of the lung, and it is fully expected to miss some centrally located cancers.

A study conducted and published by this group of Cornell investigators has shown that this type of CT scan can diagnose lung cancer much earlier than other methods currently in use. The use of CT in the diagnosis of mesothelioma is new. We cannot promise that you will receive any benefits from this study. Using the CT examination, a more sensitive diagnostic procedure, you may have greater chances of detection of an early abnormality of your lungs, but this cannot be guaranteed, cancers still may be missed. Screening is no substitute for tobacco avoidance, and it is not known whether screening leads to better outcomes.

The risk associated with the blood taking includes discomfort with the needle stick and possible slight bruising at the needle puncture site.

There is no risk associated with the sputum collection or with the PFT (breathing test).

Benefits

You may or may not receive any medical benefit from your participation in this study. Information learned from this study may benefit other patients in the future with your disease.

Confidentiality

Participation in research in general may involve loss of privacy. For study purposes, all data from your exam with your personal identifiers removed is immediately entered into the web-based interactive system.

Any information obtained during this study and identified with you will remain confidential and will be disclosed only with your permission. Information regarding the results of your tests will be sent back to you and your referring physician only. Any further information including previous radiologic or any follow-up studies would be sent to the responsible investigator by your physician (your primary physician, your GP, or a specialist responsible for your treatment) as this information is important for the study evaluation. This includes follow-up diagnostic CTs, biopsy and surgical results/reports and pathologic slides associated with such procedures. This information remains confidential and becomes part of your study file as documentation or follow-up to findings detected on your screening CT(s) scan. With your signature, you give permission to the PI and his staff to have access to your health records.

No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside your primary physician and the study doctor at UHN.

Data acquired during this study will be sent to your referring physician or occupational health clinic, and will also be linked to your permanent medical record at UHN.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care.

If you wish to withdraw, you need to inform both the study doctor at UHN (Dr. Patsios) and your primary/family physician, since both are involved in the data collection.

If you decide to withdraw from the study, regular clinical care will carry on for your condition. This regular clinical care is the same that you would have if you would decide to stay in the study. After your withdrawal, no more data will be collected for research purposes and transferred outside the treating physician(s).

Additional Analyses

Given the large number of potential candidates for the screening study, several companies are developing semi-automated software tools for the detection of pleural plaques and lung nodules on a screening CT. We are collaborating with a few companies, testing their products for validity, accuracy and usefulness in a screening situation. They get a general feedback, consisting of overall analyses and statistics. Occasionally, anonymous data and selected images might be sent to the companies for problem-solving or general interest. Any identifying information will be removed from such images before sending them to the company.

As laboratory technology develops, more sophisticated techniques may be developed to analyze more precisely the various components of sputum or blood. In addition, there is evidence that the genetic make-up of an individual may affect the predisposition of a person to asbestos-induced mesothelioma and lung cancer. It is possible that your sputum

or blood sample may be suitable for use in such studies. We ask your permission to allow the use of your sample for future studies. Such research will be conducted only after the UHN Research Ethics Board has approved the study. All conditions contain in this Consent Form will apply to such studies. The results of these studies will not be put in your health records.

My sputum and blood samples may be banked for future research purposes

YES

NO

Alternatives

While the screening CTs would not normally be performed in your situation, the clinical follow-up for any identified abnormality might be done even if you were not participating in this study.

Costs

You will be reimbursed for parking and transportation costs, as confirmed by receipts. Neither you nor your insurance carrier will be billed for either the professional or technical fees for the screening CT scan. However, if an abnormality is found on the screening CT, the additional studies are clinically indicated, and thus, you will be billed according to standard procedures (either through your medical insurance and/or other forms of medical coverage).

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. The reasonable costs of such treatment beyond that provided by your insurance will be covered by your health insurance for any injury or illness that is directly a result of participation in this trial. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Questions

If you have any questions about your rights as a research participant, or if you have any general questions about the study, you may call Dr. Demetris Patsios at 416-586-4200 ext. 5598.

If you have any questions about your rights as a research participant, please call Dr. R. Heslegrave, Chair Research Ethics Board at (416) 340-4557. This person is not involved with the research project in any way and calling him will not affect your participation in the study.

Consent

You have had the opportunity to discuss this study and your questions have been answered to your satisfaction. You consent to take part in the study with the understanding that you may withdraw at any time without affecting my medical care. You have received a signed copy of this consent form. You voluntarily consent to participate in this study.

Please check below which part(s) of the research study you do consent to:

- I consent to participate in the following in addition to the **low-dose CT study**
- the **blood** sampling
- the **sputum** sampling
- the **PFT** (breathing test)
- I consent to participate in the **low-dose CT study only**

Patient's Name (Please Print) Patient's Signature Date

I confirm that I have explained the nature and purpose of the study to the subject named above. I have answered all questions.

Name of Person Signature Date
Obtaining Consent

APPENDIX B- Sample of Database and Variables Extracted From Subjects of the Early Diagnosis of Mesothelioma and Lung Cancer in Prior Asbestos Workers Study

**EARLY DIAGNOSIS OF MESOTHELIOMA AND LUNG
CANCER IN PRIOR ASBESTOS WORKERS**

Early Screening Background Form

Study ID Medical Record Number

Date of Baseline CT

Last Name <input type="text"/>	First Name <input type="text"/>
Street address <input type="text"/>	Apartment <input type="text"/>
City <input type="text"/>	Postal Code <input type="text"/>
Province <input type="text"/>	Phone Home <input type="text"/>
Phone Work <input type="text"/>	
Email address <input type="text"/>	

Date of Birth: MM DD YY

Sex: F M Race:

Height: Weight:

Medical Conditions

Please indicate if you have been diagnosed with any of the following conditions:

Asthma	<input type="radio"/> No <input type="radio"/> Yes	Treated?	<input type="radio"/> No <input type="radio"/> Yes
Asbestosis	<input type="radio"/> No <input type="radio"/> Yes	Treated?	If treated, when? (YYYY) <input type="text"/>
Pleural Plaques	<input type="radio"/> No <input type="radio"/> Yes	Treated?	Biopsy? <input type="radio"/> No <input type="radio"/> Yes
			Results? <input type="text"/>

Emphysema or Chronic Bronchitis	<input type="radio"/> No <input type="radio"/> Yes	Treatment? <input type="radio"/> No <input type="radio"/> Yes	What kind? _____
Hypertension	<input type="radio"/> No <input type="radio"/> Yes	Treated? <input type="radio"/> No <input type="radio"/> Yes	If treated, when? (YYYY) _____
			Highest Value? _____
Heart Attack	<input type="radio"/> No <input type="radio"/> Yes	When? (YYYY) _____	Where treated? _____
Stroke	<input type="radio"/> No <input type="radio"/> Yes	When? (YYYY) _____	Where treated? _____
Heart Failure	<input type="radio"/> No <input type="radio"/> Yes	When? (YYYY) _____	Where treated? _____
Liver Disease	<input type="radio"/> No <input type="radio"/> Yes	<input type="radio"/> Mild <input type="radio"/> Moderate/Severe	
Renal Disease	<input type="radio"/> No <input type="radio"/> Yes	<input type="radio"/> Mild <input type="radio"/> Moderate/Severe	
Connective Tissue Disease	<input type="radio"/> No <input type="radio"/> Yes	Treatment? <input type="radio"/> No <input type="radio"/> Yes	What kind? _____
Other (Specify)	<input type="radio"/> No <input type="radio"/> Yes	_____	

During the past year, have you experienced any of the symptoms listed below?

No Yes (Check all that apply)

<input type="checkbox"/> Chest pain	<input type="checkbox"/> Back pain	<input type="checkbox"/> Weight loss
<input type="checkbox"/> Any cough	<input type="checkbox"/> Cough with blood	<input type="checkbox"/> Difficulty breathing
<input type="checkbox"/> Trouble swallowing	<input type="checkbox"/> Increase in abdomen	

If yes, have you seen a physician for this? No Yes

Whom? _____

If yes, are you now experiencing them? No Yes

When did you most recently have a chest X-ray? _____
(mm/dd/yyyy)

If so, where was the test done? _____

Do you know the results? _____

Would you be willing to supply us with a copy? _____

When did you most recently have a chest CT?	<input type="text" value="(mm/dd/yyyy)"/>
If so, where was the test done?	<input type="text"/>
Have you had a pulmonary function test?	<input type="radio"/> No <input type="radio"/> Yes
If yes, when and where was it done?	<input type="text" value="(mm/dd/yyyy)"/>
Have you ever had any type of cancer?	<input type="radio"/> No <input type="radio"/> Yes
If yes, please specify type and year of diagnosis:	<input type="text"/>
Have you ever had any other chest illness?	<input type="radio"/> No <input type="radio"/> Yes
If yes, please specify type and year of diagnosis:	<input type="text" value="(mm/dd/yyyy)"/>
Have you ever had a significant chest injury? (such as broken rib)	<input type="radio"/> No <input type="radio"/> Yes
If yes, please specify	<input type="text"/>

Asbestos Exposure

INDIRECT DIRECT

Name of Employer: _____

Occupation:
(If retired, also indicate previous occupation)

<input type="radio"/> Construction	<input type="radio"/> Demolition
<input type="radio"/> Ship Construction	<input type="radio"/> Repair
<input type="radio"/> Mining	<input type="radio"/> Chemical Industry
<input type="radio"/> Building Maintenance	<input type="radio"/> Other: <input type="text"/>

Cumulative time of exposure?

Starting year: _____ Age:

Ending year: _____ Age:

How often was the exposure?

<input type="radio"/> Everyday	<input type="radio"/> Once a week
<input type="radio"/> Once a month	<input type="radio"/> Other: <input type="text"/>

Did you work directly with asbestos? If yes, please describe your activities. (i.e., spraying, applying, cutting, removing)

Which type of asbestos were you in contact with?

- Serpentine/Chrysotile (white)
- Amphiboles (brown/off white)
- Crocidolite (blue)
- Unknown

Did you wear any Personal Protective Equipment? No Yes
 If yes, please describe and include years worn.

Did you work in areas where other workers were generating asbestos dust? (indirect exposure) No Yes
 If yes, please describe.

Family History

Have any members of your family had any of the following:

Lung disease? No Yes
 If so do you know which type?

Mesothelioma? No Yes
 Asbestosis? No Yes
 If yes, which relative?

Age Diagnosed Still living?

Smoking History

Do you currently smoke? No Yes Never
 Do you live with a smoker? No Yes

If non-smoker - go to Health in General

What type of tobacco or other substances have you used/smoked?
 (check all that apply)

- cigarettes cigars
- marijuana pipes
- smokeless tobacco
 (i.e. chewing tobacco, snuff, "DIP")

Have you smoked at least 100 cigarettes in your lifetime? No Yes

About how old were you when you first started smoking cigarettes regularly?

How many packs of cigarettes are you currently smoking per day?

Former Cigarette Smoker

When you were a smoker, on approximately how many days per week did you smoke cigarettes?

On the days that you did smoke, approximately how many packs of cigarettes did you smoke per day?

For approximately how many years did you smoke this amount?

Starting Year

Ending Year

Your Health in General

In general, would you say your health is:

Excellent Very good Good Fair Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

1. Moderate activities, such as moving a table, pushing a vacuum, bowling, golf?

Limited a lot Limited a little Not limited at all

2. Climbing several flights of stairs?

Limited a lot Limited a little Not limited at all

3. Walking about 1km or 2/3 of a mile?

Limited a lot Limited a little Not limited at all

If you must STOP walking, what would be the reason:

Shortness of breath

Legs/feet hurt

Dizzy

Stomach cramps

Other

Physician contact information

Please Print

Physician Name

Physician Address

City Prov P.C.

Phone Fax

Email Address

Patient Contact Information

Parents first name

This is required for IDENTIFICATION purposes only.

Mother Father

Next of Kin/Contact(1)

Name Relation

Address Phone

Next of Kin/Contact(2)

Name Relation

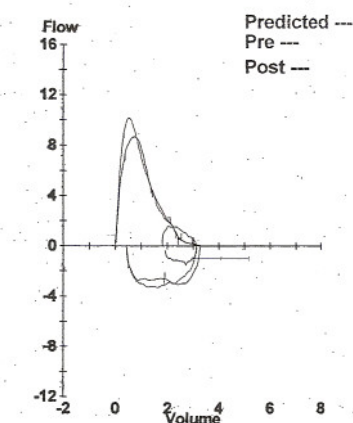
Address Phone

APPENDIX C- Sample of Pulmonary Function Test From a Subject in the Early Diagnosis of Mesothelioma and Lung Cancer in Prior Asbestos Workers Study

Bluewater Health
 Pulmonary Function Lab
 4704
 Mackenzie, Jane Sin Yan To
 DP105244/

Spirometry		Meas	% Ref	Meas	% Ref	% Chg
FVC	4.09	3.17	77	3.28	80	4
FEV1	3.32	2.66	77	2.56	77	0
FEV1/FVC	81	81		78		
FEV3	3.85	2.98	77	3.02	78	2
FEV3/FVC	94	94		92		
FEF25-75%	3.45	2.65	77	2.49	72	-6
IsoFEF25-75	3.45	2.65	77	3.05	88	15
FEF25%		10.04		8.22		-18
FEF50%		4.00		3.97		-1
PEF		10.13		8.67		-14
FET100%		7.74		8.77		13
FIVC	4.09	(2.73)	(67)	(2.83)	(69)	4
FIF50%		3.11		2.57		-17
PIF		3.31		3.06		-8
FVL ECode		001000		000000		

Lung Volumes		Meas	% Ref
VC	4.09	3.33	81
TLC	5.96	4.50	76
RV	1.84	1.17	64
RV/TLC	31	26	
FRC PL	2.98	(1.45)	(48)
ERV	1.35	(0.23)	(17)
IC	2.70	3.06	113
Diffusion			
DLCO	30.5	23.3	77
DLCO/VA	5.24	5.31	101
VA		4.39	
IVC		3.15	
BHT		10.46	
Resistance			
Raw	1.58	2.78	176
Gaw	0.716	0.360	50
Vtg (Raw)		2.97	
Arterial Blood Gases			
FIO2	pH	PCO2	PO2 HCO3 BE SaO2



Interpretation:

Comments:
 Spo2 on room air is 97% good effort. vaso/vagal response during FVL

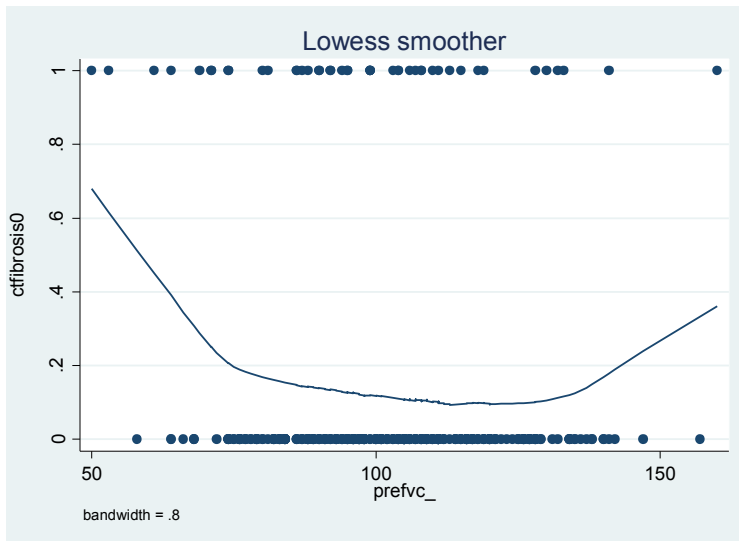
Physician's Interpretation:

No significant
 Mild re
 Normal

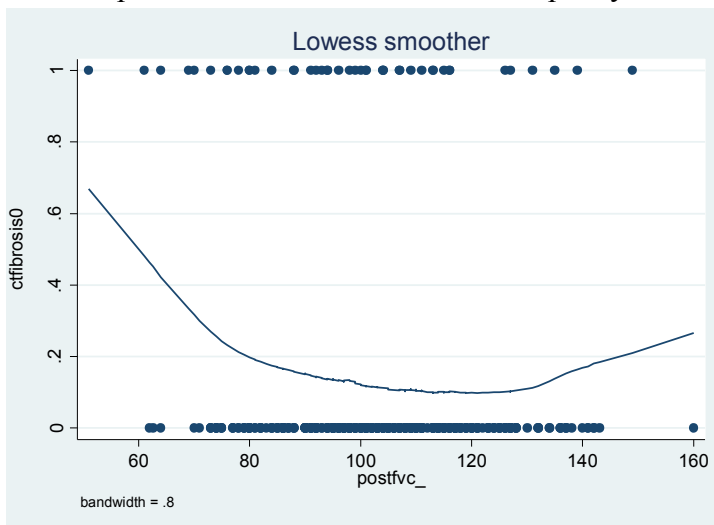
APPENDIX D

Lowess Curves for Continuous Variables Not Included in Predictive Models

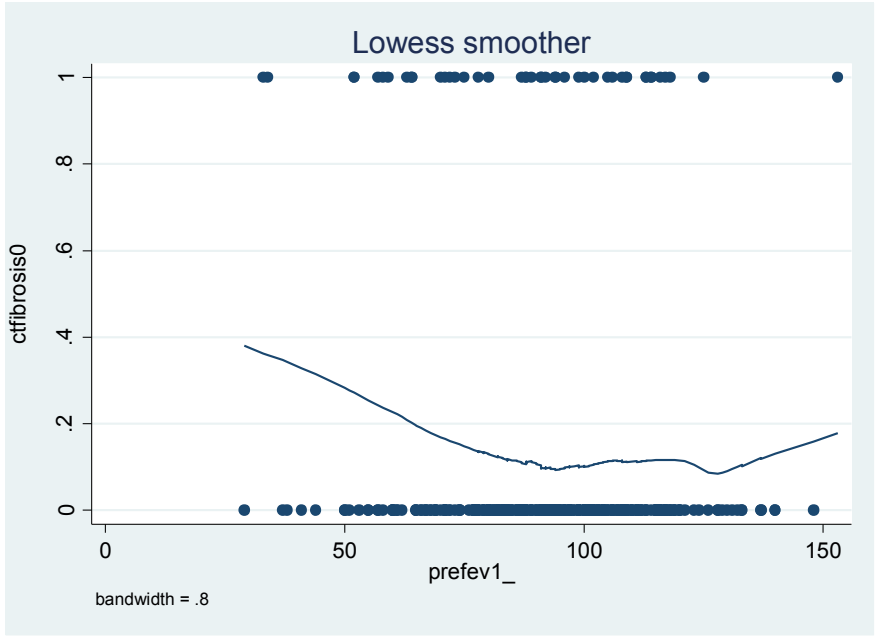
Y-axis for each graph refers to the probability of pulmonary fibrosis by LDCT. Black dots at the probability mark of 1 refer to cases. Black dots at the probability mark of 0 refer to controls. The x axis refers to various pulmonary function test variables. On each page is a set of pre- and post-bronchodilator curves.



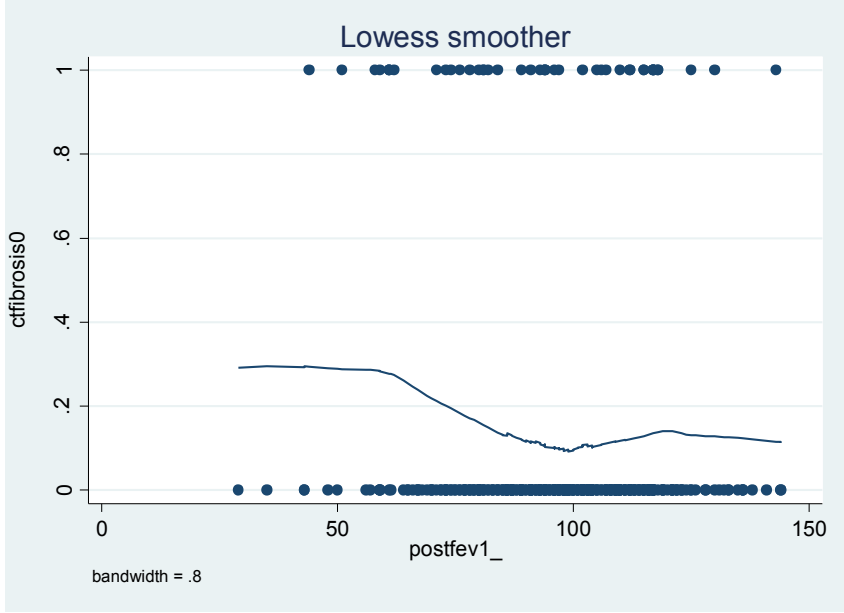
Prefvc = pre-bronchodilator forced vital capacity



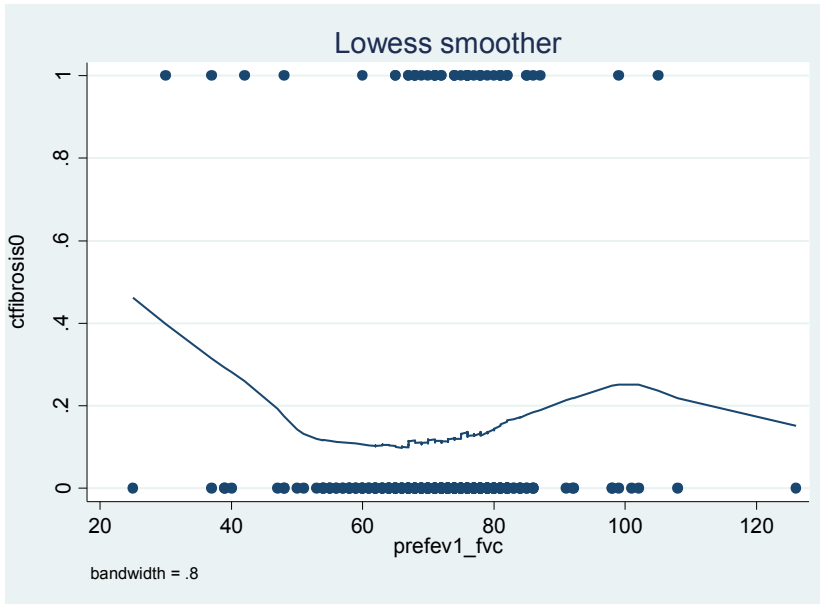
Postfvc= post-bronchodilator forced vital capacity



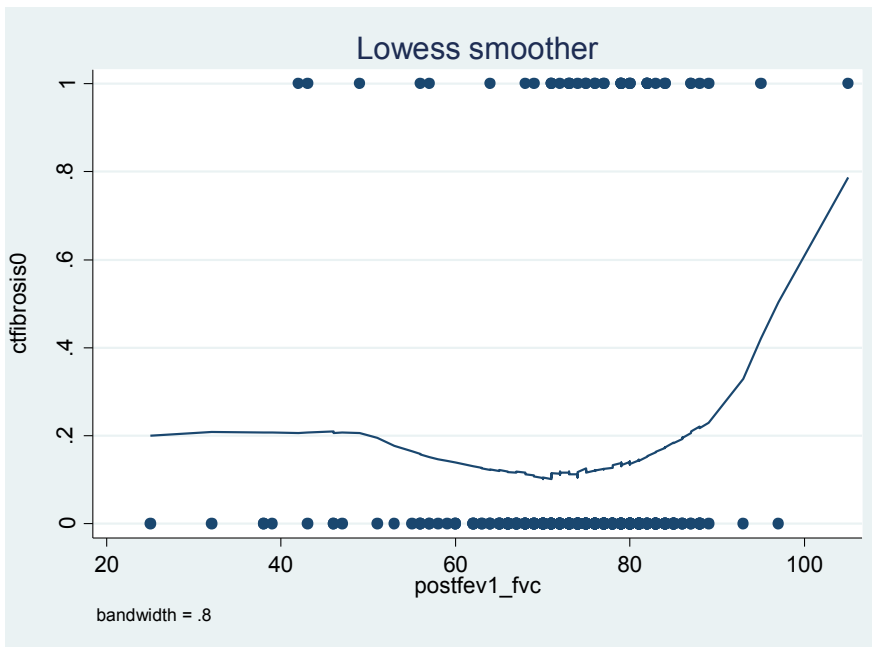
Prefev1= pre-bronchodilator forced expiratory volume in 1 second



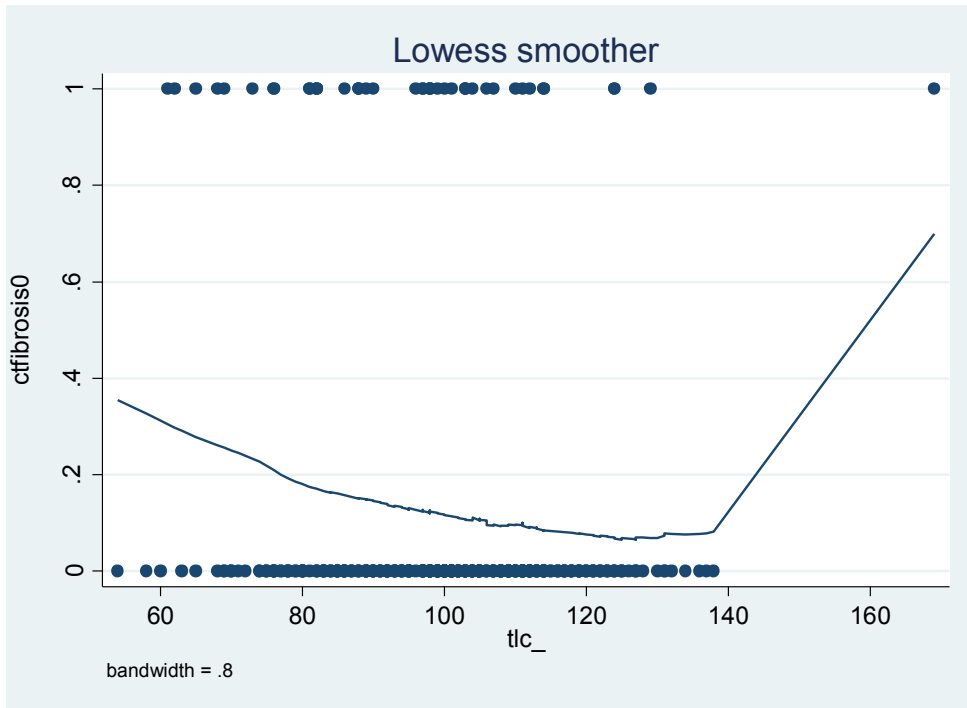
Postfev1= post-bronchodilator forced expiratory volume in 1 second



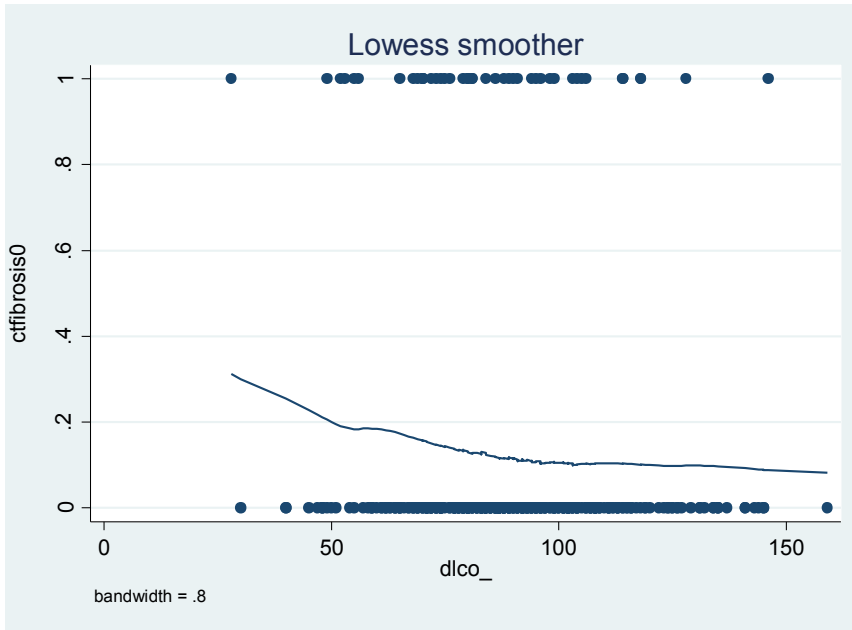
Pre fev1_fvc = pre-bronchodilator FEV1/FVC



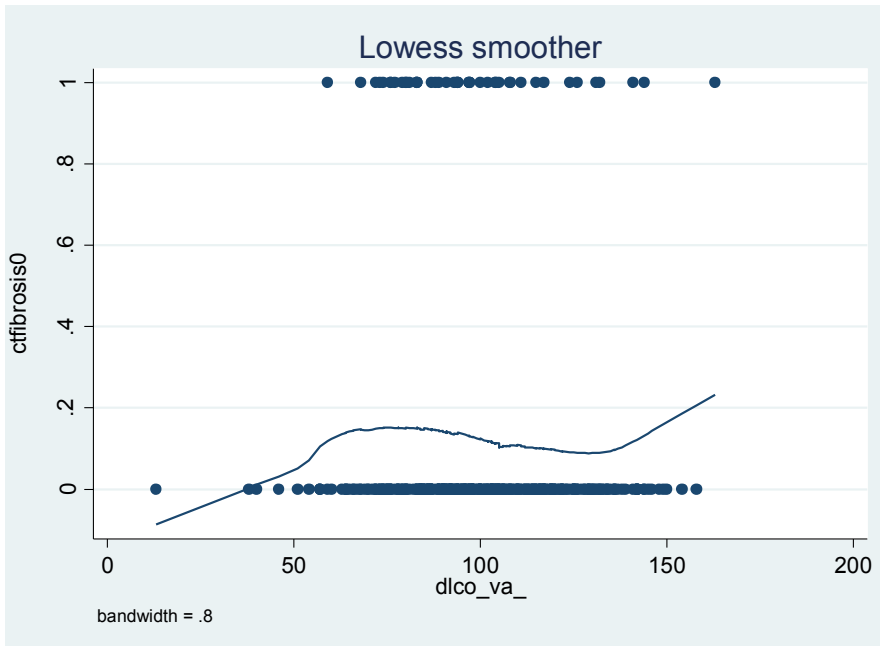
Postfev1_fvc = post-bronchodilator FEV1/FVC



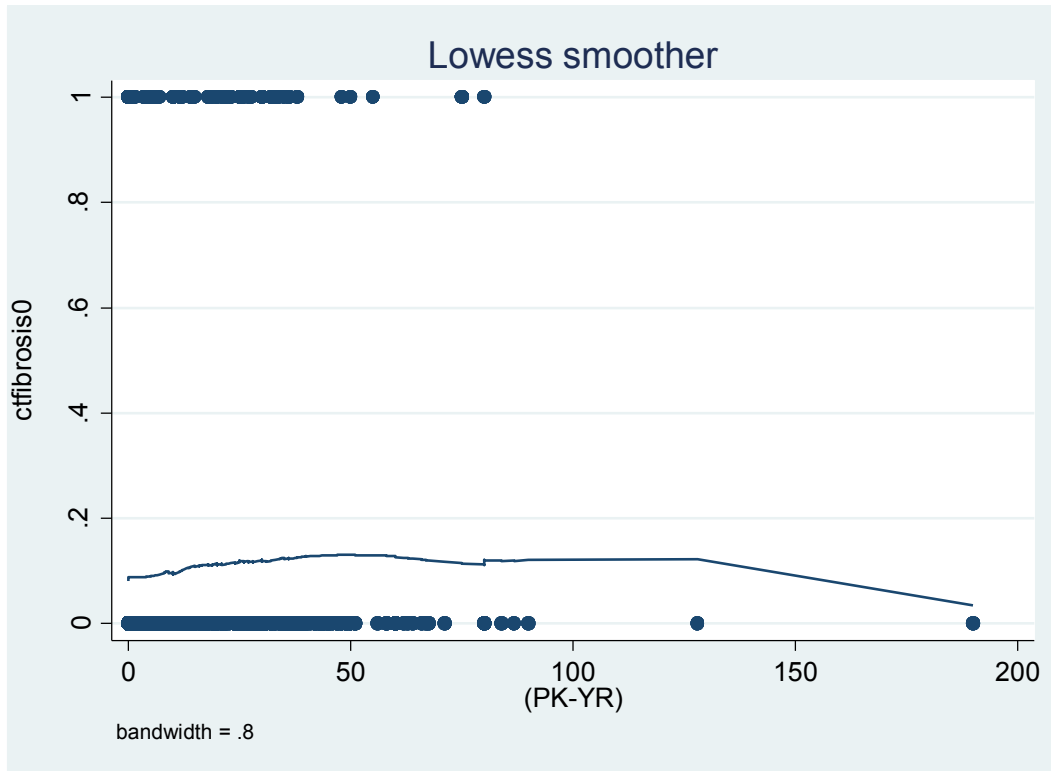
TLC = total lung capacity



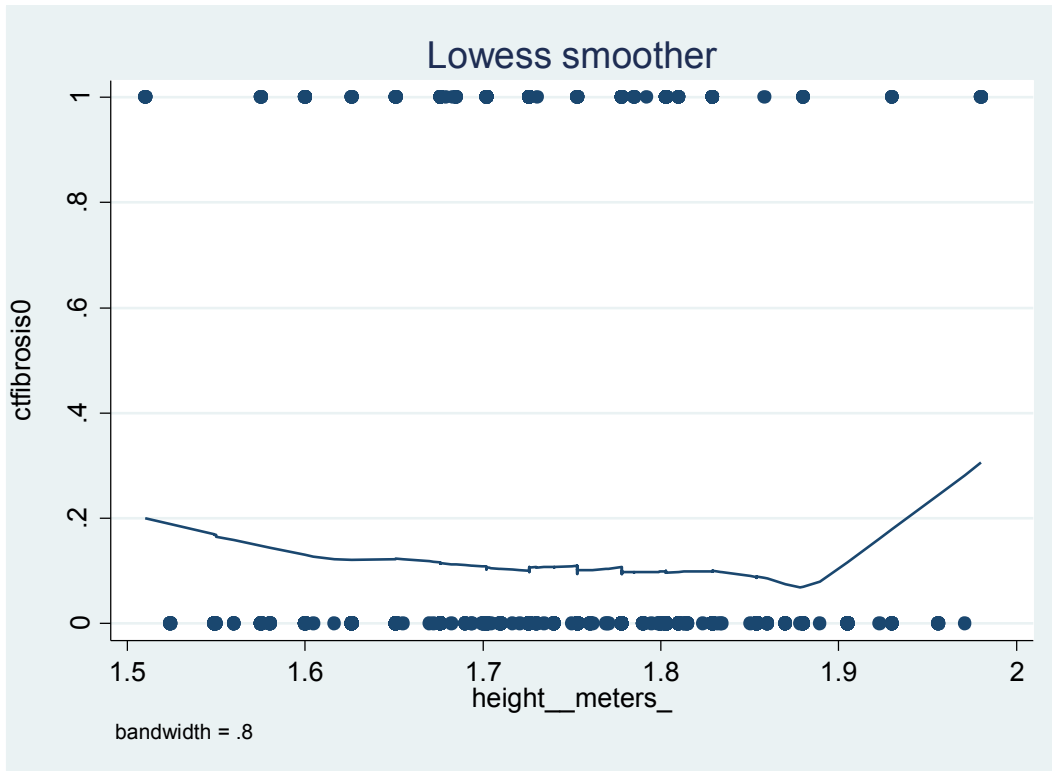
DLCO = Diffusing Lung Capacity



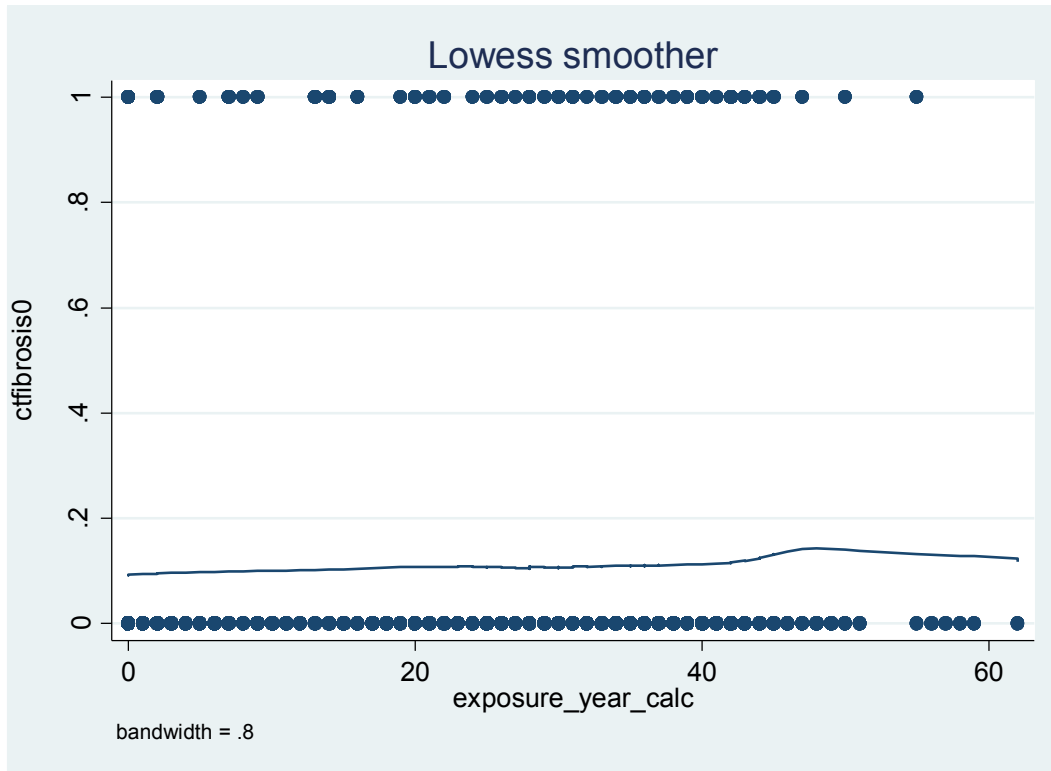
DLCO_VA = Difusing Lung Capacity, adjusted for volume



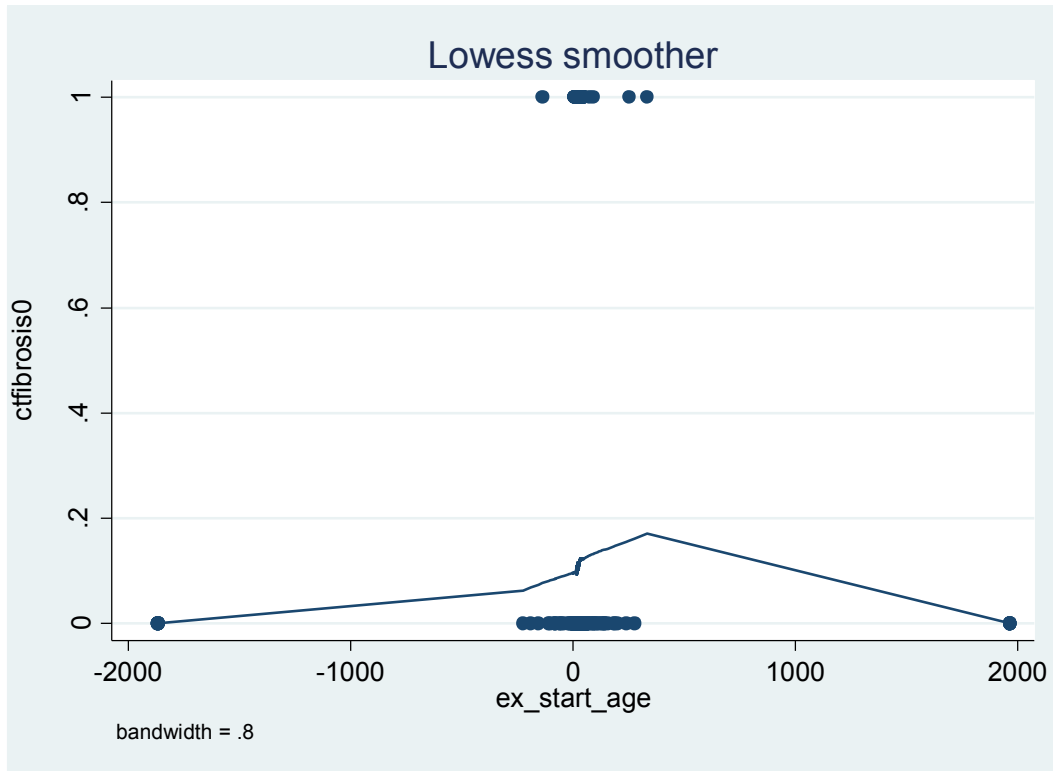
PK-YR = pack-years of cigarette smoking



Height_meters = Height in meters



Exposure_year_calc = Number of Years exposed to Asbestos

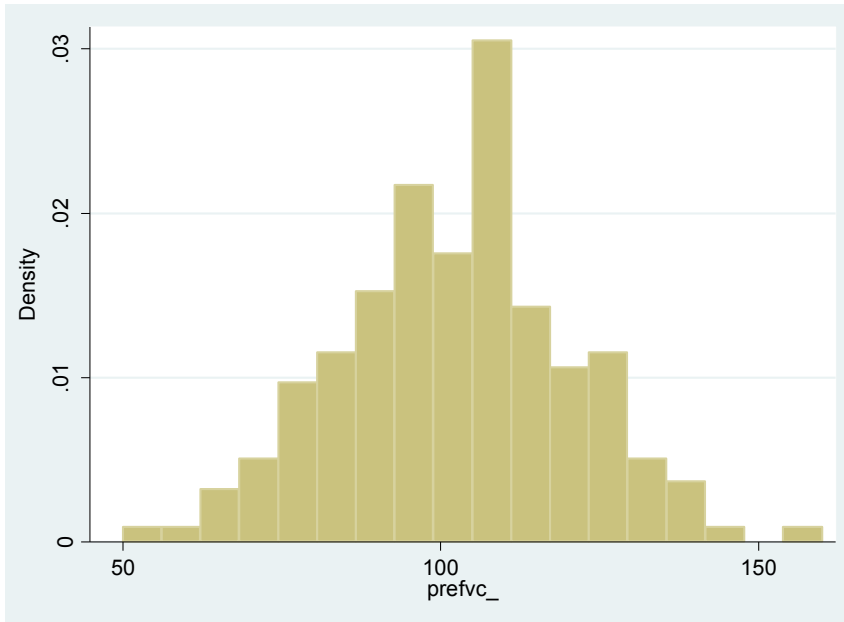


Ex_start_age = Age at start of exposure to Asbestos

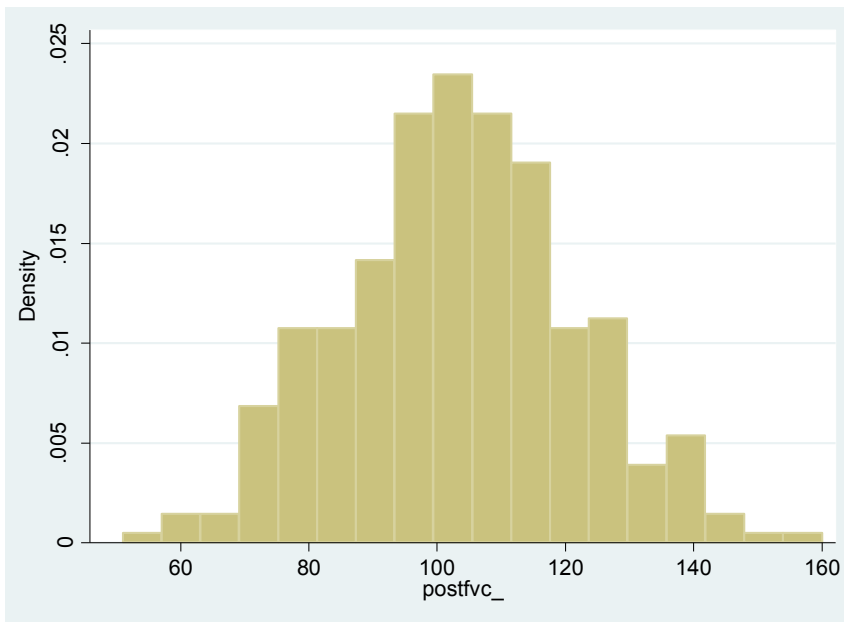
APPENDIX E

Histograms of all PFT variables

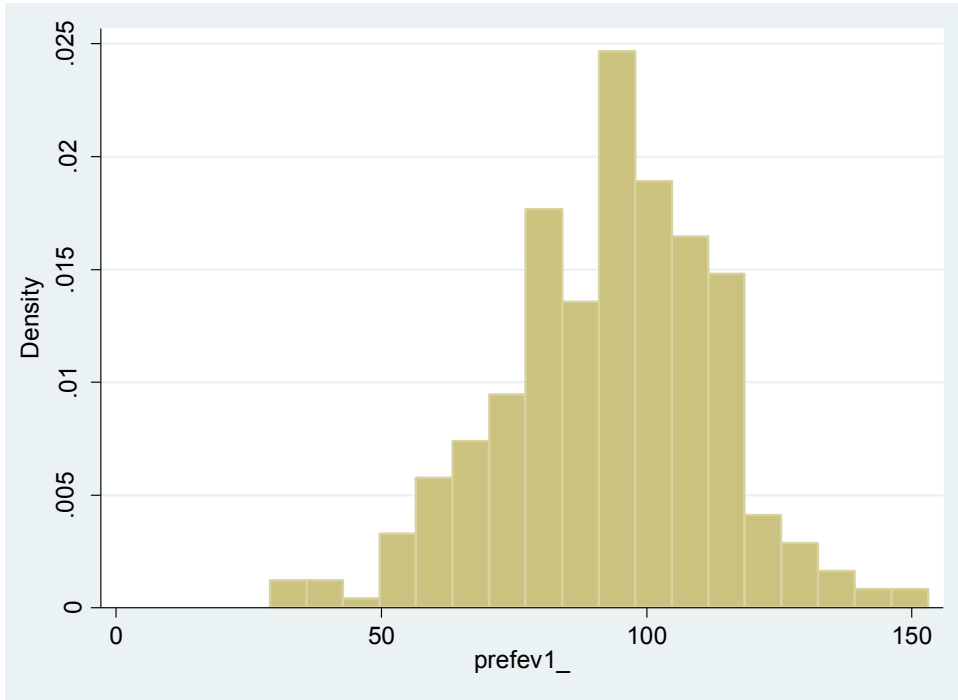
Y-axis= density which scales the height of the bars so that the sum of their areas equals 1.



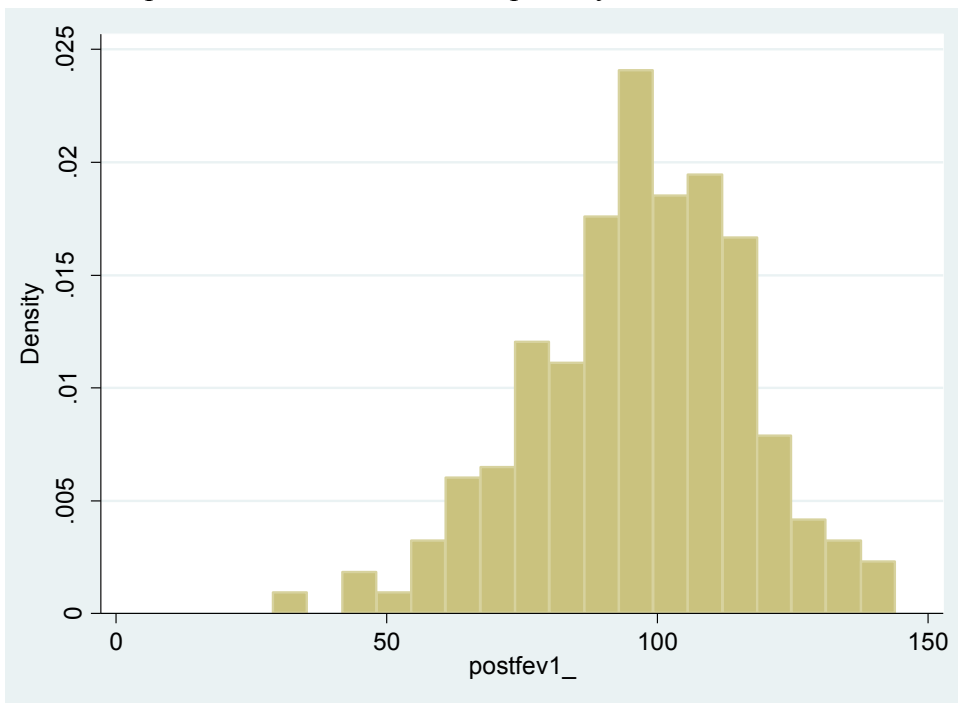
Pre-FVC = pre bronchodilator forced vital capacity



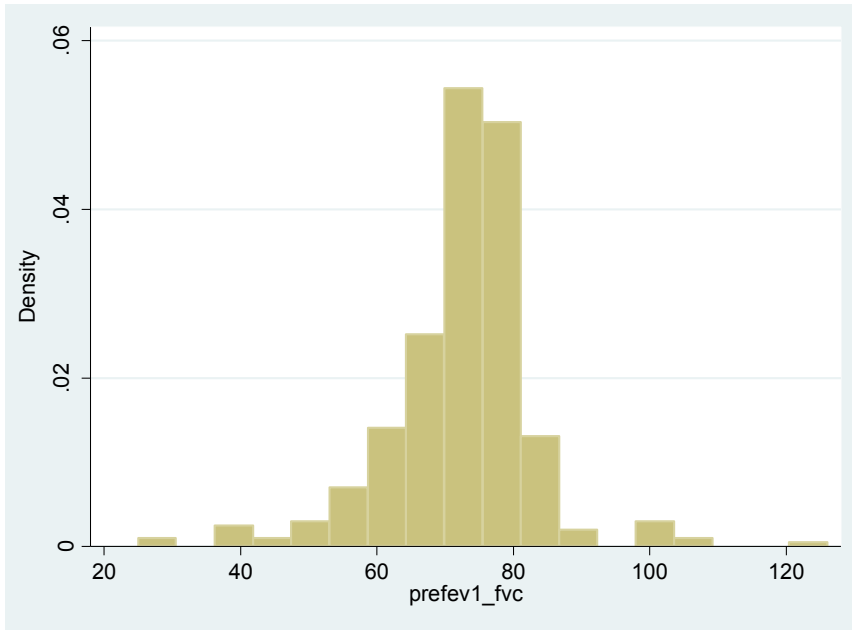
Post-FVC= post bronchodilator forced vital capacity. This variable was included in the final predictive model.



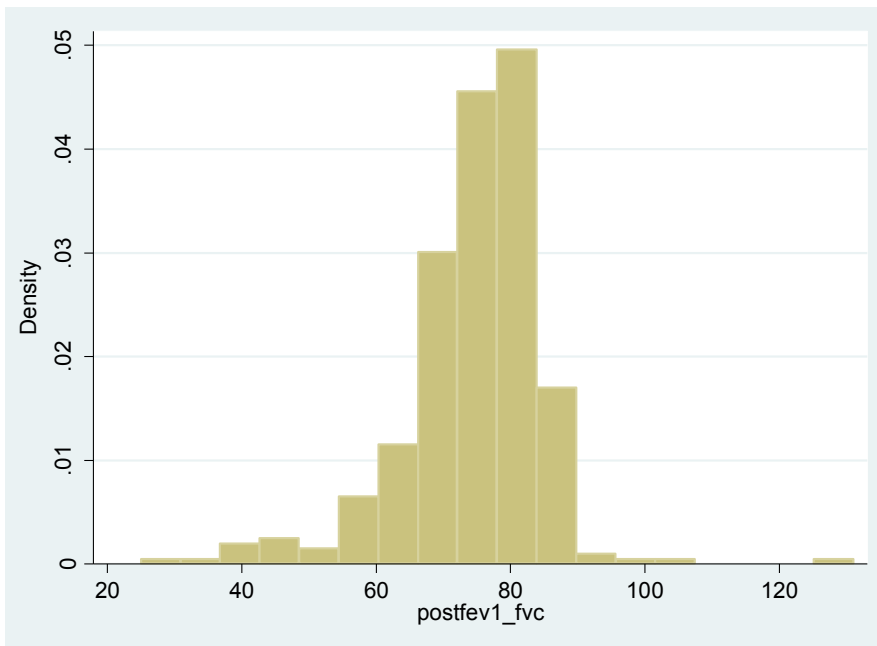
Pre-FEV1- pre bronchodilator forced expiratory volume in 1 second



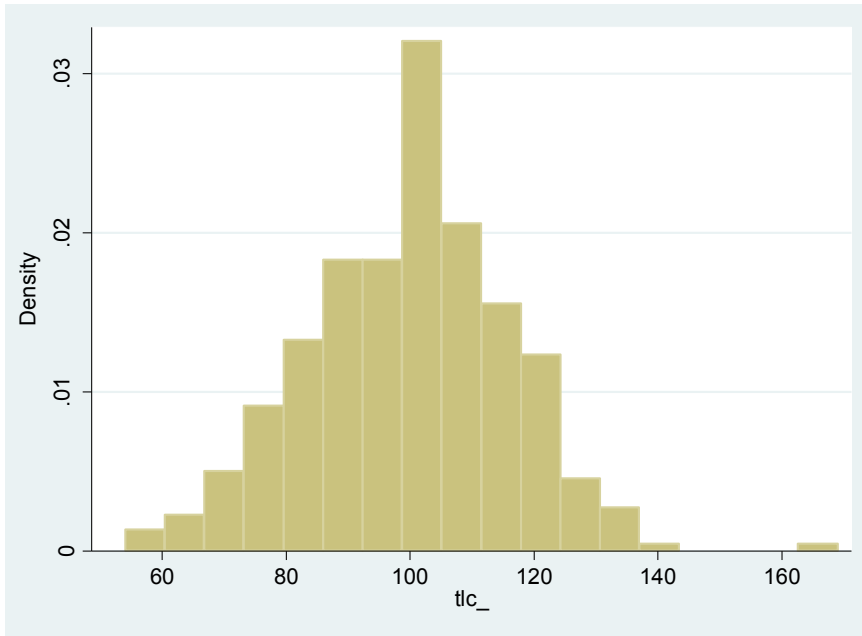
Post-FEV1- post bronchodilator forced expiratory volume in 1 second. This variable was included in the final predictive model.



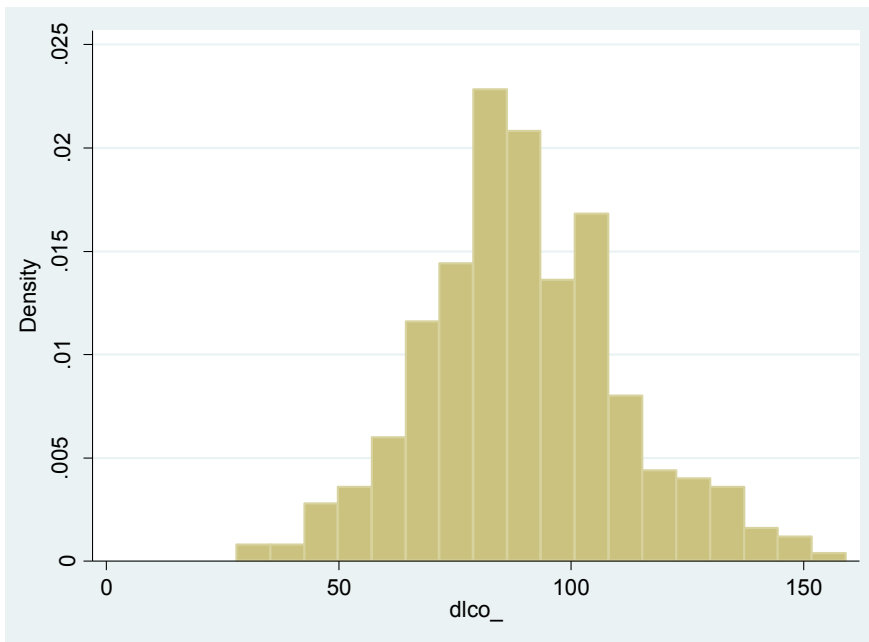
Prefev1_fvc= pre bronchodilator FEV1/FVC



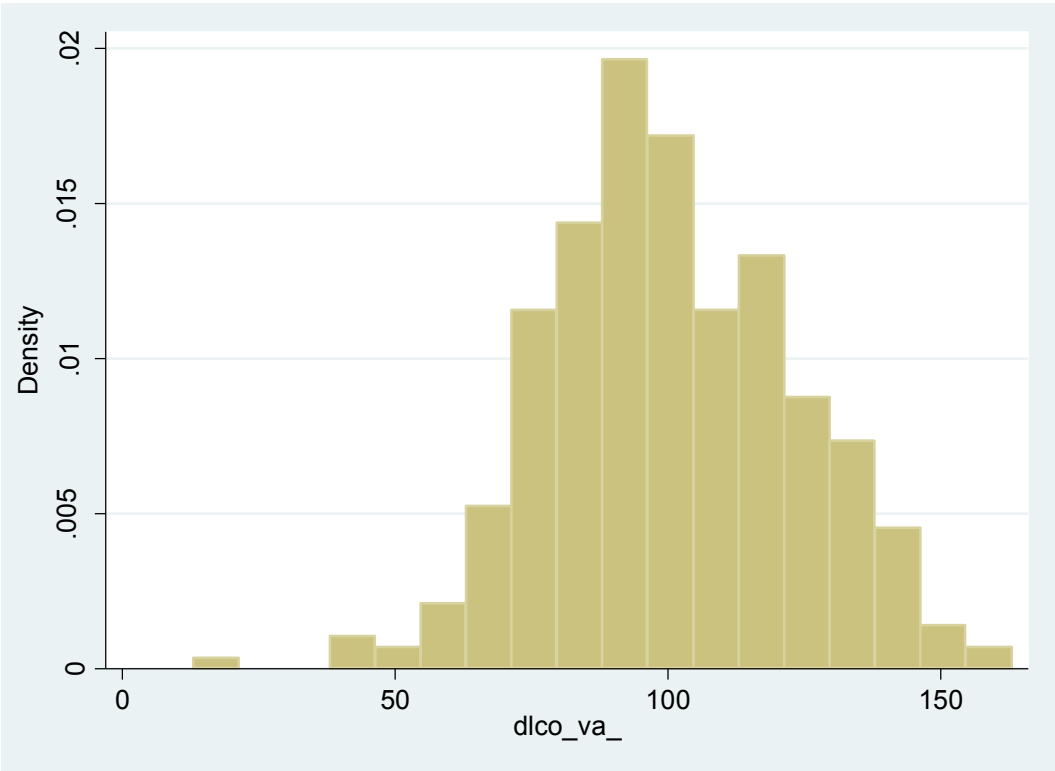
Postfev1_fvc= post bronchodilator FEV1/FVC



Tlc= total lung capacity



Dlco= diffusing lung capacity



Dlco_va= Difusing Lung Capacity, adjusted for volume

APPENDIX F

Predictive Logistic Model for Asbestosis in a Cohort of Asbestos Workers Stratified by Smoking Status ($n_{\text{smoke}}=248$; $n_{\text{nosmoke}}=65$)

	Smokers OR (95%CI)	p Value	Non Smokers OR (95%CI)	p Value
Age (10years)	1.41 (0.88-2.26)	0.149	0.75 (0.17-3.22)	0.703
Age first asbestos exposure (years)	0.98 (0.92-1.04)	0.518	0.95 (0.58-1.55)	0.845
Dyspnea	2.06 (0.94-4.50)	0.070	OMITTED	
Post FVC Spline (%)	0.95 (0.88-1.02)	0.230	1.11 (0.56-2.18)	0.758
	0.87 (0.67-1.14)	0.315	0.68 (0.08-5.74)	0.721
	2.05 (0.62-6.75)	0.235	0.09 (9.41e-07-10471.6)	0.695
Post FEV1 Spline (%)	0.96 (0.91-1.01)	0.191	11.05 (0.14-834.98)	0.276
	1.21 (1.00-1.46)	0.045	0.03 (0.0000752-14.42)	0.271
	0.42 (0.13-1.26)	0.122	4789211 (0.0001043-2.20e+17)	0.219
BMI Splines	0.88 (0.67-1.17)	0.403	0.67 (0.18-2.39)	0.537
	2.09 (0.59-7.43)	0.250	4.93 (0.02-1366.88)	0.578
	0.08 (0.00-5.82)	0.254	0.001 (4.53e-12-228258.2)	0.482
Pleural Plaques	1.69 (0.71-3.99)	0.232	4.38 (0.17-110.34)	0.369

APPENDIX G

R printout for calibration (Modeling and associated graphs)

```
> ls()
[1] "ASB12FEB10"
> attach(ASB12FEB10)
> library(Design)
Loading required package: Hmisc
Loading required package: survival
Loading required package: splines
```

```
Attaching package: 'Hmisc'
```

```
The following object(s) are masked from package:survival :
```

```
untangle.specials
```

```
The following object(s) are masked from package:base :
```

```
format.pval,
round.POSIXt,
trunc.POSIXt,
units
```

```
Design library by Frank E Harrell Jr
```

```
Type library(help='Design'), ?DesignOverview, or ?Design.Overview')
to see overall documentation.
```

```
Attaching package: 'Design'
```

```
The following object(s) are masked from package:Hmisc :
```

```
strgraphwrap
```

```
The following object(s) are masked from package:survival :
```

```
Surv
```

```
> Mfull <- lrm(case ~ age + ex_start_age + rcs(FVCpost, 5) + rcs(FEV1post, 5)
+ dyspnea + PPlaque + smkdi , x=T, y=T)
> anova(Mfull)
```

	Wald Statistics		Response: case
Factor	Chi-Square	d.f.	P
age	2.37	1	0.1239
ex_start_age	0.75	1	0.3854
FVCpost	15.85	4	0.0032
Nonlinear	5.71	3	0.1265
FEV1post	9.66	4	0.0466
Nonlinear	7.66	3	0.0537
dyspnea	1.55	1	0.2136

```

PPlaque 1.42 1 0.2342
smkdi 3.18 1 0.0744
TOTAL NONLINEAR 13.59 6 0.0346
TOTAL 27.14 13 0.0119
> valMfull <- validate(Mfull, B=200)
> print(valMfull)
      index.orig      training      test      optimism index.corrected  n
Dxy      0.498455033  0.567392375  0.42174337  0.14564900  0.35280603 200
R2      0.181137632  0.242080843  0.12834741  0.11373343  0.06740420 200
Intercept 0.000000000  0.000000000 -0.52285854  0.52285854 -0.52285854 200
Slope  1.000000000  1.000000000  0.66806099  0.33193901  0.66806099 200
Emax      0.000000000  0.000000000  0.20052786  0.20052786  0.20052786 200
D      0.099793603  0.136722585  0.06882148  0.06790111  0.03189249 200
U      -0.006079027 -0.006079027  0.01912317 -0.02520220  0.01912317 200
Q      0.105872630  0.142801612  0.04969830  0.09310331  0.01276932 200
B      0.097939677  0.092189467  0.10446826 -0.01227880  0.11021847 200
> print(Mfull)

```

Logistic Regression Model

```

lrm(formula = case ~ age + ex_start_age + rcs(FVCpost, 5) + rcs(FEVlpost,
  5) + dyspnea + PPlaque + smkdi, x = T, y = T)

```

Frequencies of Responses

```

  0  1
286 43

```

Frequencies of Missing Values Due to Each Variable

```

      case      age ex_start_age      FVCpost      FEVlpost      dyspnea
PPlaque      smkdi
0           4           4           15           276           276           0
1

```

```

      Obs  Max Deriv Model L.R.      d.f.      P      C      Dxy
Gamma  Tau-a      R2      Brier
0.501  329  4e-07  0.181  0.098  13  0.0013  0.749  0.499

```

```

      Coef      S.E.      Wald Z P
Intercept  1.723607  3.63904  0.47  0.6358
age        0.032516  0.02113  1.54  0.1239
ex_start_age -0.023682  0.02728 -0.87  0.3854
FVCpost    -0.081035  0.03955 -2.05  0.0405
FVCpost'   0.228473  0.25923  0.88  0.3781
FVCpost'' -2.333374  1.57056 -1.49  0.1374
FVCpost''' 4.749910  2.49301  1.91  0.0567
FEVlpost   0.006554  0.03194  0.21  0.8374
FEVlpost' -0.075493  0.14468 -0.52  0.6018
FEVlpost'' 2.046558  1.28054  1.60  0.1100
FEVlpost''' -4.794087  2.39876 -2.00  0.0457
dyspnea    0.463526  0.37267  1.24  0.2136
PPlaque    0.457993  0.38499  1.19  0.2342
smkdi      0.960487  0.53842  1.78  0.0744

```

```

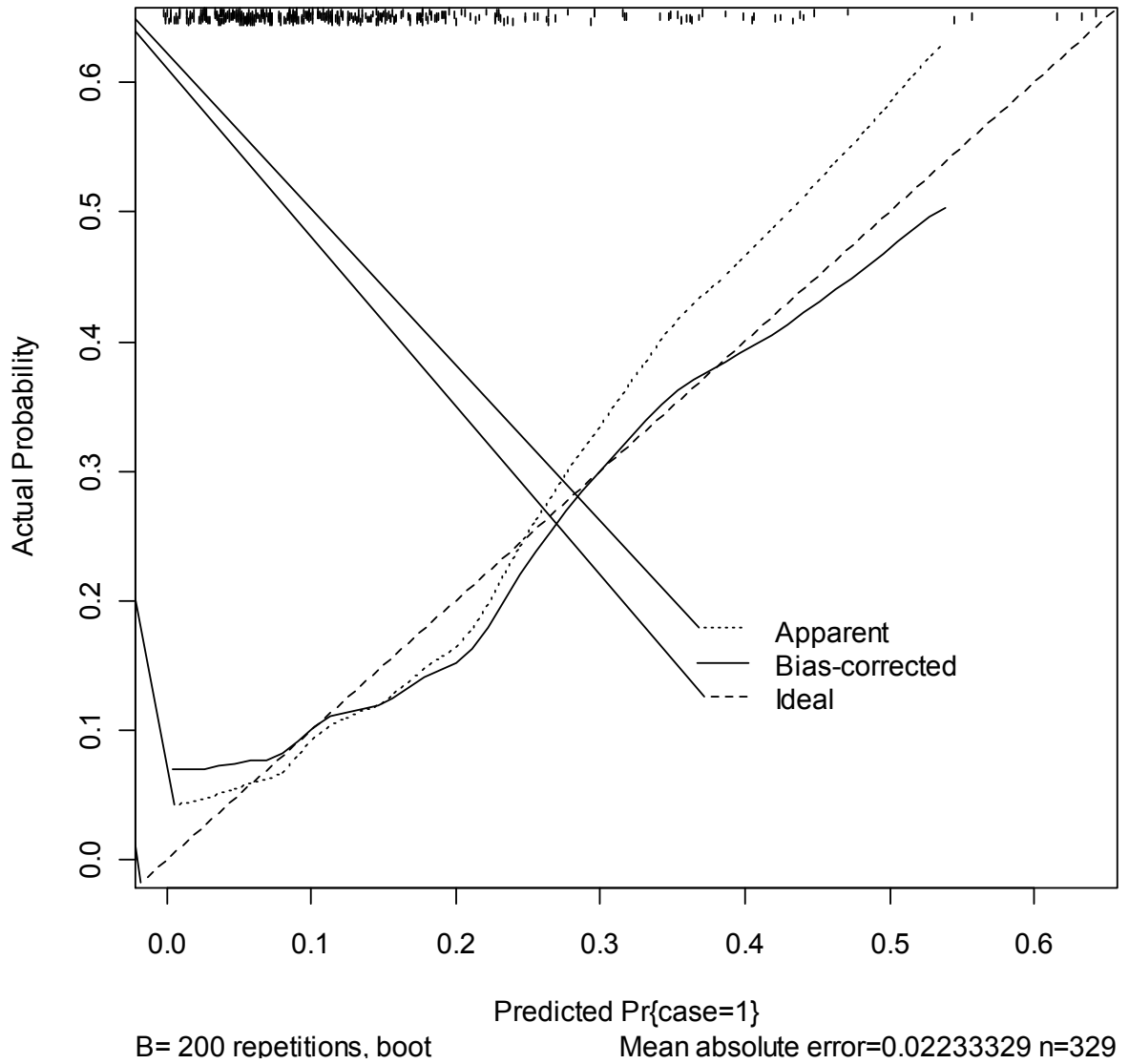
> calMfull <- calibrate(Mfull, B=200)

```

```
> plot(calMfull)
```

```
n=329 Mean absolute error=0.02233329 Mean squared error=0.0008027235  
0.9 Quantile of absolute error=0.04566853
```

```
>
```



```
> Mnest <- lrm(case ~ age + rcs(FVCpost, 5) + rcs(FEVlpost, 5) + smkdi, x=T,
y=T)
> print(Mnest)
```

Logistic Regression Model

```
lrm(formula = case ~ age + rcs(FVCpost, 5) + rcs(FEVlpost, 5) +
smkdi, x = T, y = T)
```

Frequencies of Responses

```
  0  1
294 44
```

Frequencies of Missing Values Due to Each Variable

```
case      age  FVCpost FEVlpost  smkdi
  4        4    276    276      1
```

	Obs	Max Deriv	Model L.R.	d.f.	P	C	Dxy
Gamma	338	Tau-a	R2	Brier			
0.458	0.104	1e-08	0.143	0.101	10	0.0025	0.728

	Coef	S.E.	Wald Z	P
Intercept	0.378523	3.47921	0.11	0.9134
age	0.034627	0.01991	1.74	0.0820
FVCpost	-0.069925	0.03789	-1.85	0.0650
FVCpost'	0.262213	0.24312	1.08	0.2808
FVCpost''	-2.270407	1.48738	-1.53	0.1269
FVCpost'''	4.278024	2.38060	1.80	0.0723
FEVlpost	0.008956	0.02923	0.31	0.7593
FEVlpost'	-0.119635	0.13619	-0.88	0.3797
FEVlpost''	2.118481	1.23529	1.71	0.0864
FEVlpost'''	-4.595765	2.32739	-1.97	0.0483
smkdi	1.069385	0.52627	2.03	0.0422

```
> anova(Mnest)
```

Wald Statistics Response: case

Factor	Chi-Square	d.f.	P
age	3.02	1	0.0820
FVCpost	10.77	4	0.0293
Nonlinear	4.03	3	0.2587
FEVlpost	7.14	4	0.1289
Nonlinear	6.27	3	0.0991
smkdi	4.13	1	0.0422
TOTAL NONLINEAR	10.86	6	0.0929
TOTAL	22.79	10	0.0116

```
> valMnest <- validate(Mnest, B=200)
```

```
> print(valMnest)
```

	index.orig	training	test	optimism	index.corrected	n
Dxy	0.45562771	0.51038730	0.39053185	0.119855454	0.33577225	200
R2	0.14289608	0.19105034	0.10230177	0.088748561	0.05414752	200
Intercept	0.00000000	0.00000000	-0.51995347	0.519953470	-0.51995347	200
Slope	1.00000000	1.00000000	0.69211955	0.307880450	0.69211955	200
Emax	0.00000000	0.00000000	0.19202211	0.192022106	0.19202211	200
D	0.07712528	0.10639249	0.05379094	0.052601555	0.02452373	200
U	-0.00591716	-0.00591716	0.01397733	-0.019894492	0.01397733	200
Q	0.08304244	0.11230965	0.03981361	0.072496046	0.01054640	200
B	0.10127403	0.09823886	0.10613952	-0.007900658	0.10917468	200

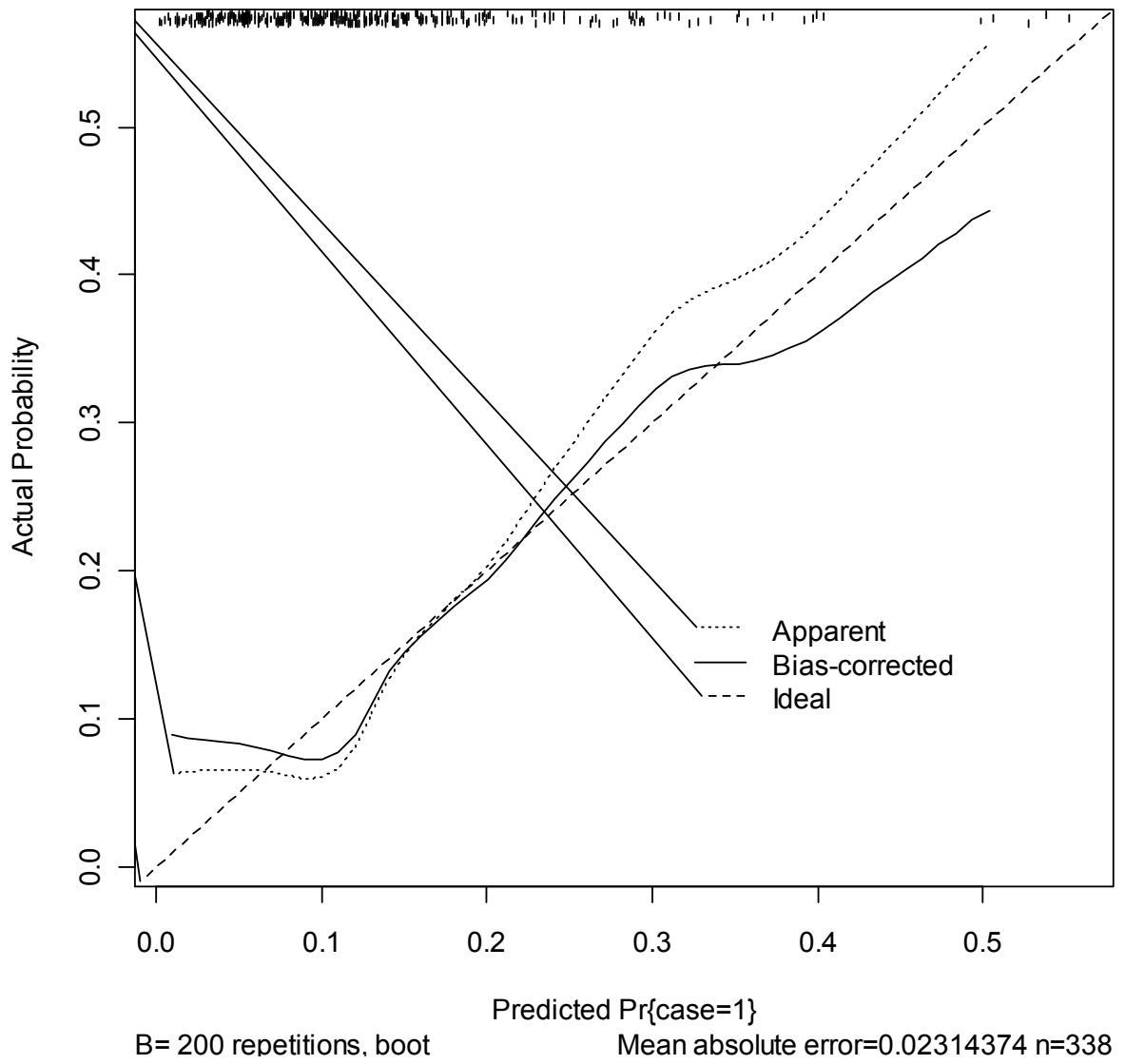
```
> calMnest <- calibrate(Mnest, B=200)
> plot(calMnest)

n=338   Mean absolute error=0.02314374   Mean squared error=0.0008741606
0.9 Quantile of absolute error=0.05359642

> plot(calMnest)

n=338   Mean absolute error=0.02314374   Mean squared error=0.0008741606
0.9 Quantile of absolute error=0.05359642

>
```




```
logistic ctfibrosis0 age10 dyspnea pleural_plaques fvc1 fvc2 fvc3 fvc4 fev11 fev12
fev13 fev14 asbdurdi29 smkdi
> asbdur_smoke
```

```
. predict Pfull, p
(277 missing values generated)
```

```
. logistic ctfibrosis0 age10 dyspnea pleural_plaques fvc1 fvc2 fvc3 fvc4 fev11 fev12
fev13 fev14 asbdurdi29 smkdi
> if e(sample)
```

```
. predict Pint, p
(277 missing values generated)
```

```
. roccomp ctfibrosis0 Pfull Pint
```

	Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf. Interval]	
Pfull	338	0.7447	0.0441	0.65825	0.83108
Pint	338	0.7342	0.0461	0.64389	0.82441

```
Ho: area(Pfull) = area(Pint)
chi2(1) = 1.11 Prob>chi2 = 0.2922
```

```
. roccomp ctfibrosis0 Pfull Pint, graph
```

DICHOTOMIZE VARIABLE

```
. generate asbdurdi29=0
```

```
. replace asbdurdi29=1 if exposure_year_calc>29
(307 real changes made)
```

```
. generate asbdur_smoke= asbdurdi29* smkdi
```