University of Alberta

Biological Factors in the Etiology of Pulmonary Sarcoidosis

by

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Abstract

Background

Sarcoidosis etiology is unknown. It is thought to be an aberrant immune response to unidentified environmental agents with ‘rural living’ emerging as a risk factor.

Objective

To determine if specific environmental factors were associated with the risk of sarcoidosis.

Methods

A case-referent study: Administrative data was used to identify adult cases first diagnosed in Alberta between 1999 and 2005, and age/sex matched referents with other respiratory conditions. Exposures were determined using an interviewer-administered telephone questionnaire. Duration was calculated.

Results

684 cases and 1454 referents participated. Cases were less likely to have ever smoked. No environmental factors had a confidence interval excluding 1 for exposure periods: birth, birth–5 years, and birth–diagnosis. Associations with un-piped water were identified when cases were compared with asthma and non-asthma referents, with cases more likely than asthma referents to drink un-piped water.

Conclusions

No strong association between environmental factors and sarcoidosis was observed.

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Chapter 1 Introduction

1.1 Background

Sarcoidosis is a multi-organ granulomatous disease of unknown etiology characterized by the presence of noncaseating epithelioid granulomas and an accumulation of Th1 lymphocytes and macrophages in affected organs, most notably in the lung. The disorder commonly becomes clinically apparent because of respiratory symptoms. Onset can be acute, with fever and malaise, or insidious over many months. The course and prognosis of the disease may correlate with the mode of onset and the extent and severity of organ involvement.(1) The clinical course of sarcoidosis is variable, ranging from self-limiting acute disease to a chronic debilitating disease and death. Fatalities (1–5% of cases) usually occur due to progressive respiratory insufficiency, or central nervous system or cardiac involvement.(2-4) Spontaneous remission or disease stabilization occurs in nearly two-thirds of patients and the course is chronic or progressive in 10 to 30%.(2) Treatment options are limited, with oral corticosteroids limiting active inflammation but not reversing organ damage.(5)

The clinical and pathological presentation of sarcoidosis may differ widely: however, in the large majority of cases there will be lung involvement. Pulmonary sarcoidosis may manifest with various radiological patterns: bilateral hilar lymph node enlargement is the most common finding, followed by interstitial lung disease. To evaluate these features, the most widely used means of assessment has been a modification of the chest radiography classification system

proposed by Scadding.(6) However, according to an international consensus statement on sarcoidosis, the diagnosis is established when clinical and radiological findings are supported by histological evidence of non-caseating epithelioid granouloma.(1) Nevertheless, where there is lung involvement, a presumptive diagnosis can be made based upon typical clinical and radiological findings alone. In a young adult with bilateral hilar lymphadenopathy on chest radiograph, a biopsy would be hard to justify as the diagnosis is likely. In the less common case of diffuse radiographic infiltrates on chest radiograph, particularly in older patients, histological confirmation from biopsy may be justified to rule out other conditions that may be treatable. Therefore, for the majority of patients with disease involving the lung, a diagnosis of sarcoidosis is reasonably certain without biopsy in patients with specific radiographic features.(7)

The diagnosis of sarcoidosis may be delayed, as the disease is often subclinical, self-limited, or the symptoms are minimal.(8) In addition, the disease can affect any organ system, such that cases are referred to a wide range of specialists. These specialists may not consider sarcoidosis in the differential diagnosis. Non-specific symptoms often suggest alternative diseases, resulting in several physician visits until the diagnosis is made.(9) Review of charts for the current study suggests that no standard diagnostic protocol has been followed. Specialist physicians, almost all specializing in internal and respiratory medicine, saw approximately 85% of cases (2554 of 3015 with a physician claim) that were diagnosed in Alberta between 1994 and 2001 inclusive.

Chapter 2 Literature Review

Sarcoidosis affects men and women of all races and ages worldwide. Sarcoidosis occurs predominantly in adults under the age of 40 years, with a peak incidence in those aged 20 to 29 years. A second peak, mainly in women, is present in patients 50 years and older.(10-12) A study in Rochester, New York indicates a slightly higher incidence of sarcoidosis in women (6.3 cases per 100 000 person-years) relative to men (5.9 cases per 100 000 person-years).(10)

Sarcoidosis prevalence estimates range from less than one case to 40 cases per 100 000 population. Ethnicity appears to contribute to susceptibility with the highest prevalence rates reported in Sweden, Denmark, and African Americans in the US.(7) In the US, the annual age-adjusted incidence is 11 cases per 100 000 population in Caucasians, whereas in African Americans, it is much higher at 35.5 cases per 100 000 population.(13)

Tobacco smoking has been associated with a reduced risk of developing sarcoidosis in a number of studies.(14-17) The lower prevalence of disease may be related to an alteration of the immune response due to smoking. Studies of other granulomatous diseases, including hypersensitivity pneumonitis and chronic beryllium disease (CBD), show similar observations where the granulomatous lung disorder is less common among smokers.(18)

Sarcoidosis shows geographical clustering. High prevalence rates occur in countries furthest from the equator(11) and in rural communities.(19-21) Studies in the US have recognized high rates of disease in the rural areas of the Middle Atlantic and South Central States

compared to other regions.(22;23) Increased rates of sarcoidosis were found proximal to the Atlantic coast in South Carolina.(24) Studies have observed seasonal clustering of sarcoidosis cases in winter and early spring.(11) Clustering of the disease by discrete location has been reported in the Isle of Man(25) and in the workplace such as hospitals.(26-28) These reports are consistent with the notion that a contagious agent may be involved in sarcoidosis, as suggested previously.(29)

Employment may be a risk factor for sarcoidosis. Clusters of sarcoidosis have been investigated in hospital staff,(30;31) firefighters,(26;32) and the US Navy.(33-35) Recently, metal machining, metal working, employment in transportation services, and education have shown elevated risks for sarcoidosis in African Americans.(27) Another study found that workers who were suppliers of building materials, hardware, and gardening material were at an increased risk of sarcoidosis, as were educators.(36) The finding that employment in education may be a risk factor for sarcoidosis is consistent with hypotheses suggesting microbial involvement in the etiology of sarcoidosis. However, in both studies, health care occupations including nurses and hospital workers (but not physicians in one study(37)) were not associated with sarcoidosis risk.

The epidemiology of the disease suggests that environmental exposures, interacting with a genetic susceptibility, may be responsible. Familial sarcoidosis has long been recognized. In a case-control study in the US attributable risk for a sibling or parent of a case was approximately 1%.(38) Familial risk and a high prevalence in some ethnic groups support a genetic component to the disease. Genetic markers for familial cases were identified using a genome-wide search for

predisposing genes.(39) The strongest genetic associations with sarcoidosis are found within the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) in humans, which encode class I and class-II genes and other genes responsible for the immune response and inflammation. HLA molecules are the most notable candidates for conferring susceptibility to environmental agents as they are important in antigen recognition and presentation. Changes with the HLA binding site may affect how the antigen complexes with the site and its subsequent recognition when presented to effector cells.

As discussed below, clinical and pathological features of sarcoidosis are similar to other antigen-induced granulomatous disorders, including CBD, and other metal-induced granulomatoses, hypersensitivity pneumonitis due to inhaled organic and inorganic antigens, and fungal and mycobacterial antigen-induced granulomatous lung disease.

The closest analogue to sarcoidosis is CBD, a disease caused by occupational exposure to beryllium. CBD provides an example of a granulomatous lung disease induced by airborne exposure to an inorganic chemical.(40) The development of CBD is associated with sensitization to beryllium salts, most commonly detected using the blood beryllium lymphocyte proliferation test (BeLPT) and more recently using immunological assays. The similarities between sarcoidosis and CBD are close and some investigators (including present authors) have hypothesized that CBD may be sarcoidosis where a cause has been identified.(41) In addition, a clear gene-environment interaction has been demonstrated for CBD with a specific HLA allele. In occupational cohorts with exposure to beryllium, workers with a HLA-DPB1 allele that contains a glutamic acid at position 69 (Glu^{69}) have an increased risk of CBD.(42)

Occupational exposures other than beryllium have been associated with the risk of developing sarcoidosis-like granulomas. Metal dusts of zirconium, nickel, and chromium may also induce granulomatous or interstitial lung disease and should be considered in the differential diagnosis of pulmonary sarcoidosis.(43) One report supports an association of sarcoidosis with man-made mineral fibres with the finding that there were deposits of mineral fibre in 6 of 14 lung tissue samples.(44) Occupation as a firefighter is a risk factor for sarcoidosis and it is thought that environmental exposures related to smoke, along with various combustion products, may be responsible. During the first year after the World Trade Center terrorist attack, New York City firefighters and rescue workers had a higher than expected incidence of sarcoidosis.(45) However, this finding may reflect increased detection rates arising from more frequent use of monitoring chest radiographs in this population after the attack.

Infectious organisms such as mycobacteria, propionibacteria and viruses have been suspected as potential causes of the disease but none of them have been proven.(29) The inability to identify microorganisms by histological staining or culture from pathological tissues continues to be one of the strongest arguments against a potential role for infectious agents in sarcoidosis pathogenesis. However, molecular analysis of sarcoidosis specimens suggests that propionibacteria or mycobacteria have a role in sarcoidosis pathogenesis as discussed below.

Mycobacterium tuberculosis catalase peroxidase (mKatG) protein has been identified as a potential sarcoidosis antigen. mKatG was identified in approximately half of sarcoidosis tissues but in none of the control tissues sampled in a 2005 study.(46) Immunoglobulin G (IgG) was directed toward the mKatG in sarcoidosis patients, indicating an adaptive immune response to

this specific mycobacterial peptide. The identification of mKatG peptide as a possible antigen prompted studies that reported the presence of mycobacterial DNA in 0 to 80% of sarcoidosis tissues.(47) Despite these studies, a etiologically link between sarcoidosis and mycobacteria has remained controversial due to the variability in results from different centers and the lack of corroborating evidence for specific mycobacterial antigens involved in driving the granulomatous inflammation. Recently, reports have documented T-cell responses to select mycobacterial proteins or peptides including a single mKatG peptide in the peripheral blood of subsets of patients with sarcoidosis.(48) T-cell responses were also demonstrated for mycolyl transferase antigen 85A, mycobacterial superoxide dismutase and early secreted antigen target 6 in the peripheral blood and bronchoalveolar lavage (BAL) from sarcoidosis patients.(49;50) Mycobacterial organisms cannot be ruled out as an etiological factor in the pathogenesis of sarcoidosis, given that multiple approaches continue to link exposure to mycobacteria with sarcoidosis.

Propionibacterial organisms have also been shown to be present in sarcoidosis tissues, though the role of these commensal organisms remains uncertain given their normal presence as endogenous flora. A recent multi-center study found DNA from Propionibacteria species in almost all Japanese and European lymph nodes biopsies (106/108 specimens); however, DNA was also reported in 57% of controls.(51) Ebe *et al.* demonstrated antibody responses to a *Propionibacterium acnes* protein fragment in approximately 40% of sarcoidosis BAL samples versus less than 5% of control BAL samples.(52) A role for Propionibacteria in sarcoidosis etiology remains a possibility, but it is yet to be established definitively.

It has been suggested that *Rickettsia helvetica*,(53) a tick-borne bacterium more commonly encountered in rural communities, might be a trigger for the disease but this was not confirmed in subsequent studies.(54;55) *Borrelia burgdorferi*, the causal agent of Lyme disease, could also be responsible for sarcoidosis. A Chinese study found elevated levels of circulating antibody in sarcoidosis patients; however, only 8 to 15% of patients had detectable DNA in the affected tissues.(56;57) Other studies found no association between *B. burgdorferi* and sarcoidosis in other ethnic groups.(58;59)

Based on limited data, cell-wall deficient organisms derived from 'atypical' Mycobacteria, rickettsia, and chlamydial species have been implicated in sarcoidosis. These studies lack confirmation by well-designed laboratory and epidemiological studies. A recent study using blood from matched cases and controls found that isolation of cell-wall deficient organisms was equally frequent in case (38%) and control (41%) groups.(60) Study subjects (197 cases and 150 controls) were a sub-sample from a large study (ACCESS), where cases were recruited from 10 clinical centers across the US and matched (age, sex, and race) controls were identified by random digit telephone dialing methods.

The etiology of sarcoidosis is not known, but a granulomatous response to an antigen in the affected tissue is likely. Etiological agents for sarcoidosis may come from a variety of environmental exposures, both organic and inorganic, as well as from the microbial triggers that have been studied. Rural living consistently emerges as a risk factor for sarcoidosis and exposures that underlie this observation have been suspected as etiological agents. These

exposures include: living and working on farms, infectious agents from untreated milk or water (Mycobacteria) or during the care of animals.

2.1 Literature Review of Environmental Exposures in Sarcoidosis Etiology

A literature search for articles published in English on epidemiological studies investigating relevant risk factors of sarcoidosis was conducted. The following databases were searched: Pubmed MEDLINE (1950-), Web of Science, Medline (Ovid), and Google. Details of the literature search and search strings were presented in Appendix A. With the exception of the ACCESS study, there was a paucity of large-scale multi-center recent epidemiological studies. A few historic, low powered studies were found.

The National Heart, Lung, and Blood Institute (NHLBI) funded A Case Control Etiologic Study of Sarcoidosis (ACCESS) to investigate the association between environmental and occupational exposures and sarcoidosis.(37;61) The study was conducted in ten centers across the US and 706 biopsy-proven cases (736 were enrolled) were compared with 706 age, race, and sex matched controls. Cases were identified using referrals to study sites; while, controls were recruited using random digit dialing methods. Information on exposures was obtained using in-person interviewer-administered questionnaires with unblinded interviewers. Matched cases and controls were analysed in univariate and multivariate models. ACCESS identified exposures associated with sarcoidosis risk, including agricultural employment, insecticides, and microbial bioaerosols.

Work in agricultural employment was reported as a risk factor for sarcoidosis. Using an aggregate variable for exposure (a combined variable that grouped similar occupations and industries), agricultural employment had an association with sarcoidosis in univariate analysis (OR: 1.46, 95% CI: 1.13 to 1.89) but not in multivariate analysis. ACCESS study investigators suggested that the relationship was clinically plausible because workers may encounter a variety of high level exposures to chemicals and aerosolized particulates (grains, bedding, silicates, animal proteins, insect proteins, fungi, bacteria, mycotoxins, and endotoxins). However, no specific exposure(s) in the farm environment was identified. Occupational use of insecticides (agricultural and industrial) had a positive association with sarcoidosis in multivariate analysis. However, the investigators did not inquire about specific categories of insecticide. They suggested that the occupational use of insecticides may be a surrogate for exposures to one or more antigens in the workplace not directly assessed in the questionnaire. In a further analysis of the ACCESS study population, Rossman *et al.* found that genetic predisposition and environmental exposure was important in at least some cases. Gene-environment interactions were detected between two HLA genes and insecticide use at work.(62)

In a study using the ACCESS study population, Kreider *et al*. investigated the relationship between a subset of environmental exposures and the clinical phenotype of sarcoidosis.(63) Cases were classified into groups depending on if they had systemic disease (with or without lung involvement) or lung-only disease. Patients were characterized as having systemic involvement if at least one non-lung organ had either definite or probable involvement, according to the ACCESS organ involvement instrument.(64) Logistic regression analysis was

used for data analysis. In multivariate models, African American cases with systemic disease were less likely to have exposure to wood smoke (OR: 0.36, 95% CI: 0.23 to 0.59) than those with lung-only involvement. Caucasian cases with systemic disease were less likely to have agricultural organic dust exposure (including farming, working with animals, exposure to vegetable dusts, or raising birds) than those with lung-only sarcoidosis (OR: 0.33, 95% CI: 0.16 to 0.71).(63)

Rural living was identified as a risk factor for sarcoidosis in four studies.(19;23;65;66) Sartwell and Edwards documented a risk for sarcoidosis in African Americans associated with living or working on a farm, with no significant risk among Caucasians in this environment.(66) The cohort study followed over a million recruits entering the Navy from 1958 to 1969 and in 1971, there were 85 Caucasian (out of 1 224 883 tested) and 49 African American (out of 59 908 tested) recruits that developed sarcoidosis.

Terris and Chaves conducted a case-control study using sarcoidosis cases seen at two chest clinics in New York City from 1961 to 1965. Cases were compared with matched controls: one with no chest disease and one with active tuberculosis on chest radiography. A single, unblinded public health nurse interviewed study subjects for exposure assessment. The investigators reported a higher proportion of cases with residence on farms at some point in their life than controls (44.2% of cases versus 35.4% of healthy controls versus 34.2% tuberculosis controls).(23) As well, no noteworthy differences in the species of animals or the type of crops grown on the farms were found.

A case-control study was conducted using 62 biopsy-proven cases diagnosed at the Johns Hopkins Hospital from 1940 to 1960.(19) Matched controls were obtained from an outpatient clinic specializing in internal medicine. Two interviewers recorded lifetime residential and occupational histories. Cases were more likely to have ever lived near a farm than controls. Early exposure to farm residence was reported as a risk factor in this study as more cases (59.6%) than controls (38.7%) were born in a rural area or a community with less than 3000 inhabitants. In addition, more cases spent greater than 20% of their lives in rural areas compared with controls; however, the timing of exposure was not reported. In the ACCESS study, cases that lived in a small town (less than 50 000 inhabitants) as a child had an increased risk of sarcoidosis. These reports suggest that the timing of exposure may be important.

Kajdasz *et al*. reported rurally-linked risk factors in the development sarcoidosis in 44 cases and 88 controls in a case-control study in South Carolina. Case exposure histories were collected using questionnaires administered in the clinical setting. Healthy controls were selected using random digit dialing and professional interviewers recorded exposure histories using a computer assisted telephone interview system. Living or working on a farm was found to be associated with sarcoidosis in univariate analysis (OR: 3.4, 95% CI: 1.2 to 9.1).(65) In addition, several rurally-linked risk factors were associated with sarcoidosis in univariate analyses including: the use of wood stoves, coal stoves, fireplaces, and non-public water supplies (OR: 2.2, 95% CI: 1.1 to 4.7). These and other exposures were suggested as etiological agents that underlie the association between rural living and sarcoidosis.

Early case control studies found more cases than controls living in homes without a public water supply. In the study from New York, the investigators found that 58.7% of cases compared with 50.5% of healthy controls ever lived in a home without a public water supply.(23) In the study from Maryland, Buck found 82.3% of cases versus 56.5% of controls used rural or non-public water.(19) Kajdasz *et al*. also found an association between the use of well or spring water and sarcoidosis (OR: 2.4, 95% CI: 1.0 to 5.6).(65) These findings suggest that untreated water may be involved in the development of sarcoidosis. Infectious agents that have been implicated as etiological agents may be transmitted to humans via consumption of untreated water or raw milk. Specific infectious agents (mycobacteria) that may be causally-linked to sarcoidosis can be transmitted through these environmental sources.

Recent epidemiological studies from the US suggest a relationship between sarcoidosis and environments with fungal growth or with high risk of fungal growth. In a study investigating occupational risk factors for sarcoidosis in siblings of an African-American cases, Kucera *et al*. observed that siblings with sarcoidosis were more likely to report indoor exposure to high humidity, water damage, or musty odours than were their unaffected siblings.(27) In the ACCESS study, investigators suggested that microbial bioaerosols were associated with the risk of sarcoidosis. Work environments with mould, mildew and musty odours were used as an indicator of exposure. Positive associations between exposure and sarcoidosis were observed in multivariate analysis (OR: 1.62, 95% CI: 1.24 to 2.11).(37) When cases were differentiated based on clinical phenotype, exposure to moulds was associated with pulmonary-only disease in univariate analysis.(63) A suggestive interaction between exposure to moulds and musty odours

and HLA DRB1*1101 was identified in cases in multivariate analysis.(67) These results appear to support a role for microbial bioaerosols exposure in at least some cases.

Another recent study suggested that exposure to fungi is related to the risk of sarcoidosis. High activities of an airborne enzyme (NAHA), a marker for fungal cell biomass, were found in homes of subjects with newly diagnosed (55 subjects), ongoing (25 subjects), or recurrent sarcoidosis (27 subjects) more often compared with those of healthy controls (30 subjects).(68) Controls were members of the staff and other contacts who were healthy, non-smoking and without respiratory symptoms. Controls appears to have been selected for convenience and they may not be representative of those individuals who would have been selected as cases had they developed the disease.

Taking care of animals was also observed as a risk factor for sarcoidosis in early investigations. In the previously cited study from New York, cases were more likely than controls to have ever taken care of farm animals (32.1% of cases versus 24.2% of healthy controls versus 19.6% of tuberculosis controls). The study found no significant differences in exposure to pets or in types of pets between the groups.(23) Another study also found that cases were more likely to have exposure to farm animals (67.7% of cases versus 38.7% of controls); while differences in exposure to pets were less apparent (87.1% of cases versus 79.0% of controls).(19) Two additional case control studies found no significant association between sarcoidosis and exposure to pets.(14;69) These results do not clarify the relationship between sarcoidosis risk and exposure to animal antigens. In the ACCESS study, reduced risk was

associated with exposures linked to allergic (Th2) responses, such as household cats (OR: 0.65, 95% CI: 0.50 to 0.83) and animal dusts (OR: 0.77, 95% CI: 0.61 to 0.97).

Pine pollen has been suggested as a possible etiologic factor in sarcoidosis. A study from the US observed that communities with a high prevalence of sarcoidosis were more likely to have lumbering and milling as principle industries compared with low prevalence communities.(70) These industries were located in areas with pine forests. In addition, the authors found that the birthplace residence of cases (from a veteran's hospital) correlated with the distribution of pine forests in the US. In Denmark, a study showed that the prevalence of sarcoidosis in counties was related to the percentage of its total area that is composed of coniferous forests.(71) In Scotland, the highest rate of sarcoidosis was in Aberdeen, a city close to the greatest concentration of pine forests in the UK.(72) Early case-controls studies identified an increased risk of sarcoidosis in cases living in close proximity to forests in the US. Terris and Chaves found that cases were more likely than controls to have ever lived in a home 'close to forests' (52.9% of cases versus 46.3% of healthy controls versus 37.9% of tuberculosis controls). The difference was only significant in blacks.(23) Buck identified residence near a forest as a risk factor for sarcoidosis (75.8% of cases versus 51.6% of controls), however, occupations in the lumber industry were not significantly different between cases and controls.(19)

In summary, associations between sarcoidosis and residence on a farm and factors related to such residence were consistently demonstrated in epidemiological studies. However the specific etiological agents in the farm environment were not identified. The investigation reported here was part of a larger case referent study assessing the contribution of environment

and gene-environment interactions in the etiology of pulmonary sarcoidosis. The present investigation was aimed at determining the importance of a spectrum of environmental contaminants (suggestive of a biological etiology) for the risk of pulmonary sarcoidosis when encountered in residences. These environmental exposures included: living on a farm, drinking untreated water or raw milk, smelling mould odours, living with animals, and living near a tract of pine trees. The impact of these exposures in early life was also assessed on sarcoidosis risk, as the timing of exposure may be important.

Chapter 3 Objectives

3.1 General Objective

The objective of this investigation was to examine whether exposure to specific biological factors in the domestic environment is associated with the risk of pulmonary sarcoidosis in adults.

3.2 Specific Objectives

1. To examine exposure to biological factors in residences from birth to diagnosis to determine which factors increased the risk of pulmonary sarcoidosis.

2. To investigate early exposure to biological risk factors in the domestic environment to determine which factors increased the risk of pulmonary sarcoidosis with critical periods of exposure at birth and between birth and age 5.

3. To determine whether risk factors were sustained when adjusting for potential confounding variables including sex, age at diagnosis, and tobacco smoking.

Chapter 4 Methods

4.1 Preliminary work

In this study, we used administrative data collected by a universal public insurance system in the province of Alberta. Alberta Health and Wellness – the government agency responsible for administering the provincial health insurance plan – used a computerized service to record service use and reimburse service providers. All claims submitted to Alberta Health and Wellness must include diagnostic data coded using the ninth revision of the International Classification of Diseases (ICD). In these submissions, physicians were required to name the condition that was the focus of treatment or the outcome of a diagnostic assessment. In the resulting dataset managed by Alberta Health and Wellness, ICD diagnosis codes were identified as primary (main reason for consultation) or secondary (other conditions found at the same time). Only one primary diagnosis was provided; while multiple secondary diagnoses might be given. Each diagnosis code began with a three digit number, a decimal, and up to two digits – to further classify the condition. Although these codes are primarily used for reimbursement and accounting purposes, physician billing claims provided a data source for the study.

In preparation for the study, administrative records were searched for information on sarcoidosis. All services coded ICD 9 135 (sarcoidosis) between 1994 and 2001 (inclusive) were extracted from the Physician Claims database of Alberta Health and Wellness, yielding the

number of individuals for whom a claim had been made in that period. Preliminary work was used to support the protocol adopted.

4.2 Study Design

A case-referent study, using individually-matched clinic-based referents, was conducted in Alberta, Canada. Cases were identified retrospectively from the beginning of 1999 to the end of 2005. The retrospective design of the study meant that those who had died or emigrated were unavailable. Rather than rely on proxy reports, deaths and emigrations were omitted from the data-set.

4.3 Study Population

The study population consisted of men and women attending specialist clinics in general internal or respiratory medicine in Alberta between 1999 and 2005 (for cases) or 2006 (for referents) inclusive.

4.3.1 Cases

Cases were adults who visited a specialist in general internal or respiratory medicine in Alberta and received a first diagnosis of sarcoidosis coded with ICD 9 135 from January 1, 1999 to December 31, 2005. Cases were aged between 18 and <61 years at the time of diagnosis. A first diagnosis meant that the Physician Claims database had no billing code of ICD 9 135 associated with the case Provincial Health Number (PHN) in the period from 1995 to 1999.

4.3.2 Referents

Referents were subjects that were referred to the same specialist clinic as cases, but with other chronic lower respiratory tract diseases. For each case identified, five referents were individually matched to cases on sex, age (± 2 years), and date of clinic visit (within 12 months after the corresponding case visit). Subjects had a diagnosis between 1999 and 2006 from the same physician with ICD 9 billing codes (466, 485, and 490 to 518), representing diagnoses of chronic respiratory conditions (or those that had the potential to be chronic). Subjects with tuberculosis, pulmonary histoplasmosis, and hypersensitivity pneumonitis (ICD 9 codes 011, 015, 495) were not selected as referents because these diagnoses may represent a misdiagnosis of sarcoidosis. Subjects with carcinoma of the lower respiratory tract (ICD 9 codes 162 to 163) and subjects with cystic fibrosis (ICD 9 code 277) were omitted. Referents were only used once.

4.4 Identification of Cases and Referents

4.4.1 Data Sources

Subjects were identified using Alberta Health and Wellness administrative databases using the participant unique PHN. The Physician Claim database, which represents province-wide coverage for services, was used to identify subjects with sarcoidosis and referent diagnoses, which were recorded as either primary or secondary (using the first 3 codes). The subjects had to be registered with the Alberta Health Care Insurance Plan (AHCIP) at the time of patient identification in order to be selected for the study. The AHCIP registry covers virtually all residents in the province except a small proportion of special population groups (members of the

Armed Forces and RCMP, federal inmates, persons from other provinces during their first 3 months in Alberta, and self-insured).

4.4.2 Specialist Collaboration

All active internal and respiratory medicine specialists in Alberta, with the exception of those unlikely to diagnose sarcoidosis because their practice was confined to a speciality listed in Appendix B, were approached to collaborate in identifying subjects. Specialists were asked to sign and return a consent form (Appendix C), indicating that they would allow Alberta Health and Wellness to access their billing information and to identify subjects for the study. Physicians who agreed to participate were asked to provide their practice identification number on the consent form and to tick a box indicating their agreement. The consent form provided the option for physicians to indicate that they do not see adult patients or have not seen adult patients since January 1999.

Alberta Health and Wellness identified subjects with an ICD 9 claim code of 135 (sarcoidosis) from any physician from 1995 to 1999. The physician claims database was searched on two separate occasions (May 2006 and April 2007) to identify cases from collaborating specialists. Diagnosis dates between 1999 and 2003 were sought in the first search and between 1999 and 2005 (newly collaborating physicians had cases from 1999 to 2003 in this search) in the second search. Cases were only selected when there was no previous claim made by any physician in the period before the study.

Alberta Health and Wellness prepared a list for each collaborating physician identifying cases and referents. The list for each physician was supplied in an opaque, sealed envelope with the name and address of the physician labelled on the front. The list was opened, under the guidance of the physician, and the chart review proceeded with a pre-scheduled visit. On the list, each case was given an identification number and matched referents (for that case) were given the identification numbers following it.

4.4.3 Chart Review

Physicians were asked to provide information on their patients through a brief chart review (conducted by JRS, JB). Information from charts was recorded on extraction forms (Appendix D) intended for either a case or a referent. All extraction sheets were labelled with the identification number provided on the list from Alberta Health and Wellness. Referents were also labelled with the corresponding case identification number.

On a lap-top computer, information for all cases and referents obtained during chart review was entered into a spreadsheet. Any documents needed to recruit subjects were prepared at the time of the chart review using the electronic spreadsheet. The list from Alberta Health and Wellness and a full-copy of the spreadsheet was saved and stored by the physician. Due to patient confidentiality, all personal identifiable information from the chart review was removed from electronic documents in study investigator files. These files were maintained separately from the questionnaire data for the purpose of tracking participants during fieldwork. Extraction

sheets with contact information did not leave the physician clinic or medical record storage facility.

4.4.3.1 Cases

The case definition was based on the clinical diagnosis of sarcoidosis made by the specialist physician; however, it included only cases with pulmonary involvement. For each case, the patient medical record was examined and the diagnostic criteria were recorded on the extraction sheets. Supporting documentation included records for symptomology, radiographic findings, pathology reports, and any additional information from further investigations. When cases had a biopsy; the tissue, site, and other details from the pathology report were recorded. Based on the information that could be obtained from the chart, cases with a previous diagnosis of sarcoidosis were excluded if the diagnosis preceded the inclusion date. As well, the medical record was used to determine as much as possible that the patient was alive and living in Alberta or another Canadian province. Although rare, subjects with very limited expected survival based on the clinical judgement of physician researchers were not followed up. Cases requiring a lung transplant were included.

4.4.3.2 Referents

The medical records of referents were also reviewed (JB, JRS) to ensure the diagnosis was consistent with the billing code. Referents were omitted when the diagnosis in the chart represented a condition that was excluded during selection (tuberculosis, hypersensitivity pneumonitis, histoplasmosis, lung cancer, cystic fibrosis) or when the diagnosis was not a

respiratory condition at all. Referents who received a diagnosis code for an acute respiratory disease that resolved completely with no underlying condition were excluded.

4.5 Subject Recruitment

Specialists were asked to sign letters personally addressed to their patients inviting them to participate in the study (Appendix E). The letters were sent, along with an information sheet and written informed consent form, to all eligible cases and referents using the addresses on file at the physician's office. A stamped self-addressed return envelope accompanied the consent form. In the letter, recipients were instructed to return the consent form and tick one of the two boxes on the form, marking whether they would agree to participate or not. Subjects who volunteered to participate were asked to write their telephone number and address on the form. When the consent form was received, a package was sent to those who agreed to participate in the study. Instructions were provided concerning the contents of the package. The package contained three forms to prompt subjects to recall information related to their residential and occupational exposures and if necessary obtain further information (Appendix F). In addition to the forms, a kit used to collect a sample of genetic material from mouthwash, as outlined in the study protocol, was provided (a DNA sample was taken to assess genetic factors involved in the disease). After one week from the date the package was sent, subjects were phoned to confirm that they received the package and to arrange a time for the telephone interview. Interviewers called the study participants at the pre-arranged time to complete the questionnaire.

Two reminder letters, which were signed by the physician at the time of the chart review, were mailed after 3 and 6 weeks to non-responders. When letters were returned to our office by the postal service, an updated address was requested from administrative staff in the physician`s office. When a new address was available, the letters were re-sent to the updated address.

4.6 Ethical Considerations

Informed consent was obtained from each study participant. All subjects were made aware that participation in the study was voluntary and that non-participation did not affect the health care they received. An information sheet (Appendix E) was provided, along with the invitation to participate, on details about the study, including how information would be processed, stored and used. A contact phone number was also provided for questions.

The study was approved by all relevant Health Ethics Review Boards in the appropriate health regions (Appendix G).

4.7 Exposure Assessment

The subject having agreed to an interview was sent the mail out questionnaire (Appendix F) to be completed and to have available at the time of interview. In a standard manner, the interviewer reviewed the information for each residence and each occupation with the participant and collected additional data if necessary. Interviewers recorded responses on a hard-copy questionnaire. Consequently, a lifetime residential and occupational history was obtained, along with a record of work in specific industries. Details on demographic information, education,

leisure activities, medical history and tobacco consumption were also recorded. For each residence, information on the presence of exposure was obtained for any residence longer than 3 months. Interviewers were blind to the case or control status of the subjects and they were not aware of the study hypotheses.

4.7.1 Questionnaire

The questionnaire was designed to test hypotheses regarding the contribution of residential, occupational, and industrial exposures in the etiology of pulmonary sarcoidosis. Environmental exposures associated with the risk of sarcoidosis suggested in previous studies were assessed on the questionnaire. To inform this process, questionnaires designed for use in an earlier study in the US (ACCESS) and others were critically evaluated. In addition, the questionnaire was tested and refined following a pilot study in subjects in the Edmonton-area.

Exposure assessments for the contaminants of interest in this investigation were taken from the domicile portion of the questionnaire, which was embedded in the larger questionnaire. The domicile portion of the questionnaire was completed for each residence reported in the participant`s life. It consisted of questions concerning specific exposures in the domestic environment with check-boxes to indicate presence or absence of exposure.

4.7.2 Data Coding and Entry

The data from questionnaires was manually coded on structured coding forms using detailed coding instructions. The coding forms were entered by a professional company and data was checked by the study investigators.

The resulting data was checked for errors by manual data checks, outlier value checks with variable frequency tables, and cross-tabulations. In the case of errors or inconsistencies, data was checked with the original questionnaire.

4.8 Variables for Analysis

4.8.1 Demographic Variables

Sex and age at diagnosis were used in the analysis. Age at diagnosis was calculated using date of birth and date of diagnosis.

For non-collaborating referents where no date of birth was available, year of birth and age at diagnosis was estimated. The referent date of birth was estimated using the date of birth plus 6 months from the corresponding individually matched case. Age at diagnosis (date of diagnosis minus date of birth) and year of birth were derived from the estimated date of birth.

4.8.2 Exposure Variables

Exposures were taken from residential histories supplied on the domicile questionnaire in Appendix H. Exposures of interest were analysed as binary (presence or absence) variables.

Exposure was present for any residence when the following were reported on the questionnaire for the sarcoidosis risk factors listed below:

- Living on a working farm (question 2) was defined as farm or hobby farm.

- Drinking untreated water (question D1 part (a)) was determined from reported water supply. Exposure was defined as no piped water from the utility company.

- Drinking raw milk (question D6) was any response where the type of milk was supplied from a farm in any capacity. These responses were: direct from a local farm or both bought in a store and direct from a local farm. Interviewers recorded other sources of milk when the source of milk was not specified as on option on the questionnaire. When the subject did not drink milk, the response was coded as not applicable.

- Smelling mouldy odours in the dwelling (question D8c) was reported as yes, no, or uncertain. Exposure to mouldy odour was defined as a response of yes.

- Living with at least one pet or animal (question D7) was reported as yes or no. Exposure to animals was defined as a response of yes.

- Close proximity to a tract (>20 trees) of evergreen trees (question D10a and question D10c) was a composite variable. The distance to the nearest tract of trees was less than 200 meters and the closest type of trees was evergreens.

Unknown was coded when the subject did not know if the exposure was present or not. The other available responses indicated absence of exposure, except when the information was missing.

Due to reported geographic differences in the distribution of sarcoidosis, birth in non-tropical regions (Canada, US, Europe, Australia) was compared with birth in tropical regions (East India, Caribbean, Central America, Africa, South East Asia, South America) using question 2 from the questionnaire. A region was considered tropical when the region (or part of the region) was located in the Tropics (between the Tropic of Cancer and Tropic of Capricorn).

4.8.3 Other Exposures

Smoking was identified as a potential confounder because of its strong relation to sarcoidosis as reported in previous studies. Information on smoking tobacco or tobacco products was obtained on the questionnaire. Smokers were subjects who reported a history of ever smoking tobacco, while non-smokers reported no tobacco smoking.

4.8.4 Exposure Time Periods

Duration of exposure was calculated using the time in each residence with exposure. Exposure variables were created by summing the questionnaire responses across residences in two periods: birth to 5 years and birth to the age at sarcoidosis diagnosis (for referents: the date of diagnosis in the corresponding case). The presence of an exposure was coded as ‘1’ or positive and the absence of an exposure was coded as ‘0’ or no exposure. When information was

missing for the whole period, it was counted as missing. However, when information was available for part of a period, it was counted as positive when positive. The number of years exposed for each variable was calculated from the dates at each residence, as reported on the questionnaire.

4.9 Statistical Methods

Data management, descriptive statistical analyses, and logistic regression analyses were performed using STATA statistical software.

4.9.1 Matched or Unmatched Analysis

The planned analysis was changed because of the small number of cases with at least one matched referent (as shown in the Results section below). The primary analysis was the unmatched analysis, allowing for sex, age, and smoking. For multivariate models, an additional matched analysis (a conditional logistic regression) was performed for cases with one or more referents to determine if the findings supported the primary analysis used in the study.

4.9.2 Unmatched Analysis

Exposure for each variable was determined for all residences throughout the participants' lifetime. Categorical data was presented using cross-tabulations of the number of cases exposed versus the number of referents exposed. Chi-square tests were used to compare proportions between case and referent groups. Continuous data was presented using means and standard

deviations. Differences in continuous variables were assessed by *t*-tests (two-tailed). Age at diagnosis was categorized into four age groups using quartiles.

Unadjusted odds ratios and 95% confidence intervals were estimated for each exposure variable in each exposure period using unconditional logistic regression analysis. For all multivariate analyses, odds ratios were adjusted for potential confounding factors including sex, age, and smoking. As a first stage, all environmental exposure variables in each time period were entered into the multivariate model. In one model, interactions between age at diagnosis and smoking were calculated and tested for significance. The significance of the interaction terms was tested by comparing the likelihood ratio of the models (with and without the interaction term). Finally, independent variables whose significance was $p \leq 0.20$ in bivariate analysis were entered into a multiple logistic regression model using a backward step-wise procedure. The significance level for the multivariate models was $p \leq 0.05$. Collinearity between variables was explored using Pearson Correlation.

4.9.3 Response Rates

Response rates in cases and referents were calculated based on the number of subjects whom we attempted to contact. In calculating this rate, response implied that the patient agreed to participate and completed the questionnaire.

4.9.4 Participants versus Non-participants

For cases and referents identified by Alberta Health and Wellness, participants and non-participants were compared on age at diagnosis, sex, and year of birth using chi-square tests for categorical variables and *t*-tests for continuous variables.

4.9.5 Subgroup Analysis

In addition to the main comparison, analyses were performed differentiating referents diagnosed with asthma and referents diagnosed with another respiratory disease. The code that was indicative of asthma (ICD-9 code 493.*, where "*" could represent any valid digit) was used to differentiate asthma referents, while all other referent ICD-9 codes were used to comprise the non-asthma referent group. Analyses (matched and unmatched) were also conducted with matched clusters, a subgroup of cases that had at least one available matched referent. Additional sub-analyses divided cases with and without tissue confirmation of sarcoidosis (noncaseating granulomas of one or more, lung or non-lung, organs on biopsy) and compared them with referents.

Chapter 5 Results

5.1 Specialist Response Rates

Six hundred and fifty two respiratory and internal medicine specialists were identified in the College of Physicians and Surgeons of Alberta directory. Of the 652 physicians identified, 467 specialists were approached to collaborate in the study. The remaining specialists were not contacted because their practice was inactive (16 physicians) or restricted to a speciality unlikely to diagnose sarcoidosis (167 physicians). These specialities included: oncology (35 physicians), bone marrow or kidney transplant (3 physicians), critical care (8 physicians), paediatrics (8 physicians), laboratory medicine (3 physicians), obstetrics or gynaecology (3 physicians), medical examiner (1 physician), clinical nutrition (1 physician), palliative care (1 physician), nephrology (34 physicians), gastroenterology or hepatology (45 physicians), geriatrics (15 physicians), sexually transmitted diseases (4 physicians) and other specialities unlikely to diagnose sarcoidosis (6 physicians).

Of the 467 specialists asked to collaborate in the study, 331 specialists replied. Two hundred and fifty four specialists agreed to collaborate, while 77 specialists did not agree. Of the 77 specialists, thirteen used the option provided on the form to indicate that they do not see adult patients or they have not seen adult patients since January 1999. Additional reasons that specialists did not agree to collaborate included: no outpatient practice (4 physicians), no suitable

sarcoidosis patients (23 physicians), not in Alberta (7 physicians), retired (8 physicians), and no explanation (24 physicians).

The physician claims database of Alberta Health and Wellness was used to identify cases diagnosed by the 254 collaborating specialists, 76.7% of the 331 specialists who replied. One hundred and ten specialists had at least one case of sarcoidosis between 1999 and 2005 (inclusive) and 1826 sarcoidosis cases were identified in total.

5.2 Subject Response Rates

The number of individuals at each stage of the study is presented in Figure 5.1. A total of 7761 subjects (1826 cases, 5935 referents) were potentially eligible for the study. However, only 6840 subjects (1629 cases, 5211 referents), 88.1% of the initial population, were screened in a chart review. The majority of the subjects who were not screened came from the Calgary health region (n=905, 98%). Reasons these subjects were not in the chart review included: the absence of generic research consent forms from one outpatient clinic that recently introduced such a form (3 physicians, 376 subjects), physician discontinued participation due to workload (4 physicians, 291 subjects), physician was unable to access records (1 physician, 243 subjects), or physician was retired and we were unable to trace them (2 physicians, 11 subjects).

Subjects were considered eligible for the study when a diagnosis, concordant with the ICD 9 code, was found in the available medical records from a subject thought to be living. Of 6840 subjects, 5473 subjects (1392 cases, 4081 referents) were approached with a letter for

participation in the study, while the remaining 1367 subjects (238 cases, 1129 referents) were not contacted, as follows.

Upon medical records review, 238 cases were not contacted based on the reasons specified in the Methods in Chapter 3. These reasons included: dead (19 subjects), coding error (52 subjects), not pulmonary sarcoidosis (51 subjects), sarcoidosis diagnosis preceded inclusion date (40 subjects), limited survival anticipated (11 subjects), lung cancer (4 subjects), outside Canada (9 subjects), and chart not found or insufficient information to contact (52 subjects). We did not invite 1129 referents to participate in the study for the following reasons: dead (172 subjects), coding error (73 subjects), no chronic pulmonary condition but not a coding error (523 subjects), previous sarcoidosis diagnosis (59 subjects), limited survival anticipated (32 subjects), lung cancer (61 subjects), tuberculosis (31 subjects), cystic fibrosis (23 subjects), hypersensitivity pneumonitis (6 subjects), histoplasmosis (5 subjects), outside Canada (5 subjects), no fixed address (3 subjects), consult not for pulmonary condition (6 subjects), and chart not found (130 subjects).

Of the 5473 subjects contacted, 2661 subjects (48.6%) responded and 2216 subjects (40.5%) agreed to participate while 445 subjects (8.1%) did not give their consent. A small portion (3.5%) of those that agreed to participate did not complete the questionnaire. A total of 684 cases (from a total of 1392 contacted) completed the questionnaire, giving 49.1% participation for cases. Participation for referents was 35.6% with a total of 1454 referents (from a total of 4081 contacted) completing the questionnaire.

Seventy cases (5% of cases contacted) returned the consent form and were not willing or able to participate in the study for the following reasons: dead (4 subjects), emigrated outside Canada (3 subjects), and no explanation (63 subjects). Three hundred-seventy five referents (9.2% of referents contacted) did not participate with the following reasons noted on the consent form: dead (38 subjects), severe illness (7 subjects), unable to speak English (3 subjects), incarcerated (1 subject), no fixed address (2 subjects), no respiratory disease (1 subject), emigrated outside of Canada (7 subjects), and no explanation (316 subjects).

For the analysis, 2138 completed the questionnaire (684 cases, 1454 referents), while we were unable to contact the remaining 78 subjects after several attempts before the end of the study (May 2009).

5.3 Participants versus Non-participants

5.3.1 Cases

More than half (56.7%) of sarcoidosis cases identified by Alberta Health and Wellness were male. Amongst the participating cases, 57.2% were male, while 56.5% of non-participants were male (Table 5.1). This difference was not statistically significant (χ^2 (1) = 0.04, P=0.94).

For sarcoidosis cases identified by Alberta Health and Wellness from collaborating specialists, the mean age at diagnosis (standard deviation or SD) was 42.0 (10.1) years. The mean age at diagnosis (SD) for case participants was 43.9 (9.60) years, while for non-participants it was 40.9 (10.3) years. Case participants were significantly older than non-

participants ($t(1824) = 6.18$, $P<0.001$). Cases that were born in earlier decades were significantly more likely to participate in the study than cases that were born in later decades as shown in Table 5.2.

5.3.2 Referents

As shown in Table 5.1, 53.8% of referent respiratory patients identified by Alberta Health and Wellness were male. Among referent participants, 49.8% were male; while among non-participants, 55.1% were male. The proportion of male referents that participated in the study was significantly less than the proportion of male referents who did not participate (χ^2 (1) = 12.5, $P<0.001$).

For all referents identified by Alberta Health and Wellness, the estimated mean age at diagnosis (SD) was 43.9 (10.3) years. Referent participants mean age at diagnosis (SD) was 45.9 (10.0) years, while non-participants had an estimated mean age at diagnosis (SD) of 43.2 (10.3) years. Older referents were significantly more likely to agree to participate in the study compared to those who were younger ($t(5933) = 8.75$, $P<0.001$). Referents born in earlier decades were significantly more likely to participate in the study than referents born in later decades as shown in Table 5.2 ($\chi^2(5) = 71.6$, $P<0.001$).

5.4 Matched Clusters

The number of participating cases with at least one corresponding matched referent was 382. Of the 382 cases belonging to a cluster, there was one referent per case in 208 clusters, two

referents per case in 93 clusters, three referents per case in 54 clusters, four referents per case in 24 clusters, and five referents per case in 3 clusters.

Chapter 6 Analysis of Study

6.1 Identification of Subgroups

6.1.1 Cases with Tissue Confirmation

Histological evidence supporting a diagnosis of sarcoidosis was obtained in 344 cases (50.3% of participating cases) using diagnostic information obtained during the chart review. Cases with biopsy of lung (with or without an additional non-lung organ) (204 subjects) and non-lung (140 subjects) tissues or no biopsy supportive of sarcoidosis (340 subjects) were considered separately. The non-lung tissues biopsied were presented in Table 6.1.

6.1.2 Referent Diagnoses

Referent diagnoses (1454 subjects) were reported in Table 6.2. During analysis it became apparent that the referents comprised two main groups, those with asthma and those with other conditions. Referents diagnosed with asthma (838 subjects) and non-asthma diagnoses (616 subjects) were considered separately for some comparisons as the results of these comparisons differed.

6.2 Demographic Characteristics

Despite matching on sex, more cases (57.2%) than referents (49.8%) were male as shown in Table 6.3 (χ^2 (1)=10.1, *P*=0.001). This difference was most apparent comparing case with

asthma referents, where the asthma referents included of a large proportion of females (53.9%). More cases than asthma referents were male (χ^2 (1)=18.6, P<0.001). However, no significant difference in sex was observed between cases and non-asthma referents (χ^2 (1)=0.69, P=0.41).

The mean age at diagnosis (SD) for the entire population was 45.2 (9.93) years. Despite matching on age, cases were younger than all referents at diagnosis (mean age (SD): 43.9 (9.60) versus 45.9 (10.0) years, respectively; t(2136)=4.44, P<0.001). The mean age at diagnosis for asthma referents was 43.2 (9.82) years and for non-asthma referents was 49.5 (9.13) years. The differences were significant for cases versus non-asthma referents (t(1298)=10.7, P<0.001); but not for cases versus asthma referents (t(1520)=1.40, P=0.16).

In multivariate analyses, age at diagnosis was treated as a categorical variable and it was divided into quartiles. The age ranges for the four quartiles (Q1-Q4) was as follows: Q1: ≤38.3 years, Q2: >38.3 to ≤46.3 years, Q3: >46.3 to ≤51.2 years, Q4: >51.2 years. As shown in Table 6.4, a higher percentage of cases (30.1%) than referents (23.4%) were diagnosed in the youngest age group (≤38.3 years). As age of diagnosis increased, the proportion of cases relative to referents decreased. Asthma referents were represented more frequently than non-asthma referents in the younger age groups. The age distribution of cases and asthma referents was similar. In contrast, non-asthma referents were over-represented in the two oldest age categories.

6.3 Smoking

The overall rate of ever smoking was 65.5%. Cases were less likely to have ever smoked than all referents (412/684, 60.2% versus 988/1454, 68.0% respectively; OR: 0.71, 95% CI: 0.59

to 0.86). No significant difference was observed between cases and asthma referents (58.9% or 494/838; OR: 1.06, 95% CI: 0.86 to 1.30) but cases were less likely to have ever smoked than non-asthma referents (80.2% or 494/616; OR: 0.37, 95% CI: 0.29 to 0.48).

6.3.1 Smoking and Sex

Among males and females the proportion of smokers was similar overall (65.8% and 65.1% respectively). Among cases, the proportion reporting ever smoking was higher in females (61.8%) than males (59.1%) whereas among referents, it was higher in males (69.5%) than females (66.4%) (Table 6.5). Non-asthma referents had substantially higher rates of smoking than asthma referents in both sexes; but this difference was more pronounced in males.

Cases were less likely to smoke than all referents among both males and females (OR: 0.63, 95% CI: 0.49 to 0.82, OR: 0.82, 95% CI: 0.62 to 1.08, respectively). No differences in reported ever smoking between cases and asthma referents were found for males (OR: 1.04, 95% CI: 0.79 to 1.39) or females (OR: 1.09, 95% CI: 0.81 to 1.47). However, cases were less likely to smoke than non-asthma referents in both males and females (OR: 0.31, 95% CI: 0.22 to 0.43 and OR: 0.47, 95% CI: 0.33 to 0.68, respectively).

6.3.2 Smoking and Age at Diagnosis

Among cases, the mean age at diagnosis was 42.8 (10.0) and 45.5 (8.69) years for ever and never smokers, respectively. In contrast, among referents, the mean age at diagnosis was 47.0 (9.65) and 43.5 (10.4) for ever smokers and never smokers, respectively.

The overall proportion of subjects that reported ever smoking increased for each age at diagnosis quartile, from 61.3% in the youngest group to 72.2% in the oldest group. However, this obscured differences between cases and referents. Among cases, the proportion of those that reported ever smoking was highest in the youngest age group (67.0%) and decreased for each subsequent age group (Table 6.6). In contrast, the proportion of referents that reported ever smoking increased for each age quartile. This was observed in both asthma and non-asthma referents. As noted previously (Table 6.4), asthma referents were over-represented among young referents; while non-asthma referents were over-represented among older referents. In general, non-asthma referents had a higher percent of smokers than asthma referents.

In the youngest age group (Q1: ≤38.3 years), cases were more likely than all referents (OR: 1.47, 95% CI: 1.03 to 2.12) to smoke. Cases were also more likely to smoke than asthma referents (OR: 1.64, 95% CI: 1.13 to 2.40). No differences in smoking between cases and non-asthma referents (OR: 0.97, 95% CI: 0.55 to 1.72) was observed in this age group.

In the second quartile (Q2: >38.3 to ≤46.3 years), the rates of smoking were not different for cases compared with all referents (OR: 0.80, 95% CI: 0.56 to 1.16) or asthma referents (OR: 1.13, 95% CI: 0.76 to 1.68). When cases were compared with non-asthma referents, cases were less likely to smoke than non-asthma referents in this age groups (OR: 0.37, 95% CI: 0.22 to 0.63)

Cases were less likely to smoke than all referents in the oldest two quartiles (Q3: >46.3 to ≤51.2 years and Q4: >51.2 years) (OR: 0.54, 95% CI: 0.37 to 0.79 and OR: 0.38, 95% CI: 0.25 to

0.57, respectively). There was no difference in smoking for cases and asthma referents in these age groups (Q3 OR: 0.82, 95% CI: 0.54 to 1.24 and Q4 OR: 0.63, 95% CI: 0.39 to 1.03). Cases were less likely to smoke than non-asthma referents (Q3 OR: 0.54, 95% CI: 0.37 to 0.79 and Q4 OR: 0.25, 95% CI: 0.16 to 0.41).

6.3.3 Smoking, Age at Diagnosis, and Sex

In Figure 6.1, the proportion of cases and referents that reported ever smoking was presented for (a) males and (b) females by age at diagnosis quartile. For both males and females, the proportion of smokers was highest among cases in the youngest age group (≤38.3 years). Among referents, smoking increased with age for both sexes. This increased was observed in asthma and non-asthma referents; however, the difference for females appeared to be a smaller.

6.1 Bivariate Analyses of Biological and Environmental Risk Factors

6.1.1 Residences from Birth to Diagnosis

Thirty-five percent of the entire population ever had residence on a farm. Overall, no significant differences were observed between cases and all referents (OR: 0.99, 95% CI: 0.82 to 1.20). Cases showed no statistically significant difference in the frequency of ever living on a farm compared with asthma and non-asthma referents (OR: 1.14, 95% CI: 0.92 to 1.41 and OR: 0.84, 95% CI: 0.66 to 1.03 respectively). (Table 6.7)

From birth to diagnosis, more than half of the population (53%) reported ever drinking un-piped water in their residences (Table 6.8). No significant differences were observed between

cases and referents overall (OR: 1.08, 95% CI: 0.90 to 1.29). Cases were **more** likely to ever drink un-piped water than asthma referents (OR: 1.36, 95% CI: 1.11 to 1.67). Cases were **less** likely to ever drink un-piped water than non-asthma referents (OR: 0.78, 95% CI: 0.62 to 0.97).

Overall, ever drinking untreated milk prior to diagnosis was reported in 27.5% of subjects (Table 6.9). No significant difference was observed between cases and all referents (OR: 1.00, 95% CI: 0.82 to 1.23). Cases were more likely than asthma referents (OR: 1.21, 95% CI: 0.96 to 1.52) and they were less likely than non-asthma referents (OR: 0.79, 95% CI: 0.63 to 1.01) to drink untreated milk. These differences approached significance.

Thirty-two percent of the population reported mouldy smell in one or more of the residences prior to diagnosis (Table 6.10). No statistically significant differences were observed between the groups in exposure to mouldy smell when cases were compared with referents (OR: 0.89, 95% CI: 0.74 to 1.09), asthma referents (OR: 0.82, 95% CI: 0.66 to 1.02), or non-asthma referents (OR: 1.00, 95% CI: 0.79 to 1.27).

The majority of subjects reported at least one pet in the home from birth to diagnosis (91.6%). Ever exposure to pets was not statistically significantly different for cases and referents (OR: 0.95, 95% CI: 0.69 to 1.32), asthma referents (OR: 1.01, 95% CI: 0.71 to 1.45), or non-asthma referents (OR: 0.88, 95% CI: 0.59 to 1.31). (Table 6.11)

A tract of evergreen trees with close proximity to residences from birth to diagnosis was reported in 30.2% of the population overall (Table 6.12). A few subjects did not know if any of their residences was close to a tract of evergreen trees (0.3%). When cases were compared with

referents (OR: 0.94, 95% CI: 0.77 to 1.15), asthma referents (OR: 1.05, 95% CI: 0.84 to 1.32), or non-asthma referents (OR: 0.81, 95% CI: 0.64 to 1.03), there were no statistically significant differences in ever exposure to a tract of evergreen trees with close proximity to residence from birth to diagnosis.

6.1.2 Birthplace Residence

Overall, 94.3% of the population was born in a non-tropical region of the world, with the majority born in Canada (86%). Birth in non-tropical regions was not different between cases and all referents (OR: 0.76, 95% CI: 0.52 to 1.10), asthma referents (OR: 0.83, 95% CI: 0.54 to 1.26), or non-asthma referents (OR: 0.66, 95% CI: 0.41 to 1.07). (Table 6.13)

Overall, 21.4% (457/2138) of the population had residence on a farm (including a hobby farm) at birth. No significant differences in farm residence were observed between cases and referents as a whole (OR: 1.13, 95% CI: 0.91 to 1.41). Cases reported birthplace residence on a farm more frequently than asthma referents (OR: 1.34, 95% CI: 1.05 to 1.73). Non-asthma referents showed no significant difference in the frequency of farm residence compared with cases (OR: 0.92, 95% CI: 0.71 to 1.19). (Table 6.14)

In birthplace residence, the overall use of un-piped water was 26.4% (564/2138). A substantial portion of the subjects did not know if the water supply was piped or not (27.2%). Overall, no significant difference in the amount of piped water was observed between cases and referents (OR: 1.05, 95% CI: 0.84 to 1.31) when unknowns were excluded. Cases were **more** likely to have un-piped water exposure in birthplace residence than referents with asthma (OR:

1.44, 95% CI: 1.12 to 1.86). In contrast, cases were **less** likely than non-asthma referents to have un-piped water exposure in birthplace residence (OR: 0.71, 95% CI: 0.55 to 0.92). (Table 6.15)

Mouldy smell in the birthplace dwelling was present in 5.3% of the study population. A substantial portion of the population (36%) was uncertain if mouldy odour was present. After excluding unknown, no statistically significant differences were observed between the groups in exposure to mouldy smell when cases were compared with referents (OR: 0.78, 95% CI: 0.51 to 1.20), asthma referents (OR: 0.74, 95% CI: 0.46 to 1.18), or non-asthma referents (OR: 0.84, 95% CI: 0.50 to 1.40). (Table 6.16)

At least one animal was kept as a household pet at the birthplace residence in 46.2% of the population. Subjects did not know if there was a household pet in 26.8%. Presence of pets was not statistically significantly different for cases compared with referents (OR: 1.03, 95% CI: 0.83 to 1.29), asthma referents (OR: 1.07, 95% CI: 0.84 to 1.36), or non-asthma referents (OR: 0.98, 95% CI: 0.75 to 1.28) when unknowns were excluded. (Table 6.17)

Overall, 5.4% of subjects reported a tract of evergreen trees within 200 meters of the birthplace residence. A substantial portion of subjects (27.4%) reported that they did not know if there was a tract of evergreen trees nearby. With unknowns excluded, there was no significant difference observed between cases and referents overall (OR: 0.96, 95% CI: 0.64 to 1.44). No statistically significant difference in the proximity of the birthplace residence to a tract of evergreen trees was observed between cases and asthma referents (OR: 0.88, 95% CI: 0.57 to 1.37), or non-asthma referents (OR: 1.10, 95% CI: 0.66 to 1.44). (Table 6.18)

6.1.3 Residences from Birth to 5 Years

In residences from birth to 5 years of age, the overall rate of farm residence was 24.6%. There was no significant difference between cases and referents as a whole (OR: 1.12, 95% CI: 0.91 to 1.38). Cases were more likely to have residence on a farm between birth and 5 years than asthma referents (OR: 1.33, 95% CI: 1.05 to 1.69). Non-asthma referents were not significantly different than cases in the frequency of farm residence (OR: 0.91, 95% CI: 0.71 to 1.16). (Table 6.19)

From birth to age 5, the rate of un-piped water use was 32.3% overall. However, 8.2% of the population did not know if the water supply was piped or not in any residence to age 5. Ever exposure to un-piped water in the first 5 years was not significantly different between cases and referents (OR: 1.11, 95% CI: 0.91 to 1.34) when unknowns were excluded. Cases were **more** likely to be exposed to un-piped water than asthma referents between birth and age 5 (OR: 1.46, 95% CI: 1.16 to 1.83). Cases were **less** likely to be exposed to un-piped water than non-asthma referents (OR: 0.78, 95% CI: 0.62 to 0.98). (Table 6.20)

Early exposure (birth to age 5) to untreated milk was reported in 21.2% of the population. Overall, 16.4% of subjects did not know the source of their milk supply from birth to age 5. No significant differences were observed between cases and referents as a whole (OR: 1.12, 95% CI: 0.89 to 1.40) when unknowns were excluded. Case were **more** likely to drink untreated milk than referents with asthma before age 5 (OR: 1.43, 95% CI: 1.10 to 1.86). Non-asthma referents

showed no significant difference in early exposure to un-treated milk compared with cases (OR: 0.83, 95% CI: 0.64 to 1.08). (Table 6.21)

Ever exposure to mouldy smell from birth to 5 years old was reported in 7.3% of the population overall. A substantial portion of the population was uncertain if a mouldy odour was present in the home from birth to 5 years old (10.2%). No statistically significant difference were observed between the groups in exposure to mouldy smell when cases were compared with referents (OR: 1.05, 95% CI: 0.74 to 1.48), asthma referents (OR: 0.98, 95% CI: 0.67 to 1.45), or non-asthma referents (OR: 1.14, 95% CI: 0.75 to 1.76) when unknowns were excluded. (Table 6.22)

Between birth and age 5, 61.3% of subjects reported a household pet. Overall, 7.5% of subjects did not know if they had a pet in these early years. Ever exposure to pets from birth to 5 was not statistically significantly different for cases and referents (OR: 1.08, 95% CI: 0.88 to 1.32), asthma referents (OR: 1.08, 95% CI: 0.86 to 1.34), or non-asthma referents (OR: 1.08, 95% CI: 0.85 to 1.38) with unknowns excluded. (Table 6.23)

In residences from birth to age 5, a close proximity between a tract of evergreen trees and the residence was reported in 7.1% of the population. However, 15.2% of subjects did not know if the residence(s) was close to a tract of evergreen trees. With unknowns excluded, no statistically significant differences were found for cases and referents overall (OR: 0.89, 95% CI: 0.62 to 1.28).There were no significant differences when comparing cases with referents

diagnosed with asthma (OR: 0.84, 95% CI: 0.56 to 1.24) or non-asthma referents (OR: 0.97, 95% CI: 0.63 to 1.51). (Table 6.24)

6.2 Multivariate Analyses

6.2.1 Demographic Characteristics and Smoking

Age at diagnosis, sex, and smoking were included in a main effects model in Table 6.25. Consistent with bivariate analyses, cases were less likely to smoke than all referents (OR: 0.74, 95% CI: 0.61 to 0.89) in the adjusted model. In addition, cases were more likely to be male and younger than all referents. An interaction term for smoking and age at diagnosis was included in the model (Table 6.25). Significant interactions were observed using the likelihood ratio (LR) test (LR $\chi^2(3)=28.1$, $P<0.001$). The adjustment in the interaction model had a substantial impact on the results. As noted previously, ever smoking was more frequent in referents overall and this was largely for older referents. Conversely, among cases, ever smoking was more frequent in youngest group and less smokers were found among older cases, especially relative to referents. This effect was observed for males and females alike, as shown in Figure 6.1 (a) and (b). As seen in Table 6.6, the proportion of ever smokers among cases diagnosed in the youngest age quartile (67.0%) declined in each age at diagnosis quartile to the oldest age group (56.2%); whereas, among referents, the proportion increased from the youngest to oldest age group (57.9% and 77.3%). Effects of age, sex, and smoking were left in the multivariate model, but interactions between them were omitted as it made the model unduly complex.

In Table 6.26, age at diagnosis, sex, and smoking were entered into a model comparing cases with asthma referents. With this adjustment, smoking was not significantly different between the groups. In addition, cases were more likely to be male. Using the youngest quartile as the reference group, no differences in age at diagnosis were found in this model.

Age at diagnosis, sex, and smoking were included in an unconditional logistic regression model comparing cases with non-asthma referents (Table 6.27). Cases were less likely to smoke than non-asthma referents (OR: 0.37, 95% CI: 0.29 to 0.48) after adjusted for age at diagnosis and sex. Cases were younger than non-asthma referents and there was no significant difference in sex between the groups.

6.2.2 Residences from Birth to Diagnosis

All of the available covariates were included in the unconditional logistic regression model (2138 subjects) and none of the biological factors related to place of residence from birth to diagnosis were associated with sarcoidosis (Table 6.28). An elevated odds ratio was observed for cases who ever drank un-piped water compared with all referents (OR: 1.24, 95% CI: 0.98 to 1.57) in the adjusted model. This association approached nominal statistical significance. Cases were more likely to be male and younger than all referents in this model. They were also less likely to smoke than all referents. Finally, the reduced (step-wise) model did not include any environmental factors. As a result, it was identical to the model presented for demographic analysis.

In a full unconditional logistic regression model comparing cases with asthma referents (1522 subjects), cases were more likely to report ever drinking un-piped water than asthma referents (OR: 1.43, 95% CI: 1.10 to 1.86). For this comparison, no other environmental factors had a confidence interval excluding 1 (Table 6.29). However, cases were less likely to report mouldy odours than asthma referents in this model (OR: 0.82, 95% CI: 0.66 to 1.03). After adjustment, cases were more likely to be male than asthma referents. In addition, there were no differences in age at diagnosis or sex between the groups. The multivariate results were consistent with the univariate analyses. When a stepwise regression analysis was conducted, the reduced model included ever drank un-piped water (OR: 1.35, 95% CI: 1.10 to 1.66), ever smelled mouldy odours (OR: 0.83, 95% CI: 0.66 to 1.03), sex, age at diagnosis, and smoking (Table 6.29). Odds ratio estimates for demographic variables in the stepwise model were almost identical to those generated in the full main effects model.

When cases were compared with non-asthma referents (1300 subjects), no association between sarcoidosis and environmental factors were observed when all covariates were included in the model (Table 6.30). After this adjustment, cases were younger and less likely to smoke than non-asthma referents with no difference in sex. In univariate analyses, cases had been less likely to report ever drinking un-piped water; however, this association became non-significant in multivariate analyses. The stepwise unconditional logistic regression analysis produced a reduced model that did not include any of the environmental factors analysed. The stepwise model was the same as the model produced in the demographic analysis in table 6.27, as described previously.

6.2.3 Birthplace Residence

All of the covariates for birthplace residence were included in the logistic regression model (1324 subjects) and none of the biological factors related to this residence were associated with sarcoidosis when cases were compared with all referents (Table 6.31). With this adjustment, cases were more likely to be male and younger than all referents. They were also less likely to report ever smoking, consistent with the univariate analyses. Using a step-wise approach, the reduced models did not include any environmental factors, resulting in a model identical to the model in the demographic analysis.

In the regression model (942 subjects) in Table 6.32, cases were more likely to report a birthplace residence with un-piped water than asthma referents when adjusting for all other covariates (OR: 1.79, 95% CI: 1.16 to 2.77). In addition to un-piped water, farm residence was also associated with sarcoidosis in univariate analysis (for cases versus asthma referents); however, this association was not observed in the full main effects model. In both analyses, cases were more likely to be male; however, no significant differences in age at diagnosis or smoking were found. The stepwise method generated a model that included: un-piped water in residence at birth (OR: 1.57, 95% CI: 1.18 to 2.09), sex, age at diagnosis, and smoking. The odds ratios for the demographic variables in the stepwise model were similar to those generated for the full main effects model.

All of the covariates for birthplace residence were included in the logistic regression model (807 subjects) and none of the biological factors related to the residence were associated

with sarcoidosis when cases were compared with non-asthma referents (Table 6.33). In univariate analysis, cases were less likely to report a birthplace residence with un-piped water (OR: 0.71, 95% CI: 0.55 to 0.92); however, the association became statistically non-significant in the full model. Consistent with the univariate analyses, cases were more likely to be male and younger than non-asthma referents in the adjusted model. They were also less likely to report ever smoking. Using a step-wise approach, the reduced models contained only demographic variables. The odds ratios for these demographic variables were similar to those generated in the full main effects model.

6.2.4 Residences from Birth to 5 Years

All of the covariates were included in the models (1568 subjects) and none of the biological factors related to place of residence were associated with sarcoidosis when cases were compared with all referents (Table 6.34). In the model, cases were more likely to be male and younger than all referents, consistent with univariate analyses. They were also less likely to smoke. In stepwise regression analysis, the model only contained demographic variables. The odds ratio estimates generated in the stepwise model were similar to those in the full main effects model.

In the unconditional logistic regression model (1112 subjects), cases were more likely to drink un-piped water than asthma referents (OR: 1.48, 95% CI: 1.02 to 2.16) after controlling for all other covariates. In univariate analyses, elevated odds ratios were observed for living on a farm, drinking un-piped water and/or untreated milk. No other environmental factors related to

residence from birth to 5 years were associated with sarcoidosis when cases were compared with asthma referents (Table 6.35). The stepwise regression analysis resulted a reduced model that included ever drank un-piped water (OR: 1.41, 95% CI: 1.09 to 1.82), sex, age at diagnosis, smoking. In this model, the odds ratio estimates did not differ importantly from those generated in the full multivariate model.

All of the covariates were included in the model (956 subjects) and none of the biological factors related to place of residence from birth to age 5 were associated with sarcoidosis when cases were compared with non-asthma referents (Table 6.35). In univariate analyses, cases were less likely to report ever drinking un-piped water, but this association was not significant in the full model. In both analyses, cases were less likely to report ever smoking than non-asthma referents. Cases were younger than non-asthma referents and there was no difference in sex. For the stepwise regression analysis, the model only contained demographic variables. This model was identical to the model generated for the demographic analysis.

6.3 Unmatched versus Matched Analyses

As discussed below, unmatched analyses were compared with matched analyses. Unmatched analyses using data pooled from the entire population and from matched sets were presented, along with the matched analyses in the tables below. An unmatched analysis of matched sets was conducted to ensure that there were no differences between the subjects that belonged to a cluster compared with those that did not.

6.3.1 Demographic Characteristics

In the matched sample, 50% of the population were male overall. There was no difference in sex between cases (198/382, 51.8%) and referents (328/667, 49.2%) (χ^2 (1)=0.69, *P*=0.41). The mean age at diagnosis (SD) was 46.8 (9.12) years in the matched sample. As expected from the protocol of matching on age up to one year after diagnosis, cases were younger than referents (mean age (SD): 45.7 (9.20) years versus 47.4 (9.01) years, respectively; $t(1047) = 2.92$, *P*=0.004). Since age and sex were the matching variables, these variables were dropped from the conditional models. As shown in the multivariate analyses below, the odds ratio estimates for smoking were identical when comparing the matched and corresponding unmatched analyses.

6.3.2 Residences from Birth to Diagnosis

When all environmental exposure variables were included in the unconditional and conditional logistic regression models, the odds ratio estimates for cases compared with all referents were nearly identical, as presented in Table 6.37. No associations were identified in the population overall (2138 subjects) or in the subgroup of subjects that belonged to a matched cluster (1049 subjects), irrespective of the type of model.

In Table 6.38, similar associations were observed when cases were compared with asthma referents in the regression analyses (unconditional and conditional), containing all environmental exposure variables. The number of cases and asthma referents (1522 subjects) and those that belonged to a matched cluster (764 subjects) were used in the unconditional models. The latter (764 subjects) were also used in the conditional model. In all analyses, cases were more likely to

drink un-piped water than asthma referents. Cases were less likely to smell mouldy odours in the home than asthma referents in all models. The odds ratios estimates were significant in the conditional model and they had border-line statistical significance in the unconditional models. Cases were more likely to live near a tract of pine trees than asthma referents. This association was not statistically significant for the whole population but it approached significance for subjects who belonged to a matched set in matched and unmatched analyses.

As shown in Table 6.39, all environmental exposure variables were included in unconditional and conditional logistical regression models comparing cases with non-asthma referents. There were 1300 subjects in the unconditional model and 661 subjects (belonging to a matched cluster) in the unconditional and conditional models. The multivariate analyses generated similar models and no environmental factors were associated with sarcoidosis.

6.3.3 Birthplace Residence

When all birthplace environmental exposure variables were entered into the logistical regression models (unconditional and conditional) for cases and all referents, no differences were observed (Table 6.40). The unconditional model (1339 subjects) was compared with the models for subjects belonging to a cluster (634 subjects).

Environmental exposure variables for the birthplace residence were entered into unconditional and conditional logistical regression models (Table 6.41) comparing cases with asthma referents. The unconditional model (942 subjects) was similar to the unconditional and conditional models for the subgroup of those in a cluster (460 subjects). As noted previously,

cases were more likely to have a birthplace residence with no piped water than asthma referents. Again, no other environmental factors were associated with sarcoidosis.

In Table 6.42, cases were compared with non-asthma referents in models containing all environmental factors encountered in birthplace residence. There were no differences between the unconditional and conditional models. The overall unconditional model (807 subjects) did not identify any environmental risk factors for sarcoidosis, and this was consistent with the analyses (unmatched and matched) of matched clusters (407 subjects).

6.3.4 Residences from Birth to 5 Years

When cases were compared with all referents for environmental factors encountered in residences from birth to age 5, the unconditional and conditional logistic regression analyses generated similar models (Table 6.43). For the overall unconditional model (1568 subjects) and the models (unconditional and conditional) for matched clusters (768 subjects), there were no environmental factor with a confidence interval excluding 1.

In Table 6.44, all environmental factors (encountered in residences from birth to age 5) for cases and asthma referents were entered into the logistical regression models (unconditional and conditional). Cases were more likely to drink untreated water than asthma referents in the overall unconditional regression analysis (1112 subjects). This association was not observed in the matched sample (553 subjects) when it was analysed in a conditional or unconditional model. For all other environmental factors, the odds ratios in all models were similar.

For cases and non-asthma referents, all environmental factors were entered into the unconditional and conditional regression analyses (Table 6.45). In the unconditional models for the entire population (956 subjects) and for matched clusters (493 subjects), no environmental factors were associated with sarcoidosis. However, in the conditional model, cases were significantly more likely to report mouldy smells than non-asthma referents (OR: 2.66, 95% CI: 1.10 to 6.44). No other environmental factors had a confidence interval excluding 1 in this model.

6.4 Cases with Tissue Confirmation

6.4.1 Biopsy proven cases versus non-biopsy proven cases

Separate analyses were conducted for cases with and without biopsy proven sarcoidosis. More biopsy proven cases (207/344, 60.2%) than those with no biopsy confirmation of disease (184/340, 54.1%) were male (χ^2 (1)=2.56, *P*=0.11). Biopsy proven cases were younger than non-biopsy proven cases (mean age at diagnosis (SD): 43.7 (9.30) versus 44.0 (9.90) years, respectively; *t*(682) = 0.41, *P*=0.66). Among ever smokers, biopsy proven cases were younger than non-biopsy proven cases (mean age at diagnosis: 42.3 (9.56) versus 43.3 (10.5) years); while amongst never smokers, they were older than non-biopsy proven cases (mean age at diagnosis: 46.0 (8.42) versus 45.0 (8.94) years). Overall, biopsy proven cases reported ever smoking more frequently than non-biopsy proven cases (210/344, 61.0% and 202/340, 59.4%; χ^2 (1)=0.19, *P*=0.66).

6.4.2 Biopsy and non-biopsy proven cases versus referents

4.4.3.3 Demographic Characteristics

Biopsy and non-biopsy proven cases were compared to all referents in univariate and multivariate analyses of demographic variables as presented in Table 6.46. When biopsy proven cases compared with all referents, cases were more likely to be male and younger. On the other hand, non-biopsy proven cases (as compared with all referents) were more likely to be younger but no differences in sex were observed. Both biopsy and non-biopsy proven cases were less likely to smoke than all referents in univariate and multivariate analyses.

In Table 6.47, biopsy and non-biopsy proven cases were compared with asthma referents in univariate and multivariate analyses. For both comparisons, no differences were observed in age at diagnosis or smoking between the groups. However, in both comparisons, cases were more likely to be male than asthma referents.

In univariate and multivariate analyses comparing biopsy and non-biopsy proven cases with non-asthma referent, no substantial differences were observed (Table 6.48). In all analyses, cases were younger and less likely to smoke with no differences in sex.

4.4.3.4 Residences from Birth to Diagnosis

In a full logistic regression model, no biological factors related to place of residence were associated with sarcoidosis when biopsy proven cases were compared with all referents, consistent with univariate analyses (Table 6.49). Non-biopsy proven cases were more likely to consume un-piped water than all referents in multivariate analysis (OR: 1.45, 95% CI: 1.07 to

1.96). In this multivariate analysis, no other environmental factor was associated with sarcoidosis. In both multivariate analyses, cases were younger and less likely to smoke than all referents. In addition, biopsy proven cases were more likely to be male than all referents; whereas, there was no statistically significant differences in sex between non-biopsy proven cases and all referents.

When biopsy proven cases were compared with asthma referents, there were no differences between the groups for any biological factors related to residence (Table 6.50). This was consistent with univariate analyses. When non-biopsy proven cases were compared to asthma referents, cases more likely to drink un-piped water (OR: 1.53, 95% CI: 1.19 to 1.98) and/or drink untreated milk (OR: 1.35, 95% CI: 1.02 to 1.78) in univariate analyses. After adjusting for all variables in the multivariate analysis, only drinking un-piped water was associated with sarcoidosis (OR: 1.70, 95% CI: 1.23 to 2.35). In both multivariate analyses, cases were more likely to be males; while there was no difference between the groups in age at diagnosis or smoking.

In univariate analysis, biopsy proven cases were less likely to drink un-piped water than non-asthma referents (OR: 0.69, 95% CI: 0.53 to 0.90) as shown in Table 6.51. Biopsy proven cases were also less likely to drink raw milk than non-asthma referents (OR: 0.71, 95% CI: 0.53 to 0.95). These univariate associations were not observed when comparing non-biopsy proven cases with non-asthma referents. When all available covariates were included in the multivariate models, no environmental factors were associated with sarcoidosis in these two models (Table

6.50). In both adjusted model, cases were younger and less likely to report ever smoking with no differences in sex.

4.4.3.5 Birthplace Residence

No environmental factors related to birthplace residence were associated with sarcoidosis when biopsy proven cases were compared with all referents in univariate or multivariate analyses (Table 6.52). Likewise, no associations were identified when non-biopsy proven cases were compared with all referents. In the adjusted models, biopsy proven cases were less likely to be male than all referents; whereas the differences in sex for non-biopsy proven cases was not significant. In addition, non-biopsy proven cases were less likely to report ever smoking; the differences for biopsy proven cases in smoking were not significant.

When biopsy proven cases were compared with asthma referents, no biological factors related to the place of residence were associated with sarcoidosis in univariate or multivariate analyses (Table 6.53). In univariate analysis, non-biopsy proven cases were more likely to report un-piped water at birthplace residence (OR: 1.55, 95% CI: 1.18 to 2.18) compared with asthma referents. They were also more likely to report residence on a farm at birth (OR: 1.46, 95% CI: 1.08 to 1.98). However, residence on a farm dropped in significance when entered into the multivariate model. In the full model, non-biopsy proven cases were more likely to report un-piped water than asthma referents (OR: 1.55, 95% CI: 1.18 to 2.18). In both adjusted models, cases were more likely to be male than asthma referents; however, the difference in sex became non-significant in the multivariate analysis using non-biopsy proven cases. The odds ratios for age at diagnosis and sex were similar in both models.

In univariate analysis, biopsy proven cases were less likely to report un-piped water at the birthplace residence than non-asthma referents (OR: 0.64, 95% CI: 0.46 to 0.88). However, when all covariates were included in the model, no environmental factors were associated with sarcoidosis (Table 6.54). When non-biopsy proven cases were compared with non-asthma referents, no environmental factors were associated with sarcoidosis in univariate or multivariate analyses. In both of these multivariate models, similar odds ratios were generated for demographic variables (age at diagnosis, sex, smoking).

4.4.3.6 Residences from Birth to 5 Years

No environmental factors were associated with sarcoidosis when biopsy proven cases were compared with all referents in the full multivariate model (Table 6.55). A similar multivariate model was generated when non-biopsy proven cases were compared with all referents. Biopsy proven cases were more likely to be male than all referents in the adjusted model; while no significant difference in sex was observed between non-biopsy proven cases and all referents. In both models, cases were less likely to report ever smoking; however, this difference was not significant when biopsy proven cases were compared with all referents.

Consistent with univariate analysis, no environmental factors related to residences from birth to age 5 were associated with sarcoidosis in the full multivariate model (Table 6.56). In univariate analyses, non-biopsy proven cases were more likely to report residence on a farm from birth to age 5 (OR: 1.47, 95% CI: 1.10 to 1.96) than asthma referents. Cases were also more likely to report drinking un-piped water (OR: 1.49, 95% CI: 1.18 to 1.88) and/or raw milk (OR: 1.51, 95% CI: 1.10 to 2.07). When all covariates were included in the logistic regression model,

these associations became non-significant. In both multivariate analyses, cases were more likely to be male, but this became non-significant for non-biopsy proven cases. The non-significant odds ratios for age at diagnosis and smoking were similar in both models.

In univariate analysis, biopsy proven cases were less likely to drink un-piped water in residences from birth to age 5 (OR: 0.70, 95% CI: 0.53 to 0.93) than non-asthma referents. However, no association between sarcoidosis and drinking un-piped water, or any other environmental factor, was observed in the full multivariate analyses (Table 6.57). Similarly, no environmental factors were associated with sarcoidosis when non-biopsy proven cases were compared with non-asthma referents. For demographic variables in the multivariate models, the odds ratio estimates were similar.

Chapter 7 Discussion

7.1 Key Results

The preceding chapters reported results from a case-referent study that examined pulmonary sarcoidosis in Alberta, Canada. We matched cases and referents diagnosed with respiratory diseases to determine if biological risk factors related to place of residence were associated with sarcoidosis. Ever exposure from birth to diagnosis for a variety of rural risk factors were analysed including: farm residence, drinking untreated water and/or raw milk, living with animals, smelling mouldy odours, and living near a tract of pine trees. Exposure to these factors in early life was also considered for their importance in sarcoidosis risk, especially considering environmental exposures may be important as the immune system develops.

Although no strong association between the biological factors encountered in the domestic environment and sarcoidosis was identified, it appeared that diagnosis mattered greatly. When cases were compared with asthma and non-asthma referents, consistent relationships were observed. In residences from birth to diagnosis, cases were more likely than asthma referents to drink un-piped water in bivariate analysis (OR: 1.36, 95% CI: 1.11 to 1.67) and in multivariate analysis allowing for all available covariates (OR: 1.43, 95% CI: 1.10 to 1.86). In contrast, cases were less likely than non-asthma referents to drink un-piped water in bivariate analysis (OR: 0.78, 95% CI: 0.62 to 0.97) and although non-significant, an inverse association was reported in multivariate analysis (OR: 0.93, 95% CI: 0.69 to 1.26). These results were suggestive of an effect in the opposite direction to that expected based on previous literature.(19;23;65) The non-asthma

referent group comprised a variety of respiratory conditions and the majority of referents were diagnosed with chronic obstructive pulmonary disease and allied conditions (ICD 9 codes 490-496). It also included subjects diagnosed with pneumoconioses and other lung diseases due to external agents (ICD 9 codes 500-508). An inverse relationship between sarcoidosis and un-piped water was found when cases were compared with referents in these diagnostic subgroups.

Early exposures related to place of residence, including farm residence and consumption of un-piped water and/or raw milk, were associated with an increased risk of developing sarcoidosis when cases were compared with asthma referents in bivariate analyses. For this comparison, the use of un-piped water was associated with sarcoidosis in multivariate analyses for birthplace residence (OR: 1.79, 95% CI: 1.16 to 2.77) and for residences from birth to age 5 (OR: 1.48, 95% CI: 1.02 to 2.16) when controlling for all covariates. Again, in contrast to the expected direction of the relationship, cases were less likely to consume un-piped water than non-asthma referents in bivariate analysis (OR: 0.71, 95% CI: 0.55 to 0.92 for birthplace residence, OR: 0.78, 95% CI: 0.62 to 0.98 for residences from birth to 5 years old). However, this relationship was not statistically significant after adjustment in the multivariate models.

These findings suggested an increased importance of an early exposure period. As demonstrated in the literature cited below, lack of childhood exposure (to infection) may increase susceptibility to allergic diseases such as asthma (the hygiene hypothesis). A large number of epidemiological studies have shown that being raised on a farm is inversely associated asthma.(73) Regular contact with farm animals has been identified as an important contributor to the protective ‘farm effect' for asthma.(74-76) Another consistently identified source of

protection is the consumption of unprocessed cow's milk, as shown in a number of studies.(76-78)

These explanatory variables may influence sarcoidosis risk independently, but they are also likely related to other explanatory variables. Strong relationships were evident between a few of the explanatory variables. As expected, those who reported farm residence were more likely to report using un-piped water (Pearson correlation r=0.61, $P<0.001$) and drinking raw milk (Pearson correlation r=0.47, $P<0.001$). Using un-piped water and drinking raw milk were also highly correlated (Pearson correlation r=0.39, $P<0.001$).

In addition to environmental exposures, smoking was also considered, as it may modify the effect of environmental exposures on sarcoidosis risk. The current study found an overall inverse relationship between cigarette smoking and sarcoidosis. As smoking is related to numerous pulmonary diseases, differences in the smoking percentages of the two groups were likely due to an increased proportion of smokers in the clinic referent group, particularly in non-asthma referents. However, we found differences in risk of sarcoidosis according to age at diagnosis and smoking. Among the youngest age at diagnosis quartile, cases were more likely to report ever smoking than all referents, asthma referents, and non-asthma referents; whereas, they were less likely to report ever smoking among the oldest age at diagnosis quartiles. This relationship requires further investigation (with a more precise measure of smoking incorporating amount and duration) and confirmation with additional studies. Similar observations have not been reported in previous literature. Although, the reduced odds ratio associated with ever smoking was consistent with several case control studies, as discussed next.

A case control study of 74 cases with sarcoidosis conducted in the state of Georgia in 1961, which included cases with hilar adenopathy on chest radiography, showed a negative association between sarcoidosis and cigarette smoking among whites, but not for blacks.(79) The study used two matched controls per case (148 subjects) and these controls were drawn from a community in Georgia that had chest radiographs for the same reason as cases, mainly case finding for previous studies. The overall mean age (36.7 years) of subjects in this study was younger than the age reported in our study (45.5 years) and we found the highest proportion of smokers among young cases. A case control study from New York also noted that 240 cases were less likely to be smokers than control patients with tuberculosis (240 subjects), matched on sex, age, race, and residence.(23) However, in this same study, the cases did not differ in smoking habits from a second, similarly matched group of 240 healthy subjects. Two studies from France reported that patients with sarcoidosis were less likely to have been smokers than controls.(16;80) In one of these studies, Hance *et al*. examined the relationship between cigarette smoking and the risk of two different interstitial lung diseases: pulmonary histiocytosis X (76 subjects) and pulmonary sarcoidosis (130 subjects) relative to healthy controls.(80) While smoking was a strong risk factor for histiocytosis X, smoking was less likely in cases with sarcoidosis than healthy controls. In the other French study, a highly significant negative association was identified when 101 biopsy proven cases from chest clinics were compared with 404 healthy matched controls from check-up clinics (OR: 3.8, 95% CI: 2.4 to 6.5).(16) Similar findings were subsequently reported in the ACCESS study. In the large multi-center US study, a history of ever smoking cigarettes was less frequent among cases than healthy controls.(37) In

other studies, pulmonary sarcoidosis patients were less likely to smoke than people of similar age in the general population.(15;17)

Nevertheless, not all studies have shown clearly that smoking reduces the incidence of sarcoidosis.(14;81) Warren found that the smoking habits of 75 sarcoidosis cases were similar to those expected from the general population using figures from the Prairie regions of Canada in 1973.(81) The mean age of these patients (42 years) was similar to our study. One recent case control study conducted in India found an insignificant negative association between active smoking and sarcoidosis.(82) Newly diagnosed biopsy proven cases (98 subjects) were identified from the outpatient departments in an Indian institute. The study recruited two healthy volunteers that accompanied other patients in the clinic as age, sex, and religion matched controls (196 subjects). Two additional studies also found a non-significant negative association between smoking and sarcoidosis.(14;69) One study used cases (51 subjects) from four hospitals in Philadelphia and in-patient and outpatients controls selected at random from a list of available controls (107 subjects) (they were frequency matched to cases);(14) while the other used biopsy proven cases (39 subjects) and healthy age and sex matched controls (109 subjects) selected from a population register.(69) In both of these studies, there was a trend of higher frequency of non-smokers in the sarcoidosis groups. In general, smaller studies did not show an effect.

7.2 Clinic-based or Population-based Controls

In case control studies, cases are often identified and recruited from medical care facilities. In order to determine if the exposure is associated with the condition of interest, the

prevalence of the exposure in the population without the condition needs to be established as a comparison. A control group is sampled from the population that gave rise to the cases for this purpose. Advantages and disadvantages for using a control group selected from a medical facility or the general population, as suggested by Cole and others,(83;84) were summarized below.

Clinic controls tend to be accessible, cooperative, and more likely to be able to recall exposures like cases. In addition, cases and controls from the same medical facilities are also more likely to resemble each other with regard to selective factors that led to the use of the facility. However, if there are associations between the reasons for obtaining medical care and factors of etiological interest, the resulting conclusions may be invalid.

Controls drawn from the general population have the advantage of providing an estimate of the frequency of exposure which is not altered by associations with illness or hospitalization. These controls are usually selected randomly from the source population. However, several problems prevent unbiased estimates from population control groups. These problems include difficulty locating controls, particularly those who are likely to participate. As well, when controls are identified, their ability to recall past events is likely to be different than that of cases. Random digit dialing is one methodology used to select population controls where telephone numbers are generated without relying on a directory. However, this method is particularly susceptible to selection bias because of high rates of non-response and refusals. In general, the goal for control selection is a random sample of eligible subjects, not of telephone numbers. This may be a problem because incomplete phone coverage. Additionally, many households will have

more than one eligible control. Alternatively, households with more than one phone line have a higher probability of being selected.

7.3 Comparison with Published Studies

While there is evidence that environmental factors may be involved in sarcoidosis etiology, a single specific exposure has not been identified in this investigation or in previous epidemiological studies. Although several rural risk factors have been identified, our conclusions did not always match those drawn in previous studies. The differences in results may be due to differences in the study population. Cases were generally recruited from hospitals, general practice or specialist clinics. Comparisons of the results of this study with those obtained by others, mostly, reflect the impact of different control groups upon the results.

Previous studies have reported associations between sarcoidosis and rural living.(19;23;65;66) The nature of rural residence as an exposure was likely to be highly heterogeneous, which may explain inconsistency between studies. In addition, most studies reporting associations between sarcoidosis and rural living were published in the 1960's and 70's. Different definitions of rural residency may contribute to discrepant results between studies. Regardless, ever living on a working farm from birth to diagnosis was not associated with sarcoidosis in our study. In a previously cited case control study, the proportion reporting residence on a farm was significantly greater for those patients with sarcoidosis than control subjects.(23) The study reported on a series of cases recruited from 1961 to 1965 from two referal clinics in the New York City area. These cases were matched to two control subjects

identified through chest clinics: one with tuberculosis and one with a normal chest radiograph. The latter were obtained from mass surveys, pre-employment assessments, annual examinations, and referrals; however, no information on clinical history or respiratory conditions was provided. A single unblind public health nurse interviewed the study subjects for exposure assessment. It is unclear how this may have impacted the study findings. Another study found an association between living and working on a farm and sarcoidosis (OR: 3.4, 95% CI: 1.2 to 9.1).(65) Biopsy proven cases (44 subjects) were identified in various clinics in South Carolina. Matched controls (88 subjects) were identified through random digit dialing. Assessment of exposure was done using questionnaires administered by an interviewer in the clinical setting for cases and over the telephone for controls. The increased odds ratio reported likely reflects measurement bias due to the differences in exposure assessment methods between cases and controls. In addition, residents of rural areas may have used the University of South Carolina ambulatory care system because there were no other facilities available in the remote setting. The reduced access to care in these areas may have result in an overrepresentation of cases from a geographic areas not covered with random digit dialing area codes.

We found an association between sarcoidosis and birthplace residence on a working farm in bivariate analyses; however, the relationship was only observed when cases were compared with asthma referents. A similar association was also observed between sarcoidosis and farm residence when exposure occurred from birth to age 5. An early well-designed, case-control study found an association between sarcoidosis and birthplace in rural areas.(19) The study's results, which were confined to residents of Maryland seen at one hospital between 1940 and

1960, were based on data obtained from 62 biopsy proven cases and 62 controls. Cases were matched in a 1:1 ratio on age, sex, and race to other outpatient controls that were registered at the clinic where cases were identified. They were seen for hypertension, syphilis, and other diseases in the field of internal medicine. The study population had an over-representation of African Americans (95%). In addition, a relatively large proportion of the controls were selected from individuals with syphilis; however, these controls did not report residence on a farm less frequently than the other controls. A rural area was defined as a community with less than 3000 people. An urban area had more than 30000 people; while an intermediate area had 3000 to 30000 people. An additional finding was that a larger proportion of cases spent more than 20 percent of their lifetime in rural areas. Similarly, another study showed that black males recruited to the Navy who were lifetime residents of rural counties had a higher incidence of sarcoidosis when compared with a similar age group who were lifetime residents of urban areas.(66) This difference was not observed in whites.

While rural living was not observed as an independent risk factor in the ACCESS study, agricultural employment was identified as a risk factor for sarcoidosis. However, this association was not statistically significant when entered into the multivariate model.(37) In this study, biopsy proven cases were identified through referrals clinics from 10 centers across the US between November 1996 and June 1999; whereas matched controls were identified though random digit dialing. On average, 216 random phone calls were made to recruit one control per case. Exposures were assessed using an interviewer-administered questionnaire; however, it appeared that the subject was required to classify the community of residence as rural or not.

This may have lead to exposure misclassification, which may have weakened a possible association.

Farming is a diverse occupational field and it may involve different crops, herds, and practices. Early studies found that taking care of farm animals was associated with an increased risk of sarcoidosis.(19;23) In these two previously cited matched case control study, no differences in herds or crops were identified. Further investigation among those who reported living on a working farm should be undertaken to determine the types of crops and animals farmed. This association between farm animals and sarcoidosis was not evaluated in the current investigation. However, we found no increased risk of sarcoidosis for individuals living with pets, consistent with previous reports.(14;69) The ACCESS study identified a negative association between sarcoidosis and animal dust exposure.(37) Further investigation of different types of animals may explain reports of increased risk.

Another possibility included common exposures to rural areas, which were related to an increased risk of sarcoidosis. These may have included: drink untreated water and/or raw milk. Therefore, we have examined particular aspects of rural living separately.

The current study found an elevated risk of sarcoidosis for drinking un-piped water from birth to diagnosis in the full multivariate model but the results were statistically non-significant (OR: 1.24, 95% CI: 0.98 to 1.57). In addition, increased risk was observed for cases compared with asthma referents. An inverse association was found when cases were compared with non-asthma referents. Exposure to contaminated water may account for differences in developing or

driving different immunological vulnerabilities like asthma and sarcoidosis. As described previously, a consistent relationship was observed when cases were compared to referent subgroups. Compared with asthma referents, cases were more likely to drink un-piped water. In contrast, drinking un-piped water was found to be associated with non-asthma referent diagnoses.

A few studies have observed a positive relationship between sarcoidosis and the use of non-public water supplies.(19;23;65) In these case-control studies, controls were often selected from the same general sampling frame as cases such as the same hospital or clinic, or from the general population with methods such as random digit dialing. As described, the method of control selection and recruitment came with advantages and disadvantages. Of all the limitations in assessing lifetime exposures, the potential for selective recall bias by individuals with chronic disease was the greatest threat to validity of the data. People with chronic diseases may have overestimated their exposure if they perceived it to be involved in the etiology of their condition. Likewise, healthy controls may have underestimated their exposures as they perceived them to be unimportant. Both population- and clinic- based controls were used in these studies. Two studies used participants with other chronic ailments including diseases encountered in internal medicine (hypertension, syphilis)(19) and tuberculosis.(23) One also used ‘healthy’ controls as determined from a normal chest radiography;(23) another study only used random digit dialing to select healthy population controls.(65) Although most of these studies were historical with non-significant results, they found elevated risk of sarcoidosis with consumption of untreated water. However, it was possible that an aspect of untreated water in specific locations may be

important for sarcoidosis etiology. Mycobacteria, a suspected etiological agent, inhabit a diverse range of natural environments and water may be an important vehicle for transmission of these ubiquitous organisms.(85) Even though studies have not been conducted in Alberta on mycobacteria in water, a variety of mycobacterial species have been recovered from raw source waters, including drinking water, in several locations around the world.(86-88)

The ACCESS study found that conditions favourable to the production of microbial bioaerosols, presumably from exposure to aerosolized fungal spores, were associated with sarcoidosis.(37) The indicator of exposure was mouldy or musty odours at work. Mould, musty odours, and water damage encountered in the workplace was also identified as a risk factor in another study comparing cases with their African American siblings.(27) Kucera *et al*. used 921 subjects in 273 sibships (that had been identified through a sarcoidosis case) to examine associations between sarcoidosis and occupation or occupationally-related exposures. The current investigation only assessed exposures related to place of residence. A non-significant inverse association was observed for ever smelling mouldy odours from birth to diagnosis when cases were compared with non-asthma referents. Although the microbial bioaersols hypothesis represents a biologically plausible explanation for the development of sarcoidosis, especially given that suspected microbes may dwell in standing water, the link between indicators of exposure and the suggested association was doubtful. Obtaining an accurate assessment of mouldy odours is difficult, particularly when historical rather than current exposures were of interest. Recent investigations have used markers of fungal cell biomass for exposure assessment in homes; however, only current exposures were measured.(68) Sufficiently accurate and

detailed information about environmental exposures remains a major challenge in retrospective epidemiological studies, especially for studies that rely on self-reported data. A more detailed exposure assessment of jobs with these specific occupational exposures may uncover the link of this exposure to sarcoidosis because a job exposure matrix would improve data quality and reduce recall bias.

Living near forests, lumbering, and wood milling have been associated with the development of sarcoidosis. Studies have suspected pine pollen or pine needles as the etiological agents responsible, given that the geographic distribution of sarcoidosis cases appeared to follow aspects of forest distribution in which pine trees predominated.(70;71) We examined the association between sarcoidosis and proximity to a tract of pine trees near the place of residence. No association was observed. However, the study recruited referents matched on the clinic that they attended, thus matching for geography and possibly for regional environmental factors.

The choice of analysis may have had an impact on our results. The analysis used in the study was not the planned analysis. Individual matching was used in previously published studies(37;65) and these studies used matched analyses to account for the matched design. Our study was also designed with individual matching, which intended to provide a balanced distribution of subjects for age and sex, thus permitting a more efficient (statistical) analysis. However, the number of available matched clusters was 382, making the matched analysis less attractive because of loss of data. Studies have suggested that pooling of matched or stratified data for analysis will result in risk estimates which are conservatively biased in comparison with those obtained using the matched analysis.(89) In this study, the pooled and matched estimates

did not differ much at all. As anticipated, the conditional maximum likelihood estimates were similar to the unconditional maximum likelihood estimates.

The seemingly contradictory findings with past studies raised concerns that our study population may not be representative of all sarcoidosis patients. The case definition in the current study relied on a clinical diagnosis of sarcoidosis made by a specialist. It included only those with lung involvement based on clinical, radiological, or histological evidence as determined through a chart review. Previous studies have employed similar case definitions; however, some studies such as the ACCESS study and others had a requirement for tissue confirmation.(19;37;69) In addition, the ACCESS study case definition was not restricted to cases with lung involvement. Histological confirmation from biopsy was not deemed necessary for the current study as the diagnosis was considered sufficient when typical clinical and radiological findings were noted in a patient with lung involvement. Fifty percent of cases who participated in our study had biopsy confirmation of their diagnosis. Biopsy and non-biopsy proven cases were considered separately in further analyses – where they were compared with all referents, asthma referents, and non-asthma referents. The differences between biopsy and non-biopsy proven cases did not have a substantial effect on the study results. The consequence of outcome misclassification might include a reduction in the strength of an association; however, this was not observed in subgroup analysis.

The reliance on clinical judgement for diagnosis posed the problem of differences in opinion for what constitutes the diagnosis of sarcoidosis. Although there was no standard diagnostic protocol for sarcoidosis, the choice to use cases seen by specialists may have reduced

the likelihood of misdiagnosis. Consequently, it was expected that cases with unconfirmed diagnoses or mild disease would be excluded from a study population restricted to those seen by specialists.

7.4 Strengths and Limitations

This study was the first epidemiological study of sarcoidosis in Canada. By taking advantage of a population-based administrative data source, the current investigation was able to identify a large sample of cases and individually matched referents. One of the main advantages of using administrative data was the possibility of obtaining such large, representative samples. In our case-referent study, participants were selected from men and women attending specialist clinics in Alberta. Cases were adults that received a first diagnosis of sarcoidosis. Referents were diagnosed with a chronic respiratory condition by the same specialist within 12 months of the case diagnosis. Cases and referents were identified and recruited in the same way. The collection of cases and referents was designed to make the groups comparable with respect to their exposure history. The strengths of this investigation included a detailed collection of medical, occupational, and environmental history. In particular, information concerning the timing and duration of exposure was collected, which was considered to determine the impact of these factors on the results.

The use of referents with lung diseases had important implications. There was a risk of overmatching if exposures of interest were also associated with the diagnosis of the referent. In such circumstances, we would be less likely to detect an effect. While matching on clinic may

result in overmatching on particular environmental exposures, the risk was reduced because lifetime exposures were of interest rather than only recent exposures. Overmatching, if it were present, would not introduce an association; it would only reduce the effect estimate. A variety of diagnoses were selected to comprise the referent group. As a result, if a particular referent disease was associated with any exposure of interest, the effects of this association would be diluted when cases were compared with referents overall.

Although a variety of respiratory diagnoses were selected for the referent group, asthma referents comprised a large proportion of the referent group. Two referent series were used in the analysis: asthma referents and non-asthma referents. There were important differences between the two referent groups. Importantly, the exposure distribution for asthma referents was different than other controls in the population. As mentioned previously, residence on a farm during childhood was inversely associated with asthma, which produced an apparent (univariate) association between farm residence and sarcoidosis. While an elevated odds ratio may reflect either an increased risk for cases or a reduced risk for referents, previous studies have suggested the latter. In addition, farm residence was highly correlated with drinking un-piped water and/or raw milk, which also had a univariate association with sarcoidosis for this comparison.

Even though referents were identified from the same clinics as cases, the catchments for different diseases within the same clinic may be different. Referents drawn from the same clinic as cases were assumed to be from the same source population as cases. This assumption may not always be valid as it does not take into account the referral patterns that exist for different

diseases. However, referral bias was probably reduced by using referents from the same clinics as cases.

The study was reliant on self-reports from questionnaire data for assessment of lifetime residential and occupational exposures. The use of other patients as referents reduced the likelihood of recall or reporting bias. Study participants and interviewers were not supposed to know if the subject had the diagnosis of interest. However, the Health Ethics Review board in Calgary revised the information sheet (Appendix E) to inform participants of the diagnosis of primary interest for the study.

One benefit of using clinic referents, approached through their specialist physician, was that they would be more likely to participate. However, one important limitation of the study was its low participation rates, specifically in the referent group. The overall participation rate was 39%. Forty-nine percent of cases (684/1392) and 36% (1454/4081) of referents participated. If characteristics of study participants were related to any reported exposure or to disease susceptibility, they may have produced associations that were different from the target population. However, study participants would not have introduced bias in the study if there was no such relationship, even though they may have influenced the external validity of the study. Unfortunately, no information was available on the frequency of exposures in non-participants.

Participants were different than non-participants with respect to demographic characteristics. Case and referent participants were more likely to be older than non-participants. No difference in sex was observed between case participants and non-participants. Males were

more likely to be non-participants in the referent group. We assumed that those who did not reply (non-responders) to our request to participate in the study were refusals. Therefore, the study response rate may be too conservative because non-responders may not have had an opportunity to see the letter if they moved or died.

The study intended to identify all adult cases seen by specialists in Alberta from 1999 to 2005 inclusive. Out of 377 specialists who replied to our request for collaboration, there were 254 specialists throughout Alberta that agreed, giving an overall participation rate of 77%. Most of the specialists who did not agree to participate indicated that they did not have any sarcoidosis patients in the study period. Since the participation rate among specialists was high, the study was expected to recruit a large sample of cases. Although a complex procedure was required to obtain subject informed consent, specialists were not deterred from participation.

Even a coordinated effort between all practicing specialists in a geographic area to identify all sarcoidosis cases would still omit those with undiagnosed sarcoidosis and those relying on GP treatment only. This may have limited the applicability of the study findings. However, as discussed in the background section, specialist physicians submitted the majority (85%) of claims for sarcoidosis (using ICD-9 code 135) in Alberta.

The closer the study population represented the population to whom the results would be extrapolated, the more valid the results. Generalisability of the study results may have been reduced if there were important differences between the clinic attendees and people with sarcoidosis who do not attend these clinics. However the results obtained from a clinic-based

series would only be non-generalisable to the general population if there were etiologically-relevant differences between cases who attended the clinics and cases who did not.

7.5 Future Research and Conclusions

There remains much to be learned about the effect of environmental exposures on the development of sarcoidosis. Since the etiology of sarcoidosis is unknown, it is not possible to estimate latency or the time from exposure to the onset of disease. The timing of this exposure might occur any time from conception. Measurements of exposure to possible etiological agents are limited as well because the amount and intensity of exposure (dose) varies between subjects and over time. Etiological agents may initiate disease at very low doses of exposure and it is difficult to obtain historical data of sufficient detail about past exposures. Both latency and low doses of exposure may have impaired our ability to determine etiological agents. Another important question that could be answered with more thorough investigation is the effect of asthma diagnosis on our study findings. Additional analyses using cases and referents stratified by asthma diagnosis may provide further insight about the importance of rural risk factors in sarcoidosis etiology, particularly when consumption of untreated water is analysed.

This study examined risk factors related to rural living from birth to diagnosis and in early life. Analysis did not identify important etiological factors for sarcoidosis. Further investigation of rural risk factors in this study population may include a distinction on the type of farming plus information on the crops and animals involved. The source of the water supply including streams, wells, or springs may also help to explain the observed associations. In

addition, linking (early) residential exposures with subsequent sensitization from possible occupational exposures will be investigated. In addition, investigation of potential interaction between multiple factors may contribute to our understanding of sarcoidosis etiology. The possibility that environmental exposures interact with genetic factors to additively or synergistically increase risk will be considered.

Table 5.1. Sex of non-participants and participants: cases and referents identified by Alberta Health and Wellness

Sex	Case non-participants, N (%)	Case participants, N (%)	Total	Referent non-participants, N (%)	Referent participants, N (%)	Total
Male	645 (56.5)	391 (57.2)	1036	2470 (55.1)	724 (49.8)	3194
Female	497 (43.5)	293 (42.8)	790	2011 (44.9)	730 (50.2)	2741
Total	1142 (100.0)	684 (100.0)	1826	4481 (100.0)	1454 (100.0)	5935
Statistic	$\chi^2(1) = 0.04$, $P = 0.84$			$\chi^2(1) = 12.5$, $P < 0.001$		

Table 5.2. Birth year of non-participants and participants: cases and referents identified by Alberta Health and Wellness

Birth year	Case non-participants, N (%)	Case participants, N (%)	Total	Referent non-participants, N (%)	Referent participants, N (%)	Total
>1980	27 (2.4)	11 (1.6)	38	109 (2.4)	24 (1.7)	133
1970–1979	254 (22.2)	92 (13.5)	346	733 (16.4)	152 (10.5)	885
1960–1969	359 (31.4)	204 (29.8)	563	1312 (29.3)	359 (24.7)	1671
1950–1959	334 (29.2)	219 (32.0)	553	1412 (31.5)	510 (35.1)	1922
1940–1949	167 (14.6)	157 (23.0)	324	875 (19.5)	396 (27.2)	1271
<1939	1 (0.2)	1 (0.1)	2	40 (0.9)	13 (0.8)	53
Total	1142 (100.0)	684 (100.0)	1826	4481 (100.0)	1454 (100.0)	5935
Statistic	$\chi^2(5) = 36.9$, $P<0.001$			$\chi^2(5) = 71.6$, $P<0.001$		

Table 6.1. Tissues biopsied in cases

Tissue Biopsied	N (%)
No tissue biopsy	340 (49.7)
Lung, with or without a non-lung tissue	204 (29.8)
Lymph node	99 (14.5)
Skin	24 (3.5)
Liver	3 (0.4)
Muscle	3 (0.4)
Stomach	1 (0.1)
Sinus	1 (0.1)
Kidney	1 (0.1)
Multiple non-lung tissue	8 (1.2)
Total	684 (100.0)

Table 6.2. Billing codes on which referents were selected

ICD 9 referent billing codes (description and code, where * represents a valid digit)	N (%)
Acute bronchitis and bronchiolitis, 466.*	8 (0.55)
Bronchitis, not specified as acute or chronic, 490	44 (3.0)
Chronic bronchitis, 491.*	95 (6.5)
Emphysema, 492.*	123 (8.5)
Asthma, 493.*	838 (57.6)
Bronchiectasis, 494	32 (2.2)
Chronic airway obstruction, not elsewhere classified, 496	97 (6.7)
Asbestosis, 501	4 (0.28)
Pneumoconiosis due to other silica or silicates, 502	1 (0.07)
Pneumonitis due to solids and liquids, 507	1 (0.07)
Empyema, 510	10 (0.69)
Pleurisy, 511.*	62 (4.3)
Pneumothorax, 512	8 (0.55)
Abscess of lung and mediastinum, 513	2 (0.14)
Pulmonary congestion and hypostasis, 514	1 (0.07)
Post-inflammatory pulmonary fibrosis, 515	30 (2.1)
Other alveolar and parietoalveolar pneumonopathy, 516	34 (2.3)
Lung involvement in conditions classified elsewhere, 517	7 (0.48)
Other disease of lung, 518.*	57 (3.9)
Total	1454 (100.0)

Table 6.3. Cases and referents by sex

Sex	Cases, N (%)	Asthma referents, N (%)	Non-asthma referents, N (%)	All referents, N (%)	Total
Male	391 (57.2)	386 (46.1)	338 (54.9)	724 (49.8)	1115
Female	293 (42.8)	452 (53.9)	278 (45.1)	730 (50.2)	1023
Total	684 (100.0)	838 (100.0)	616 (100.0)	1454 (100.0)	2138

Table 6.4. Cases and referents by age at diagnosis

Age at diagnosis quartile†	Cases, N (%)	Asthma referents, N (%)	Non-asthma referents, N (%)	All referents, N (%)	Total
1 (youngest)	206 (30.1)	266 (31.7)	74 (12.0)	340 (23.4)	546
2	186 (27.2)	223 (26.6)	120 (19.5)	343 (23.6)	529
3	162 (23.7)	201 (24.0)	173 (28.1)	374 (25.7)	536
4 (oldest)	130 (19.0)	148 (17.7)	249 (40.4)	397 (27.3)	527
Total	684 (100.0)	838 (100.0)	616 (100.0)	1454 (100.0)	2138

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.5. Tobacco smoking status among cases and referents by sex

Tobacco smoking	Male					Female				
	Cases, N (%)	Asthma referents, N (%)	Non-asthma referents, N (%)	All referents, N (%)	Total	Cases, N (%)	Asthma referents, N (%)	Non-asthma referents, N (%)	All referents, N (%)	Total
Never smoked	160 (40.9)	162 (42.0)	59 (17.4)	221 (30.5)	381	112 (38.2)	182 (40.3)	63 (22.7)	245 (33.6)	357
Ever smoked	231 (59.1)	224 (58.2)	279 (82.5)	503 (69.5)	734	181 (61.8)	270 (59.7)	215 (77.3)	485 (66.4)	666
Total	391 (100.0)	386 (100.0)	338 (100.0)	724 (100.0)	1115	293 (100.0)	452 (100.0)	278 (100.0)	730 (100.0)	1023

Table 6.6. Tobacco smoking status among cases and referents by age at diagnosis

Age at diagnosis quartile†	Ever smoked, N (row %)				Never smoked, N (row %)			
	Cases	Asthma referents	Non-asthma referents	All referents	Cases	Asthma referents	Non-asthma referents	All referents
1 (youngest)	138 (67.0)	147 (55.3)	50 (67.6)	197 (57.9)	68 (33.0)	119 (44.7)	24 (32.4)	143 (42.1)
2	109 (58.6)	124 (55.6)	95 (79.2)	219 (63.8)	77 (41.4)	99 (44.4)	25 (20.8)	124 (36.2)
3	92 (56.8)	124 (61.7)	141 (81.5)	265 (70.9)	70 (43.2)	77 (38.3)	32 (18.5)	109 (29.1)
4 (oldest)	73 (56.2)	99 (67.3)	208 (83.5)	307 (77.3)	57 (43.8)	49 (32.7)	41 (16.5)	90 (22.7)
Total	412	494	494	988	272	344	122	466

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.7. Residence on a working farm from birth to diagnosis

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	443 (64.8)	567 (67.7)	1.00	371 (60.2)	1.00	938 (64.5)	1.00
Ever	241 (35.2)	271 (32.3)	1.14 (0.92–1.41)	245 (39.8)	0.84 (0.66–1.03)	516 (35.5)	0.99 (0.82–1.20)
Total known	684 (100.0)	838 (100.0)	–	616 (100.0)	–	1454 (100.0)	–

Table 6.8. Exposure to un-piped water from birth to diagnosis

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	310 (45.3)	444 (53.0)	1.00	241 (39.1)	1.00	685 (47.1)	1.00
Ever	374 (54.7)	394 (47.0)	**1.36 (1.11–1.67)**	375 (60.9)	**0.78 (0.62–0.97)**	769 (52.9)	1.08 (0.90–1.29)
Total known	684 (100.0)	838 (100.0)	–	616 (100.0)	–	1454 (100.0)	–

Table 6.9. Exposure to untreated milk from birth to diagnosis

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	496 (72.5)	637 (76.1)	1.00	417 (67.7)	1.00	1054 (72.5)	1.00
Ever	188 (27.5)	200 (23.9)	1.21 (0.96–1.52)	199 (32.3)	0.79 (0.63–1.01)	399 (27.5)	1.00 (0.82–1.23)
Total known	684 (100.0)	837 (100.0)	–	616 (100.0)	–	1453 (100.0)	–
Unknown	0	1	–	0	–	1	–
Total	684	838	–	616	–	1454	–

Table 6.10. Exposure to mouldy smell from birth to diagnosis

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All Referents, N (% known)	OR (95% CI)
Never	477 (69.7)	549 (65.5)	1.00	430 (69.8)	1.00	979 (67.3)	1.00
Ever	207 (30.3)	289 (34.5)	0.82 (0.66–1.02)	186 (30.2)	1.00 (0.79–1.27)	475 (32.7)	0.89 (0.74–1.09)
Total known	684 (100.0)	838 (100.0)	–	616 (100.0)	–	1454 (100.0)	–

Table 6.11. Exposure to pets from birth to diagnosis

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All Referents, N (% known)	OR (95% CI)
Never	59 (8.6)	73 (8.7)	1.00	47 (7.6)	1.00	120 (8.3)	1.00
Ever	625 (91.3)	765 (91.3)	1.01 (0.71–1.45)	569 (92.4)	0.88 (0.59–1.31)	1334 (91.7)	0.95 (0.69–1.32)
Total known	684 (100.0)	838 (100.0)	–	616 (100.0)	–	1454 (100.0)	–

Table 6.12. Exposure to evergreen trees within 200 meters from birth to diagnosis

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	482 (70.6)	598 (71.6)	1.00	405 (66.1)	1.00	1003 (69.3)	1.00
Ever	201 (29.4)	237 (28.4)	1.05 (0.84–1.32)	208 (33.9)	0.81 (0.64–1.03)	445 (30.7)	0.94 (0.77–1.15)
Total known	683 (100.0)	835 (100.0)	–	613 (100.0)	–	1448 (100.0)	–
Unknown	1	3	–	3	–	6	–
Total	684	838	–	616	–	1454	–

Table 6.13. Location (tropical countries versus non-tropical countries) of birthplace residence

Place of birth	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Tropical countries	46 (6.7)	47 (5.6)	1.00	28 (4.5)	1.00	75 (5.2)	1.00
Non-tropical countries	638 (93.3)	790 (94.4)	0.83 (0.54–1.26)	588 (94.5)	0.66 (0.41–1.07)	1378 (94.8)	0.76 (0.52–1.10)
Total known	684 (100.0)	837 (100.0)	–	616 (100.0)	–	1453 (100.0)	–
Unknown	0	1	–	0	–	1	–
Total	684	838	–	616	–	1454	–

Table 6.14. Residence on a working farm at birth

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
No farm	524 (76.7)	677 (80.8)	1.00	461 (74.8)	1.00	1138 (78.3)	1.00
Living on a farm	158 (22.8)	152 (18.1)	**1.34 (1.05–1.73)**	151 (24.2)	0.92 (0.71–1.19)	303 (20.7)	1.13 (0.91–1.41)
Total known	682 (100.0)	829 (100.0)	–	612 (100.0)	–	1441 (100.0)	–
Unknown	2	9	–	4	–	13	–
Total	684	838	–	616	–	1454	–

Table 6.15. Exposure to piped or un-piped water supply in birthplace residence

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Piped water	316 (62.9)	434 (71.0)	1.00	242 (54.6)	1.00	676 (64.1)	1.00
No piped water	186 (37.1)	177 (29.0)	**1.44 (1.12–1.86)**	201 (45.4)	**0.71 (0.55–0.92)**	378 (35.9)	1.05 (0.84–1.31)
Total known	502 (100.0)	611 (100.0)	–	443 (100.0)	–	1054 (100.0)	–
Unknown	182	227	–	173	–	400	–
Total	684	838	–	616	–	1454	–

Table 6.16. Exposure to mouldy smell in birthplace residence

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
No mouldy smell in dwelling	405 (92.9)	483 (90.6)	1.00	361 (91.6)	1.00	844 (91.0)	1.00
Mouldy smell in dwelling	31 (7.1)	50 (9.4)	0.74 (0.46–1.18)	33 (8.4)	0.84 (0.50–1.40)	83 (9.0)	0.78 (0.51–1.20)
Total known	436 (100.0)	533 (100.0)	–	394 (100.0)	–	927 (100.0)	–
Unknown	248	305	–	222	–	527	–
Total	684	838	–	616	–	1454	–

Table 6.17. Exposure to pets in birthplace residence

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
No pets	183 (36.4)	234 (37.9)	1.00	160 (36.0)	1.00	394 (37.1)	1.00
Pets	320 (63.6)	383 (62.1)	1.07 (0.84–1.36)	285 (64.0)	0.98 (0.75–1.28)	668 (62.9)	1.03 (0.83–1.29)
Total known	503 (100.0)	617 (100.0)	–	445 (100.0)	–	1062 (100.0)	–
Unknown	181	221	–	171	–	392	–
Total	684	838	–	616	–	1454	–

Table 6.18. Exposure to evergreen within 200 meters in birthplace residence

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
No tract of evergreens in 200 meters	471 (92.7)	560 (91.8)	1.00	406 (93.3)	1.00	966 (92.4)	1.00
Tract of evergreens within 200 meters	37 (7.3)	50 (8.2)	0.88 (0.57–1.37)	29 (6.7)	1.10 (0.66–1.82)	79 (7.6)	0.96 (0.64–1.44)
Total known	508 (100.0)	610 (100.0)	–	435 (100.0)	–	1045 (100.0)	–
Unknown	176	228	–	181	–	409	–
Total	684	838	–	616	–	1454	–

Table 6.19. Residence on a working farm from birth to 5 years old

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	506 (74.3)	663 (79.1)	1.00	444 (72.1)	1.00	1107 (76.1)	1.00
Ever	178 (26.0)	175 (20.9)	**1.33 (1.05–1.69)**	172 (27.9)	0.91 (0.71–1.16)	347 (23.9)	1.12 (0.91–1.38)
Total known	684 (100.0)	838 (100.0)	–	616 (100.0)	–	1454 (100.0)	–

Table 6.20. Exposure to non-piped water from birth to 5 years old

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	399 (63.3)	549 (71.6)	1.00	324 (57.3)	1.00	873 (65.5)	1.00
Ever	231 (36.7)	218 (28.4)	**1.46 (1.16–1.83)**	241 (42.7)	**0.78 (0.62–0.98)**	459 (34.5)	1.11 (0.91–1.34)
Total known	630 (100.0)	767 (100.0)	–	565 (100.0)	–	1332 (100.0)	–
Unknown	54	71	–	51	–	122	–
Total	684	838	–	616	–	1454	–

Table 6.21. Exposure to untreated milk from birth to 5 years old

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	416 (73.2)	560 (79.7)	1.00	359 (69.4)	1.00	919 (75.3)	1.00
Ever	152 (26.8)	143 (20.3)	**1.43 (1.10–1.86)**	158 (30.6)	0.83 (0.64–1.08)	301 (24.7)	1.12 (0.89–1.40)
Total known	568 (100.0)	703 (100.0)	–	517 (100.0)	–	1220 (100.0)	–
Unknown	116	135	–	99	–	234	–
Total	684	838	–	616	–	1454	–

Table 6.22. Exposure to mouldy smell from birth to 5 years old

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	559 (91.6)	690 (91.5)	1.00	514 (92.6)	1.00	1204 (92.0)	1.00
Ever	51 (8.4)	64 (8.5)	0.98 (0.67–1.45)	41 (7.4)	1.14 (0.75–1.76)	105 (8.0)	1.05 (0.74–1.48)
Total known	610 (100.0)	754 (100.0)	–	555 (100.0)	–	1309 (100.0)	–
Unknown	74	84	–	61	–	145	–
Total	684	838	–	616	–	1454	–

Table 6.23. Exposure to pets from birth to 5 years old

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	206 (32.6)	266 (34.3)	1.00	196 (34.4)	1.00	462 (34.3)	1.00
Ever	426 (67.4)	510 (65.7)	1.08 (0.86–1.34)	374 (65.6)	1.08 (0.85–1.38)	884 (65.7)	1.08 (0.88–1.32)
Total known	632 (100.0)	776 (100.0)	–	570 (100.0)	–	1346 (100.0)	–
Unknown	52	62	–	46	–	108	–
Total	684	838	–	616	–	1454	–

Table 6.24. Exposure to evergreen trees within 200 meters from birth to 5 years old

Exposure	Cases, N (% known)	Asthma referents, N (% known)	OR (95% CI)	Non-asthma referents, N (% known)	OR (95% CI)	All referents, N (% known)	OR (95% CI)
Never	538 (92.3)	649 (90.9)	1.00	476 (92.1)	1.00	1125 (91.4)	1.00
Ever	45 (7.7)	65 (9.1)	0.84 (0.56–1.24)	41 (7.9)	0.97 (0.63–1.51)	106 (8.6)	0.89 (0.62–1.28)
Total known	583 (100.0)	714 (100.0)	–	517 (100.0)	–	1231 (100.0)	–
Unknown	101	124	–	99	–	223	–
Total	684	838	–	616	–	1454	–

Table 6.25. Cases versus all referents demographic analyses (2138 subjects)

Variable	Main Effects Model		Interaction Model	
	OR	**95% CI**	**OR**	**95% CI**
Age at diagnosis quartile†				
1	1.00	–	1.00	–
2	0.89	0.70 to 1.15	1.28	0.86 to 1.94
3	**0.73**	**0.57 to 0.94**	1.37	0.90 to 2.07
4	**0.57**	**0.43 to 0.74**	1.38	0.89 to 2.15
Sex				
Male	1.00	–	1.00	–
Female	**0.75**	**0.63 to 0.91**	**0.74**	**0.61 to 0.89**
Smoking				
Non-smoker	1.00	–	1.00	–
Smoker	**0.74**	**0.61 to 0.89**	**1.47**	**1.03 to 2.12**
Smoking * Age at diagnosis quartile†				
Smoker * 1	–	–	1.00	–
Smoker * 2	–	–	0.82	0.57 to 1.18
Smoker * 3	–	–	**0.54**	**0.36 to 0.79**
Smoker * 4	–	–	**0.36**	**0.24 to 0.55**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.26. Cases versus asthma referents demographic analysis (1522 subjects)

Variable	Main Effects Model	
	OR	**95% CI**
Age at diagnosis quartile†		
1 (youngest)	1.00	–
2	1.08	0.82 to 1.41
3	1.06	0.81 to 1.40
4 (oldest)	1.19	0.67 to 1.26
Sex		
Male	1.00	–
Female	**0.63**	**0.52 to 0.78**
Smoking		
Non-smoker	1.00	–
Smoker	0.94	0.76 to 1.15

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.27. Cases versus non-asthma referents demographic analysis (1300 subjects)

Variable	Main Effects Model	
	OR	**95% CI**
Age at diagnosis quartile†		
1 (youngest)	1.00	–
2	**0.54**	**0.38 to 0.77**
3	**0.33**	**0.23 to 0.47**
4 (oldest)	**0.19**	**0.13 to 0.26**
Sex		
Male	1.00	–
Female	0.97	0.77 to 1.23
Smoking		
Non-smoker	1.00	–
Smoker	**0.37**	**0.29 to 0.48**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.28. Environmental factors among cases and all referents from birth to diagnosis (2138 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	0.99	0.82 to 1.20	0.90	0.70 to 1.17	–	–
Piped water	1.00	–	1.00	–	–	–
Non-piped water	1.08	0.90 to 1.29	1.24	0.98 to 1.57	–	–
No untreated milk	1.00	–	1.00	–	–	–
Untreated milk	1.00	0.82 to 1.23	1.07	0.84 to 1.35	–	–
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	0.89	0.74 to 1.09	0.88	0.72 to 1.08	–	–
No pets	1.00	–	1.00	–	–	–
Pets	0.95	0.69 to 1.32	1.01	0.72 to 1.40	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	0.94	0.77 to 1.15	0.94	0.76 to 1.15	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	0.90	0.70 to 1.15	0.86	0.67 to 1.10	0.89	0.70 to 1.15
3	**0.72**	**0.56 to 0.92**	**0.69**	**0.53 to 0.89**	**0.73**	**0.57 to 0.94**
4 (oldest)	**0.54**	**0.42 to 0.70**	**0.52**	**0.40 to 0.69**	**0.57**	**0.43 to 0.74**
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	**0.74**	**0.62 to 0.89**	**0.76**	**0.63 to 0.92**	**0.75**	**0.63 to 0.91**
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.71**	**0.59 to 0.86**	**0.75**	**0.62 to 0.90**	**0.74**	**0.61 to 0.89**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.29. Environmental factors among cases and asthma referents from birth to diagnosis (1522 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	1.14	0.92 to 1.41	0.87	0.65 to 1.16	–	–
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	**1.36**	**1.11 to 1.67**	**1.43**	**1.10 to 1.86**	**1.37**	**1.11 to 1.69**
No untreated milk	1.00	–	1.00	–	–	–
Untreated milk	1.21	0.96 to 1.52	1.13	0.86 to 1.47	–	–
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.82	0.66 to 1.02	0.82	0.66 to 1.03	0.83	0.66 to 1.03
No pets	1.00	–	1.00	–	–	–
Pets	1.01	0.71 to 1.45	1.00	0.69 to 1.44	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	1.05	0.84 to 1.32	1.09	0.88 to 1.34	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	1.08	0.83 to 1.41	1.02	0.78 to 1.34	1.03	0.78 to 1.35
3	1.04	0.79 to 1.37	0.97	0.73 to 1.29	0.99	0.74 to 1.31
4 (oldest)	1.13	0.84 to 1.53	1.06	0.78 to 1.44	1.07	0.79 to 1.45
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	**0.64**	**0.52 to 0.78**	**0.64**	**0.52 to 0.79**	**0.64**	**0.52 to 0.79**
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	1.06	0.86 to 1.30	1.09	0.88 to 1.34	1.09	0.88 to 1.34

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.30. Environmental factors among cases and non-asthma referents from birth to diagnosis (1300 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	0.84	0.66 to 1.03	0.96	0.70 to 1.32	–	–
Piped water	1.00	–	1.00	–	–	–
Non-piped water	**0.78**	**0.62 to 0.97**	0.93	0.69 to 1.26	–	–
No untreated milk	1.00	–	1.00	–	–	–
Untreated milk	0.79	0.63 to 1.01	0.99	0.74 to 1.33	–	–
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	1.00	0.79 to 1.27	0.99	0.76 to 1.29	–	–
No pets	1.00	–	1.00	–	–	–
Pets	0.88	0.59 to 1.31	0.91	0.59 to 1.41	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	0.81	0.64 to 1.03	0.83	0.65 to 1.07	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	**0.56**	**0.39 to 0.79**	**0.52**	**0.36 to 0.75**	**0.54**	**0.38 to 0.77**
3	**0.34**	**0.24 to 0.47**	**0.32**	**0.22 to 0.45**	**0.33**	**0.23 to 0.47**
4 (older)	**0.19**	**0.13 to 0.26**	**0.18**	**0.13 to 0.26**	**0.19**	**0.13 to 0.26**
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	0.91	0.73 to 1.14	0.98	0.77 to 1.24	0.97	0.77 to 1.23
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.37**	**0.29 to 0.48**	**0.37**	**0.29 to 0.49**	**0.37**	**0.29 to 0.48**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.31. Environmental factors among cases and all referents at birth (1324 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	1.13	0.91 to 1.41	1.13	0.78 to 1.66	–	–
Piped water	1.00	–	1.00	–	–	–
Non-piped water	1.05	0.84 to 1.31	1.15	0.81 to 1.64	–	–
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	0.78	0.51 to 1.20	0.78	0.50 to 1.20	–	–
No pets	1.00	–	1.00	–	–	–
Pets	1.03	0.83 to 1.29	1.08	0.84 to 1.39	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	0.96	0.64 to 1.44	0.88	0.65 to 1.37	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	0.90	0.70 to 1.15	1.03	0.74 to 1.42	0.89	0.70 to 1.15
3	**0.72**	**0.56 to 0.92**	0.76	0.55 to 1.05	**0.73**	**0.57 to 0.94**
4 (oldest)	**0.54**	**0.42 to 0.70**	**0.63**	**0.45 to 0.90**	**0.57**	**0.43 to 0.74**
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	**0.74**	**0.62 to 0.89**	**0.78**	**0.62 to 0.99**	**0.75**	**0.63 to 0.91**
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.71**	**0.59 to 0.86**	**0.75**	**0.59 to 0.96**	**0.74**	**0.61 to 0.89**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.32. Environmental factors among cases and asthma referents at birth (942 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	**1.34**	**1.05 to 1.73**	0.85	0.53 to 1.36	–	–
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	**1.44**	**1.12 to 1.86**	**1.79**	**1.16 to 2.77**	**1.57**	**1.18 to 2.09**
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	0.74	0.46 to 1.18	0.73	0.45 to 1.18	–	–
No pets	1.00	–	1.00	–	–	–
Pets	1.07	0.84 to 1.36	1.09	0.83 to 1.44	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	0.88	0.57 to 1.37	0.77	0.47 to 1.26	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	1.08	0.83 to 1.41	1.18	0.83 to 1.67	1.19	0.84 to 1.68
3	1.04	0.79 to 1.37	1.07	0.75 to 1.53	1.08	0.76 to 1.54
4 (oldest)	1.13	0.84 to 1.53	1.23	0.83 to 1.83	1.24	0.84 to 1.85
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	**0.64**	**0.52 to 0.78**	**0.63**	**0.48 to 0.82**	**0.63**	**0.49 to 0.82**
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	1.06	0.86 to 1.30	1.10	0.84 to 1.43	1.09	0.83 to 1.43

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.33. Environmental factors among cases and non-asthma referents at birth (807 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	0.92	0.71 to 1.19	1.44	0.91 to 2.27	–	–
Piped water	1.00	–	1.00	–	–	–
Non-piped water	**0.71**	**0.55 to 0.92**	0.69	0.45 to 1.05	–	–
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	0.84	0.50 to 1.40	0.89	0.51 to 1.56	–	–
No pets	1.00	–	1.00	–	–	–
Pets	0.98	0.75 to 1.28	1.01	0.74 to 1.39	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	1.10	0.66 to 1.44	0.94	0.53 to 1.68	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	**0.56**	**0.39 to 0.79**	0.67	0.43 to 1.07	**0.54**	**0.38 to 0.77**
3	**0.34**	**0.24 to 0.47**	**0.36**	**0.23 to 0.56**	**0.33**	**0.23 to 0.47**
4 (oldest)	**0.19**	**0.13 to 0.26**	**0.24**	**0.16 to 0.38**	**0.19**	**0.13 to 0.26**
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	0.91	0.73 to 1.14	1.05	0.78 to 1.42	0.97	0.77 to 1.23
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.37**	**0.29 to 0.48**	**0.40**	**0.29 to 0.55**	**0.37**	**0.29 to 0.48**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.34. Environmental factors among cases and all referents from birth to 5 years (1568 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	1.12	0.91 to 1.38	0.94	0.66 to 1.33	–	–
Piped water	1.00	–	1.00	–	–	–
Non-piped water	1.11	0.91 to 1.34	1.18	0.86 to 1.62	–	–
No untreated milk	1.00	–	1.00	–	–	–
Untreated milk	1.12	0.89 to 1.40	1.16	0.85 to 1.57	–	–
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	1.05	0.74 to 1.48	0.96	0.65 to 1.42	–	–
No pets	1.00	–	1.00	–	–	–
Pets	1.08	0.88 to 1.32	1.10	0.87 to 1.39	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	0.89	0.62 to 1.28	0.82	0.56 to 1.21	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	0.90	0.70 to 1.15	0.91	0.68 to 1.21	0.89	0.70 to 1.15
3	**0.72**	**0.56 to 0.92**	**0.69**	**0.52 to 0.93**	**0.73**	**0.57 to 0.94**
4 (oldest)	**0.54**	**0.42 to 0.70**	**0.54**	**0.39 to 0.74**	**0.57**	**0.43 to 0.74**
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	**0.74**	**0.62 to 0.89**	**0.78**	**0.63 to 0.97**	**0.75**	**0.63 to 0.91**
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.71**	**0.59 to 0.86**	**0.77**	**0.62 to 0.97**	**0.74**	**0.61 to 0.89**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.35. Environmental factors among cases and asthma referents from birth to 5 years (1112 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	**1.33**	**1.05 to 1.69**	0.81	0.53 to 1.23	–	–
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	**1.46**	**1.16 to 1.83**	**1.48**	**1.02 to 2.16**	**1.41**	**1.09 to 1.82**
No untreated milk	1.00	–	1.00	–	–	–
Untreated milk	**1.43**	**1.10 to 1.86**	1.27	0.90 to 1.80	–	–
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	0.98	0.67 to 1.45	0.91	0.59 to 1.39	–	–
No pets	1.00	–	1.00	–	–	–
Pets	1.08	0.86 to 1.34	1.04	0.80 to 1.35	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	0.84	0.56 to 1.24	0.77	0.50 to 1.19	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	1.08	0.83 to 1.41	1.08	0.79 to 1.48	1.10	0.80 to 1.50
3	1.04	0.79 to 1.37	0.97	0.70 to 1.34	1.00	0.76 to 1.54
4 (oldest)	1.13	0.84 to 1.53	1.08	0.74 to 1.56	1.12	0.84 to 1.85
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	**0.64**	**0.52 to 0.78**	**0.66**	**0.52 to 0.84**	**0.66**	**0.52 to 0.84**
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	1.06	0.86 to 1.30	1.12	0.88 to 1.43	1.12	0.87 to 1.42

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.36. Environmental factors among cases and non-asthma referents from birth to 5 years (956 subjects): logistic regression analyses

Variable	Univariate Analyses		Main Effects Model		Stepwise Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	–	–
Farm residence	0.91	0.71 to 1.16	1.04	0.68 to 1.61	–	–
Piped water	1.00	–	1.00	–	–	–
Non-piped water	**0.78**	**0.62 to 0.98**	0.87	0.59 to 1.28	–	–
No untreated milk	1.00	–	1.00	–	–	–
Untreated milk	0.83	0.64 to 1.08	1.06	0.73 to 1.54	–	–
No mouldy smell	1.00	–	1.00	–	–	–
Mouldy smell	1.14	0.75 to 1.76	1.02	0.62 to 1.69	–	–
No pets	1.00	–	1.00	–	–	–
Pets	1.08	0.85 to 1.38	1.11	0.82 to 1.49	–	–
No evergreens within 200 meters	1.00	–	1.00	–	–	–
Evergreens within 200 meters	0.97	0.63 to 1.51	0.89	0.54 to 1.46	–	–
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	1.00	–
2	**0.56**	**0.39 to 0.79**	**0.59**	**0.39 to 0.89**	**0.54**	**0.38 to 0.77**
3	**0.34**	**0.24 to 0.47**	**0.35**	**0.24 to 0.53**	**0.33**	**0.23 to 0.47**
4 (oldest)	**0.19**	**0.13 to 0.26**	**0.21**	**0.14 to 0.31**	**0.19**	**0.13 to 0.26**
Sex						
Male	1.00	–	1.00	–	1.00	–
Female	0.91	0.73 to 1.14	1.00	0.76 to 1.32	0.97	0.77 to 1.23
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.37**	**0.29 to 0.48**	**0.41**	**0.30 to 0.55**	**0.37**	**0.29 to 0.48**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Table 6.37. Environmental factors among cases and all referents from birth to diagnosis: unmatched versus matched logistic regression analyses

Variable	Unmatched (N=2138)		Unmatched (N=1049)		Matched (N=1049)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	0.90	0.70 to 1.17	0.89	0.63 to 1.26	0.95	0.65 to 1.37
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	1.24	0.98 to 1.57	1.24	0.90 to 1.70	1.23	0.89 to 1.71
No untreated milk	1.00	–	1.00	–	1.00	–
Untreated milk	1.07	0.84 to 1.35	0.94	0.67 to 1.30	0.84	0.60 to 1.19
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.88	0.72 to 1.08	0.79	0.59 to 1.05	0.77	0.57 to 1.04
No pets	1.00	–	1.00	–	1.00	–
Pets	1.01	0.72 to 1.40	0.91	0.57 to 1.45	0.96	0.59 to 1.57
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.94	0.76 to 1.15	1.12	0.85 to 1.48	1.15	0.85 to 1.54
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	0.86	0.67 to 1.10	0.70	0.48 to 1.02	–	–
3	**0.69**	**0.53 to 0.89**	**0.65**	**0.45 to 0.94**	–	–
4 (oldest)	**0.52**	**0.40 to 0.69**	**0.53**	**0.36 to 0.78**	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	**0.76**	**0.63 to 0.92**	0.93	0.72 to 1.20	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.75**	**0.62 to 0.90**	**0.71**	**0.54 to 0.92**	**0.71**	**0.54 to 0.94**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.38. Environmental factors among cases and asthma referents from birth to diagnosis: unmatched and matched logistic regression analyses

Variable	Unmatched (N=1522)		Unmatched (N=764)		Matched (N=764)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	0.87	0.65 to 1.16	0.81	0.55 to 1.20	0.73	0.46 to 1.17
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	**1.43**	**1.10 to 1.86**	**1.49**	**1.04 to 2.14**	**1.63**	**1.07 to 2.47**
No untreated milk	1.00	–	1.00	–	1.00	–
Untreated milk	1.13	0.86 to 1.47	0.87	0.60 to 1.26	0.89	0.58 to 1.36
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.82	0.66 to 1.03	0.74	0.54 to 1.01	**0.68**	**0.47 to 0.99**
No pets	1.00	–	1.00	–	1.00	–
Pets	1.00	0.69 to 1.44	0.87	0.52 to 1.47	0.92	0.50 to 1.67
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	1.09	0.88 to 1.34	1.35	0.98 to 1.85	1.44	0.99 to 2.10
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	1.02	0.78 to 1.34	0.83	0.56 to 1.25	–	–
3	0.97	0.73 to 1.29	0.91	0.61 to 1.37	–	–
4 (oldest)	1.06	0.78 to 1.44	1.16	0.75 to 1.80	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	**0.64**	**0.52 to 0.79**	0.81	0.61 to 1.08	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	1.09	0.88 to 1.34	1.05	0.79 to 1.42	0.98	0.69 to 1.38

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.39. Environmental factors among cases and non-asthma referents from birth to diagnosis: unmatched and matched logistic regression analyses

Variable	Unmatched (N=1300)		Unmatched (N=661)		Matched (N=661)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	0.96	0.70 to 1.32	1.06	0.68 to 1.65	1.07	0.65 to 1.75
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	0.93	0.69 to 1.26	0.90	0.59 to 1.37	0.99	0.63 to 1.56
No untreated milk	1.00	–	1.00	–	1.00	–
Untreated milk	0.99	0.74 to 1.33	1.02	0.66 to 1.58	0.91	0.56 to 1.46
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.99	0.76 to 1.29	0.88	0.61 to 1.28	1.04	0.68 to 1.59
No pets	1.00	–	1.00	–	1.00	–
Pets	0.91	0.59 to 1.41	0.82	0.43 to 1.54	0.86	0.43 to 1.74
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.83	0.65 to 1.07	0.89	0.63 to 1.26	0.98	0.65 to 1.49
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	**0.52**	**0.36 to 0.75**	**0.39**	**0.21 to 0.72**	–	–
3	**0.32**	**0.22 to 0.45**	**0.27**	**0.15 to 0.49**	**–**	–
4 (oldest)	**0.18**	**0.13 to 0.26**	**0.15**	**0.08 to 0.27**	**–**	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	0.98	0.77 to 1.24	1.09	0.78 to 1.52	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.37**	**0.29 to 0.49**	**0.35**	**0.24 to 0.51**	**0.39**	**0.25 to 0.60**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.40. Environmental factors among cases and all referents at birth: unmatched and matched logistic regression analyses

Variable	Unmatched (N=1339)		Unmatched (N=634)		Matched (N=634)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	1.13	0.78 to 1.66	1.02	0.61 to 1.71	0.76	0.41 to 1.43
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	1.15	0.81 to 1.64	1.23	0.76 to 1.99	1.36	0.74 to 2.48
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.78	0.50 to 1.20	1.05	0.57 to 1.93	1.75	0.81 to 3.80
No pets	1.00	–	1.00	–	1.00	–
Pets	1.08	0.84 to 1.39	1.09	0.76 to 1.54	1.11	0.73 to 1.68
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.88	0.65 to 1.37	1.03	0.54 to 1.96	1.26	0.59 to 2.70
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	1.03	0.74 to 1.42	0.69	0.42 to 1.13	–	–
3	0.76	0.55 to 1.05	0.64	0.40 to 1.04	–	–
4 (oldest)	**0.63**	**0.45 to 0.90**	**0.58**	**0.35 to 0.96**	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	**0.78**	**0.62 to 0.99**	0.91	0.66 to 1.27	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.75**	**0.59 to 0.96**	**0.70**	**0.49 to 0.98**	**0.64**	**0.42 to 0.98**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.41. Environmental factors among cases and asthma referents at birth: unmatched and matched logistic regression analyses

Variable	Unmatched (N=942)		Unmatched (N=460)		Matched (N=460)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	0.85	0.53 to 1.36	0.60	0.31 to 1.17	0.46	0.18 to 1.20
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	**1.79**	**1.16 to 2.77**	**2.23**	**1.19 to 4.18**	**2.51**	**1.01 to 6.25**
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.73	0.45 to 1.18	0.84	0.42 to 1.65	0.87	0.25 to 2.98
No pets	1.00	–	1.00	–	1.00	–
Pets	1.09	0.83 to 1.44	1.12	0.75 to 1.67	1.05	0.62 to 1.79
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.77	0.47 to 1.26	0.74	0.37 to 1.50	1.16	0.48 to 2.80
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	1.17	0.83 to 1.66	0.80	0.47 to 1.38	–	–
3	1.07	0.75 to 1.53	0.86	0.51 to 1.46	–	–
4 (oldest)	1.23	0.83 to 1.83	1.31	0.74 to 2.34	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	**0.63**	**0.48 to 0.82**	0.73	0.50 to 1.06	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	1.10	0.84 to 1.43	1.08	0.74 to 1.58	0.99	0.57 to 1.73

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.42. Environmental factors among cases and non-asthma referents at birth: unmatched and matched logistic regression analyses

Variable	Unmatched (N=807)		Unmatched (N=407)		Matched (N=407)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	1.44	0.91 to 2.27	1.60	0.84 to 3.07	1.06	0.46 to 2.48
Piped water	1.00	–	1.00	–	1.000	–
Non-piped water	0.69	0.45 to 1.05	0.72	0.40 to 1.30	.98	0.43 to 2.25
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.89	0.51 to 1.55	1.54	0.68 to 3.49	2.55	0.94 to 6.93
No pets	1.00	–	1.00	–	1.00	–
Pets	1.01	0.74 to 1.39	1.00	0.64 to 1.57	1.28	0.67 to 2.43
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.94	0.52 to 1.68	1.62	0.61 to 4.28	1.54	0.34 to 6.88
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	0.67	0.43 to 1.06	0.52	0.24 to 1.12	–	–
3	**0.36**	**0.23 to 0.56**	**0.35**	**0.17 to 0.71**	–	–
4 (oldest)	**0.24**	**0.16 to 0.38**	**0.21**	**0.10 to 0.43**	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	1.05	0.78 to 1.42	1.18	0.77 to 1.81	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.40**	**0.29 to 0.55**	**0.35**	**0.22 to 0.57**	**0.35**	**0.18 to 0.69**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.43. Environmental factors among cases all referents from birth to 5 years: unmatched and matched logistic regression analyses

Variable	Unmatched (N=1568)		Unmatched (N=768)		Matched (N=768)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	0.94	0.66 to 1.33	1.03	0.64 to 1.65	0.90	0.49 to 1.63
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	1.18	0.86 to 1.62	1.19	0.77 to 1.84	1.36	0.09 to 2.37
No untreated milk	1.00	–	1.00	–	1.00	–
Untreated milk	1.16	0.85 to 1.57	0.98	0.64 to 1.65	0.84	0.52 to 1.34
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.96	0.65 to 1.42	1.27	0.73 to 2.20	1.47	0.77 to 2.81
No pets	1.00	–	1.00	–	1.00	–
Pets	1.10	0.87 to 1.39	1.06	0.77 to 1.47	1.06	0.72 to 1.58
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.82	0.56 to 1.21	0.79	0.46 to 1.39	0.79	0.41 to 1.51
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	0.91	0.68 to 1.21	0.71	0.46 to 1.09	–	–
3	**0.69**	**0.52 to 0.93**	**0.66**	**0.43 to 1.00**	–	–
4 (oldest)	**0.54**	**0.39 to 0.74**	**0.56**	**0.36 to 0.89**	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	**0.78**	**0.63 to 0.97**	0.91	0.68 to 1.23	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.77**	**0.62 to 0.97**	0.75	0.55 to 1.02	0.78	0.54 to 1.12

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.44. Environmental factors among cases asthma referents from birth to 5 years: unmatched and matched logistic regression analyses

Variable	Unmatched (N=1112)		Unmatched (N=553)		Matched (N=553)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	0.81	0.53 to 1.23	0.94	0.54 to 1.66	0.72	0.33 to 1.55
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	**1.48**	**1.01 to 2.16**	1.45	0.85 to 2.46	1.65	0.82 to 3.33
No untreated milk	1.00	–	1.00	–	1.00	–
Untreated milk	1.27	0.90 to 1.80	0.99	0.61 to 1.63	0.78	0.43 to 1.42
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	0.91	0.59 to 1.39	1.15	0.61 to 2.14	0.76	0.31 to 1.88
No pets	1.00	–	1.00	–	1.00	–
Pets	1.04	0.80 to 1.35	1.04	0.71 to 1.50	1.13	0.70 to 1.83
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.77	0.50 to 1.19	0.65	0.36 to 1.19	0.67	0.31 to 1.47
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	1.08	0.79 to 1.48	0.90	0.56 to 1.45	–	–
3	0.97	0.70 to 1.34	0.92	0.58 to 1.46	–	–
4 (oldest)	1.08	0.74 to 1.56	1.29	0.76 to 2.19	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	**0.66**	**0.52 to 0.84**	0.77	0.55 to 1.09	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	1.12	0.87 to 1.43	1.11	0.79 to 1.57	0.97	0.62 to 1.53

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.45. Environmental factors among cases non-asthma referents from birth to 5 years: unmatched and matched logistic regression analyses

Variable	Unmatched (N=956)		Unmatched (N=493)		Matched (N=493)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–
Farm residence	1.04	0.68 to 1.60	1.12	0.61 to 2.05	0.78	0.34 to 1.78
Piped water	1.00	–	1.00	–	1.00	–
Non-piped water	0.87	0.59 to 1.28	0.94	0.54 to 1.63	1.19	0.56 to 2.54
No untreated milk	1.00	–	1.00	–	1.00	–
Untreated milk	1.06	0.73 to 1.53	0.95	0.55 to 1.65	1.11	0.59 to 2.08
No mouldy smell	1.00	–	1.00	–	1.00	–
Mouldy smell	1.02	0.62 to 1.69	1.45	0.70 to 3.00	**2.66**	**1.10 to 6.44**
No pets	1.00	–	1.00	–	1.00	–
Pets	1.11	0.82 to 1.49	1.03	0.68 to 1.57	0.84	0.48 to 1.49
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.89	0.54 to 1.46	1.12	0.52 to 2.40	0.96	0.37 to 2.51
Age at diagnosis quartile†						
1 (youngest)	1.00	–	1.00	–	–	–
2	**0.59**	**0.39 to 0.89**	**0.37**	**0.19 to 0.73**	–	–
3	**0.35**	**0.24 to 0.53**	**0.29**	**0.15 to 0.56**	–	–
4 (oldest)	**0.21**	**0.14 to 0.31**	**0.17**	**0.09 to 0.32**	–	–
Sex						
Male	1.00	–	1.00	–	–	–
Female	1.00	0.76 to 1.31	1.12	0.76 to 1.64	–	–
Smoking						
Non-smoker	1.00	–	1.00	–	1.00	–
Smoker	**0.40**	**0.30 to 0.55**	**0.40**	**0.26 to 0.61**	**0.48**	**0.28 to 0.83**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.46. Biopsy or non-biopsy proven cases versus all referents demographic analyses

Variable	Biopsy proven cases versus all referents (N=1798)				Non-biopsy proven cases versus all referents (N=1794)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	0.95	0.70 to 1.30	0.95	0.70 to 1.31	0.84	0.61 to 1.16	0.84	0.61 to 1.17
3	**0.71**	**0.51 to 0.98**	0.73	0.53 to 1.01	**0.72**	**0.52 to 1.00**	0.74	0.54 to 1.03
4 (oldest)	**0.49**	**0.34 to 0.69**	**0.51**	**0.36 to 0.73**	**0.60**	**0.43 to 0.83**	**0.63**	**0.45 to 0.89**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.66**	**0.52 to 0.83**	**0.67**	**0.52 to 0.85**	0.84	0.66 to 1.07	0.84	0.66 to 1.07
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.74**	**0.58 to 0.94**	**0.78**	**0.61 to 1.00**	**0.69**	**0.54 to 0.88**	**0.72**	**0.56 to 0.92**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=number of subjects

Table 6.47. Biopsy or non-biopsy proven cases versus asthma referents demographic analyses

Variable	Biopsy proven cases versus asthma referents (N=1182)				Non-biopsy proven cases versus asthma referents (N=1178)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	1.15	0.83 to 1.59	1.15	0.83 to 1.60	1.01	0.72 to 1.41	1.01	0.72 to 1.41
3	1.03	0.73 to 1.45	1.07	0.76 to 1.51	1.05	0.75 to 1.48	1.06	0.75 to 1.50
4 (oldest)	1.02	0.70 to 1.49	1.07	0.73 to 1.57	1.25	0.87 to 1.80	1.29	0.89 to 1.85
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.57**	**0.44 to 0.73**	**0.56**	**0.44 to 0.73**	**0.72**	**0.56 to 0.93**	**0.72**	**0.56 to 0.92**
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	1.09	0.84 to 1.41	1.11	0.86 to 1.44	1.02	0.79 to 1.32	1.01	0.78 to 1.31

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.48. Biopsy or non-biopsy proven cases versus non-asthma referents demographic analyses

Variable	Biopsy proven cases versus non-asthma referents (N=964)				Non-biopsy proven cases versus non-asthma referents (N=960)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	**0.59**	**0.40 to 0.88**	**0.59**	**0.39 to 0.88**	**0.52**	**0.35 to 0.78**	**0.53**	**0.35 to 0.80**
3	**0.33**	**0.22 to 0.50**	**0.33**	**0.22 to 0.50**	**0.34**	**0.23 to 0.51**	**0.35**	**0.23 to 0.53**
4 (oldest)	**0.17**	**0.11 to 0.25**	**0.17**	**0.11 to 0.26**	**0.21**	**0.14 to 0.31**	**0.22**	**0.15 to 0.33**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	0.81	0.62 to 1.05	0.86	0.65 to 1.15	1.03	0.79 to 1.35	1.04	0.9 to 1.38
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.39**	**0.29 to 0.52**	**0.39**	**0.29 to 0.54**	**0.36**	**0.27 to 0.49**	**0.38**	**0.28 to 0.52**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.49. Biopsy or non-biopsy proven cases versus all referents for environmental exposures from birth to diagnosis

Variable	Biopsy proven cases versus all referents (N=1798)				Non-biopsy proven cases versus all referents (N=1794)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	0.97	0.76 to 1.25	1.03	0.74 to 1.44	1.00	0.79 to 1.29	0.78	0.56 to 1.09
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	0.96	0.76 to 1.21	1.07	0.79 to 1.46	1.21	0.96 to 1.54	**1.45**	**1.07 to 1.96**
No untreated milk	1.00	–	1.00	–	1.00	–	1.00	–
Untreated milk	0.89	0.68 to 1.17	0.96	0.70 to 1.31	1.12	0.86 to 1.45	1.20	0.88 to 1.63
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	0.87	0.67 to 1.12	0.86	0.66 to 1.12	0.92	0.71 to 1.19	0.90	0.69 to 1.17
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.15	0.73 to 1.80	1.23	0.78 to 1.94	0.92	0.71 to 1.19	0.85	0.56 to 1.28
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.96	0.74 to 1.25	0.97	0.75 to 1.27	0.92	0.71 to 1.19	0.90	0.69 to 1.17
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	0.95	0.70 to 1.30	0.93	0.68 to 1.27	0.84	0.61 to 1.16	0.80	0.58 to 1.11
3	**0.71**	**0.51 to 0.98**	**0.70**	**0.50 to 0.98**	**0.72**	**0.52 to 1.00**	**0.69**	**0.49 to 0.96**
4 (oldest)	**0.49**	**0.34 to 0.69**	**0.49**	**0.34 to 0.70**	**0.60**	**0.43 to 0.83**	**0.56**	**0.40 to 0.80**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.66**	**0.52 to 0.83**	**0.67**	**0.53 to 0.86**	0.84	0.66 to 1.07	0.85	0.67 to 1.08
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.74**	**0.58 to 0.94**	**0.78**	**0.61 to 1.00**	**0.69**	**0.54 to 0.88**	**0.73**	**0.57 to 0.93**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.50. Biopsy or non-biopsy proven cases versus asthma referents for environmental exposures from birth to diagnosis

Variable	Biopsy proven cases versus asthma referents (N=1182)				Non-biopsy proven cases versus asthma referents (N=1178)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	1.12	0.86 to 1.46	1.02	0.71 to 1.47	1.16	0.89 to 1.51	0.73	0.51 to 1.05
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	1.21	0.94 to 1.55	1.21	0.87 to 1.69	**1.53**	**1.19 to 1.98**	**1.70**	**1.23 to 2.35**
No untreated milk	1.00	–	1.00	–	1.00	–	1.00	–
Untreated milk	1.08	0.81 to 1.44	0.99	0.71 to 1.38	**1.35**	**1.02 to 1.78**	1.29	0.92 to 1.79
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	0.80	0.61 to 1.05	0.80	0.61 to 1.06	0.85	0.65 to 1.11	0.85	0.64 to 1.13
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.22	0.76 to 1.95	1.21	0.75 to 1.96	0.86	0.56 to 1.32	0.81	0.53 to 1.26
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	1.08	0.82 to 1.42	1.08	0.81 to 1.43	1.03	0.78 to 1.37	1.02	0.77 to 1.36
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	1.15	0.83 to 1.59	1.10	0.79 to 1.53	1.01	0.72 to 1.41	0.95	0.67 to 1.34
3	1.03	0.73 to 1.45	1.01	0.71 to 1.43	1.05	0.75 to 1.48	0.95	0.67 to 1.35
4 (oldest)	1.02	0.70 to 1.49	0.98	0.66 to 1.46	1.25	0.87 to 1.80	1.13	0.77 to 1.64
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.57**	**0.44 to 0.73**	**0.57**	**0.44 to 0.74**	**0.72**	**0.56 to 0.93**	**0.72**	**0.56 to 0.93**
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	1.09	0.84 to 1.41	1.12	0.86 to 1.45	1.01	0.79 to 1.32	1.04	0.80 to 1.36

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.51. Biopsy or non-biopsy proven cases versus non-asthma referents for environmental exposures from birth to diagnosis

Variable	Biopsy proven cases versus non-asthma referents (N=960)				Non-biopsy proven cases versus non-asthma referents (N=956)			
	Univariate Analyses		Main Effects Model		Univarate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	0.81	0.62 to 1.07	1.05	0.71 to 1.53	0.84	0.64 to 1.10	0.86	0.59 to 1.27
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	**0.69**	**0.53 to 0.90**	0.86	0.64 to 1.15	0.88	0.67 to 1.15	1.04	0.73 to 1.49
No untreated milk	1.00	–	1.00	–	1.00	–	1.00	–
Untreated milk	**0.71**	**0.53 to 0.95**	0.90	0.63 to 1.29	0.89	0.66 to 1.18	1.11	0.78 to 1.58
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	0.97	0.73 to 1.30	0.94	0.68 to 1.29	1.03	0.78 to 1.38	0.99	0.72 to 1.36
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.05	0.64 to 1.75	1.09	0.63 to 1.90	0.74	0.47 to 1.18	0.79	0.48 to 1.31
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.83	0.63 to 1.11	0.89	0.65 to 1.21	0.79	0.59 to 1.06	0.79	0.58 to 1.07
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	**0.59**	**0.40 to 0.88**	**0.58**	**0.38 to 0.87**	**0.52**	**0.35 to 0.78**	**0.50**	**0.33 to 0.76**
3	**0.33**	**0.24 to 0.50**	**0.33**	**0.22 to 0.50**	**0.34**	**0.23 to 0.51**	**0.33**	**0.22 to 0.50**
4 (oldest)	**0.17**	**0.11 to 0.25**	**0.18**	**0.11 to 0.27**	**0.21**	**0.14 to 0.31**	**0.21**	**0.14 to 0.32**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	0.81	0.62 to 1.05	0.86	0.64 to 1.15	1.03	0.79 to 1.35	1.05	0.79 to 1.39
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.39**	**0.29 to 0.52**	**0.39**	**0.29 to 0.53**	**0.36**	**0.27 to 0.49**	**0.39**	**0.29 to 0.53**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.52. Biopsy or non-biopsy proven cases versus all referents for environmental exposures at birth

Variable	Biopsy proven cases versus all referents (N=1106)				Non-biopsy proven cases versus all referents (N=1117)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	1.04	0.78 to 1.38	1.07	0.65 to 1.75	1.23	0.93 to 1.63	1.18	0.73 to 1.90
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	0.94	0.71 to 1.26	1.11	0.70 to 1.77	1.17	0.88 to 1.55	1.21	0.77 to 1.90
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	0.83	0.47 to 1.44	0.83	0.47 to 1.47	0.73	0.42 to 1.30	0.72	0.40 to 1.28
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.04	0.78 to 1.38	1.06	0.77 to 1.47	1.03	0.77 to 1.37	1.10	0.80 to 1.51
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	1.06	0.64 to 1.77	1.04	0.60 to 1.81	0.87	0.50 to 1.49	0.72	0.40 to 1.33
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	0.95	0.70 to 1.30	1.19	0.79 to 1.81	0.84	0.61 to 1.16	0.89	0.59 to 1.35
3	**0.71**	**0.51 to 0.98**	0.84	0.55 to 1.29	**0.72**	**0.52 to 1.00**	0.70	0.46 to 1.06
4 (oldest)	**0.49**	**0.34 to 0.69**	0.64	0.40 to 1.03	**0.60**	**0.43 to 0.83**	**0.62**	**0.40 to 0.97**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.66**	**0.52 to 0.83**	**0.68**	**0.49 to 0.92**	0.84	0.66 to 1.07	0.88	0.65 to 1.20
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.74**	**0.58 to 0.94**	0.88	0.64 to 1.22	**0.69**	**0.54 to 0.88**	**0.65**	**0.48 to 0.89**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.53. Biopsy or non-biopsy proven cases versus asthma referents for environmental exposures at birth

Variable	Biopsy proven cases versus asthma referents (N=724)				Non-biopsy proven cases versus asthma referents (N=735)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	1.23	0.90 to 1.68	0.81	0.46 to 1.45	**1.46**	**1.08 to 1.98**	0.90	0.52 to 1.57
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	1.29	0.95 to 1.77	1.70	0.99 to 2.92	**1.55**	**1.18 to 2.18**	**1.84**	**1.09 to 3.09**
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	0.79	0.44 to 1.41	0.78	0.43 to 1.44	0.70	0.38 to 1.27	0.69	0.37 to 1.27
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.07	0.79 to 1.46	1.06	0.75 to 1.50	1.06	0.79 to 1.44	1.11	0.79 to 1.55
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.97	0.57 to 1.67	0.90	0.50 to 1.63	0.79	0.45 to 1.40	0.66	0.35 to 1.24
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	1.15	0.83 to 1.59	1.37	0.89 to 2.12	1.01	0.72 to 1.41	0.99	0.64 to 1.53
3	1.03	0.73 to 1.45	1.19	0.75 to 1.87	1.05	0.75 to 1.48	0.96	0.62 to 1.49
4 (oldest)	1.02	0.70 to 1.49	1.25	0.75 to 2.08	1.25	0.87 to 1.80	1.16	0.72 to 1.88
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.57**	**0.44 to 0.73**	**0.55**	**0.39 to 0.77**	**0.72**	**0.56 to 0.93**	0.73	0.52 to 1.01
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	1.09	0.84 to 1.41	1.27	0.91 to 1.79	1.02	0.79 to 1.32	0.93	0.67 to 1.29

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.54. Biopsy or non-biopsy proven cases versus non-asthma referents for environmental exposures at birth

Variable	Biopsy proven cases versus non-asthma referents (N=589)				Non-biopsy proven cases versus non-asthma referents (N=600)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	0.84	0.61 to 1.16	1.27	0.73 to 2.20	1.00	0.74 to 1.36	1.46	0.85 to 2.50
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	**0.64**	**0.46 to 0.88**	0.71	0.43 to 1.18	0.79	0.58 to 1.08	0.73	0.44 to 1.21
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	0.89	0.48 to 1.66	0.92	0.48 to 1.80	0.79	0.42 to 1.49	0.77	0.39 to 1.53
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	0.99	0.71 to 1.36	1.00	0.68 to 1.46	0.98	0.71 to 1.35	1.01	0.69 to 1.48
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	1.21	0.67 to 2.19	1.11	0.57 to 2.18	0.99	0.53 to 1.84	0.68	0.33 to 1.43
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	**0.59**	**0.40 to 0.88**	0.80	0.47 to 1.35	**0.52**	**0.35 to 0.78**	0.61	0.36 to 1.05
3	**0.33**	**0.24 to 0.50**	**0.42**	**0.25 to 0.70**	**0.34**	**0.23 to 0.51**	**0.34**	**0.21 to 0.58**
4 (oldest)	**0.17**	**0.11 to 0.25**	**0.26**	**0.15 to 0.44**	**0.21**	**0.14 to 0.31**	**0.25**	**0.15 to 0.43**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	0.81	0.62 to 1.05	0.90	0.62 to 1.30	1.03	0.79 to 1.35	1.16	0.81 to 1.66
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.39**	**0.29 to 0.52**	**0.49**	**0.23 to 0.72**	**0.36**	**0.27 to 0.49**	**0.36**	**0.25 to 0.53**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.55. Biopsy or non-biopsy proven cases versus all referents for environmental exposures from birth to 5 years old

Variable	Biopsy proven cases versus all referents (N=1456)				Non-biopsy proven cases versus all referents (N=1469)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	1.02	0.77 to 1.34	0.86	0.53 to 1.37	1.00	0.75 to 1.35	1.01	0.65 to 1.57
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	0.99	0.77 to 1.29	1.18	0.78 to 1.79	0.86	0.65 to 1.14	1.20	0.80 to 1.79
No untreated milk	1.00	–	1.00	–	1.00	–	1.00	–
Untreated milk	1.06	0.79 to 1.42	1.12	0.75 to 1.67	0.89	0.66 to 1.18	1.20	0.82 to 1.76
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	1.02	0.65 to 1.61	0.99	0.60 to 1.64	1.17	0.70 to 1.95	0.95	0.58 to 1.56
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.06	0.81 to 1.37	1.15	0.84 to 1.57	1.11	0.83 to 1.49	1.06	0.78 to 1.42
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.98	0.61 to 1.55	0.82	0.49 to 1.36	0.88	0.51 to 1.52	0.83	0.50 to 1.37
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	0.95	0.70 to 1.30	0.98	0.68 to 1.43	0.84	0.61 to 1.16	0.84	0.58 to 1.22
3	**0.71**	**0.51 to 0.98**	0.69	0.47 to 1.03	**0.72**	**0.52 to 1.00**	0.70	0.48 to 1.02
4 (oldest)	**0.49**	**0.34 to 0.69**	**0.50**	**0.32 to 0.78**	**0.60**	**0.43 to 0.83**	**0.56**	**0.37 to 0.85**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.66**	**0.52 to 0.83**	**0.66**	**0.42 to 0.88**	0.84	0.66 to 1.07	0.91	0.69 to 1.20
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.74**	**0.58 to 0.94**	0.84	0.62 to 1.13	**0.69**	**0.54 to 0.88**	**0.73**	**0.55 to 0.97**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.56. Biopsy or non-biopsy proven cases versus asthma referents for environmental exposures from birth to 5 years old

Variable	Biopsy proven cases versus asthma referents (N=953)				Non-biopsy proven cases versus asthma referents (N=966)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	1.21	0.89 to 1.62	0.75	0.44 to 1.28	**1.47**	**1.10 to 1.96**	0.86	0.52 to 1.43
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	1.31	0.99 to 1.74	1.47	0.92 to 2.34	**1.49**	**1.18 to 1.88**	1.48	0.94 to 2.33
No untreated milk	1.00	–	1.00	–	1.00	–	1.00	–
Untreated milk	1.36	0.98 to 1.88	1.21	0.78 to 1.88	**1.51**	**1.10 to 2.07**	1.33	0.87 to 2.03
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	0.96	0.59 to 1.56	0.94	0.55 to 1.60	1.01	0.62 to 1.62	0.91	0.54 to 1.53
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.05	0.80 to 1.39	1.08	0.77 to 1.50	1.10	0.84 to 1.46	0.99	0.72 to 1.37
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	0.92	0.56 to 1.50	0.77	0.45 to 1.33	0.76	0.45 to 1.26	0.81	0.47 to 1.37
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	1.15	0.83 to 1.59	1.18	0.80 to 1.75	1.01	0.72 to 1.41	0.99	0.67 to 1.46
3	1.03	0.73 to 1.45	0.98	0.65 to 1.49	1.05	0.75 to 1.48	0.95	0.64 to 1.42
4 (oldest)	1.02	0.70 to 1.49	0.99	0.62 to 1.60	1.25	0.87 to 1.80	1.10	0.70 to 1.71
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	**0.57**	**0.44 to 0.73**	**0.56**	**0.41 to 0.76**	**0.72**	**0.56 to 0.93**	0.77	0.58 to 1.04
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	1.09	0.84 to 1.41	1.21	0.88 to 1.65	1.02	0.79 to 1.32	1.03	0.76 to 1.39

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

Table 6.57. Biopsy or non-biopsy proven cases versus non-asthma referents for environmental exposures from birth to 5 years old

Variable	Biopsy proven cases versus non-asthma referents (N=775)				Non-biopsy proven cases versus non-asthma referents (N=788)			
	Univariate Analyses		Main Effects Model		Univariate Analyses		Main Effects Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No farm residence	1.00	–	1.00	–	1.00	–	1.00	–
Farm residence	0.82	0.61 to 1.11	0.92	0.55 to 1.55	1.00	0.75 to 1.35	1.13	0.68 to 1.88
Piped water	1.00	–	1.00	–	1.00	–	1.00	–
Non-piped water	**0.70**	**0.53 to 0.93**	0.90	0.56 to 1.43	0.86	0.65 to 1.14	0.88	0.55 to 1.40
No untreated milk	1.00	–	1.00	–	1.00	–	1.00	–
Untreated milk	0.79	0.57 to 1.09	1.03	0.65 to 1.62	0.87	0.64 to 1.20	1.10	0.71 to 1.72
No mouldy smell	1.00	–	1.00	–	1.00	–	1.00	–
Mouldy smell	1.12	0.67 to 1.88	1.03	0.56 to 1.90	1.17	0.70 to 1.95	0.97	0.53 to 1.76
No pets	1.00	–	1.00	–	1.00	–	1.00	–
Pets	1.06	0.79 to 1.42	1.15	0.80 to 1.66	1.11	0.83 to 1.49	1.06	0.75 to 1.51
No evergreens within 200 meters	1.00	–	1.00	–	1.00	–	1.00	–
Evergreens within 200 meters	1.07	0.63 to 1.81	0.89	0.48 to 1.63	0.88	0.51 to 1.52	0.84	0.46 to 1.53
Age at diagnosis quartile†								
1 (youngest)	1.00	–	1.00	–	1.00	–	1.00	–
2	**0.59**	**0.40 to 0.88**	0.64	0.40 to 1.03	**0.52**	**0.35 to 0.78**	**0.56**	**0.35 to 0.90**
3	**0.33**	**0.24 to 0.50**	**0.36**	**0.23 to 0.59**	**0.34**	**0.23 to 0.51**	**0.37**	**0.23 to 0.58**
4 (oldest)	**0.17**	**0.11 to 0.25**	**0.20**	**0.12 to 0.34**	**0.21**	**0.14 to 0.31**	**0.23**	**0.14 to 0.37**
Sex								
Male	1.00	–	1.00	–	1.00	–	1.00	–
Female	0.81	0.62 to 1.05	0.83	0.59 to 1.17	1.03	0.79 to 1.35	1.11	0.80 to 1.54
Smoking								
Non-smoker	1.00	–	1.00	–	1.00	–	1.00	–
Smoker	**0.39**	**0.29 to 0.52**	**0.44**	**0.31 to 0.64**	**0.36**	**0.27 to 0.49**	**0.40**	**0.29 to 0.57**

†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years
N=Number of subjects

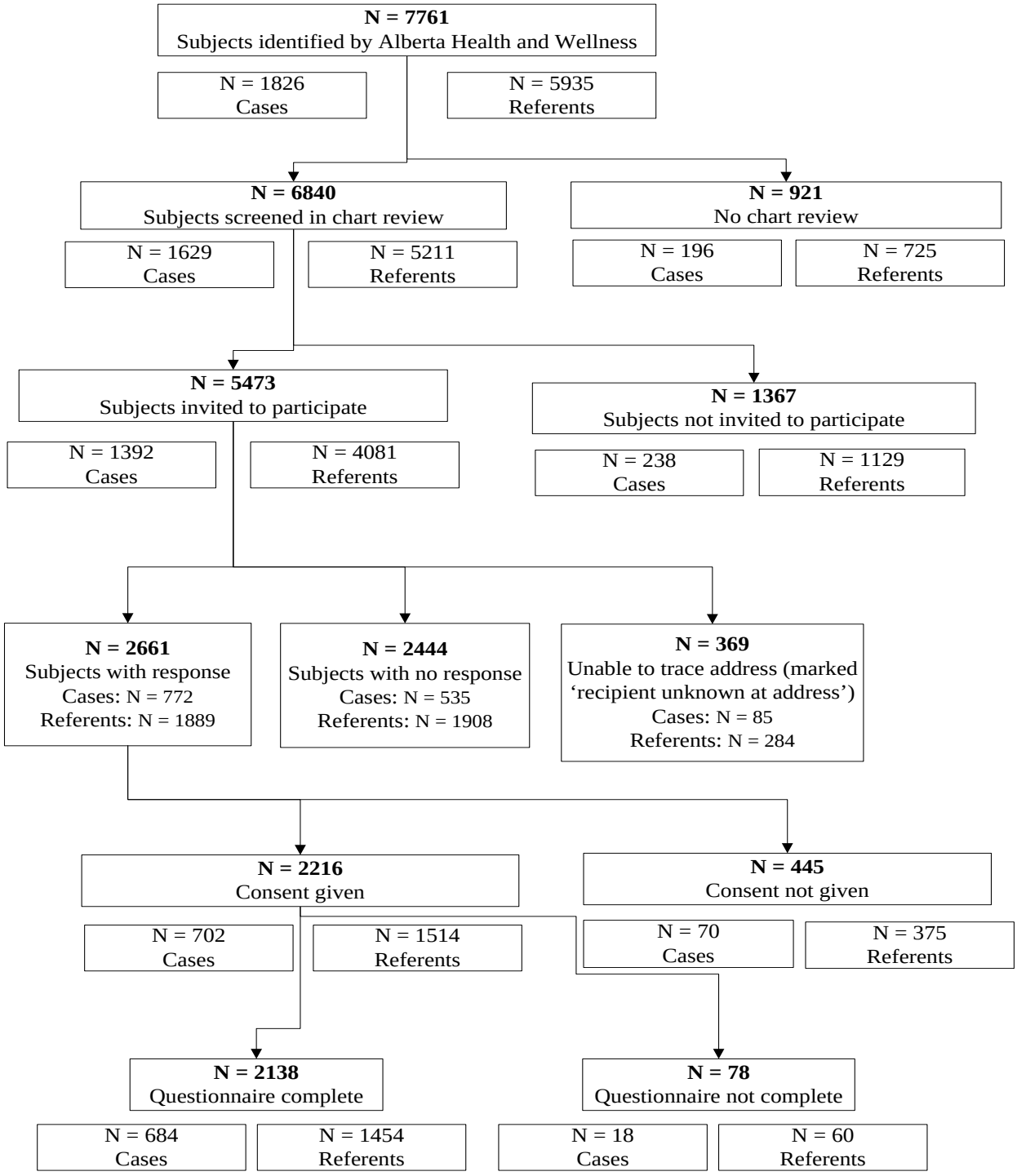
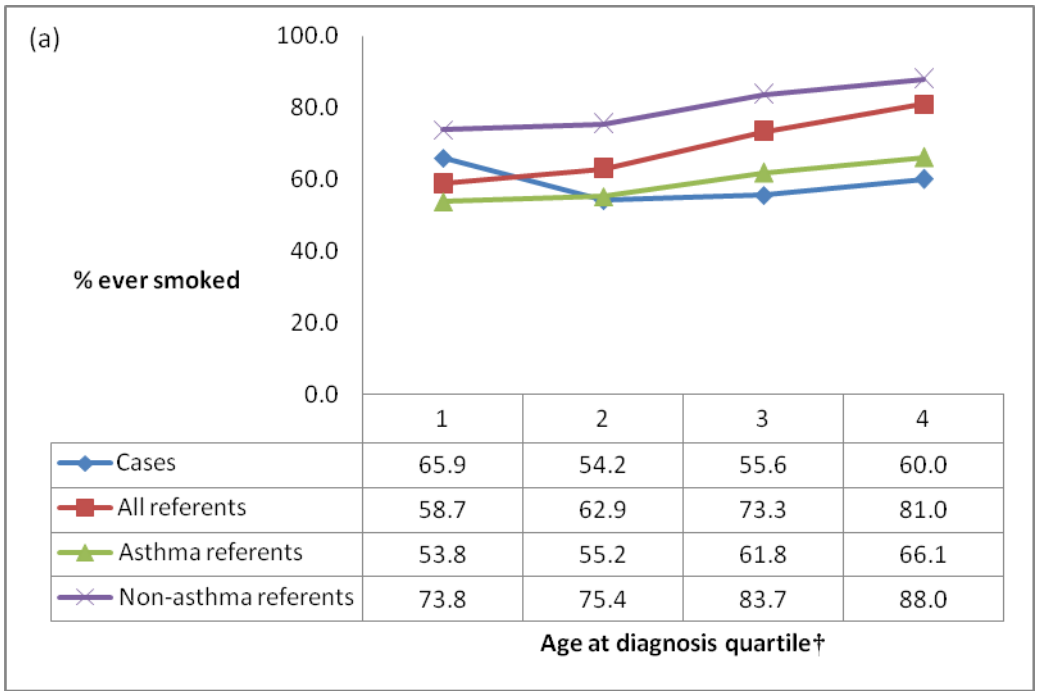
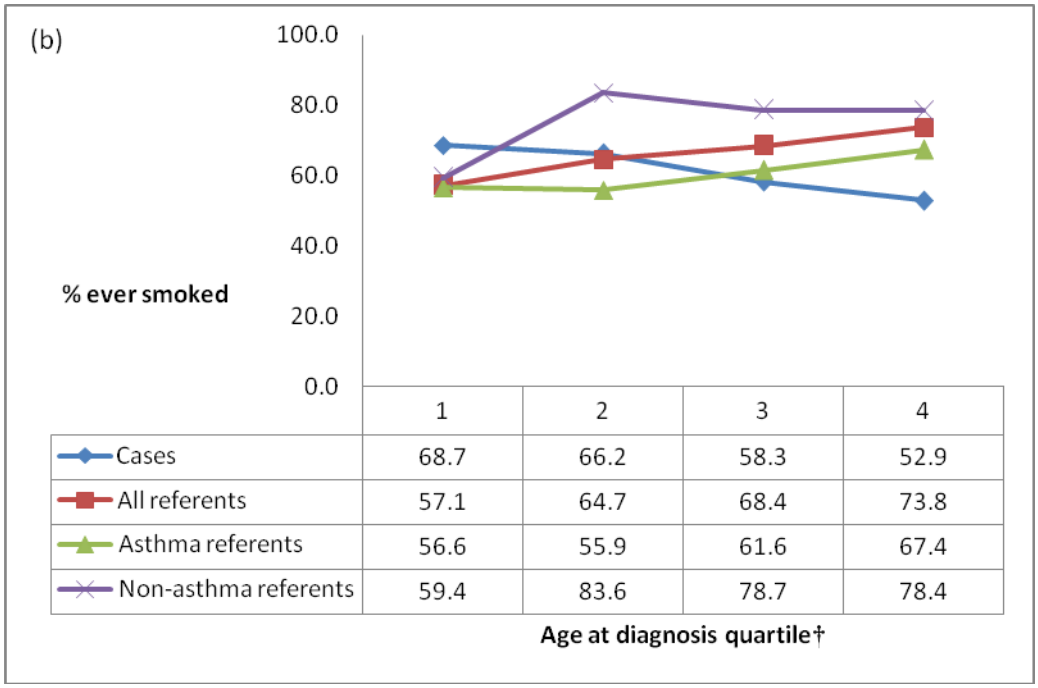


Figure 5.1. Subject recruitment flow-diagram





†Quartile age ranges: 1: ≤38.3 years, 2: >38.3 to ≤46.3 years, 3: >46.3 to ≤51.2 years, 4: >51.2 years

Figure 6.1. Tobacco smoking among cases and referents in (a) males and (b) females by age at diagnosis

7.6 References

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Appendix A. Literature Search and Search String

We searched for analytical epidemiological studies published in English using electronic databases in May 2009 and July 2011. We used a stepwise approach to search databases with the following subject heading terms used alone or in combination: sarcoidosis, environment, rural, and epidemiology. In order to account for multiple forms of the same root/stem word, the search statement included the following truncations/wildcards: sarcoid*, environm*, and epi*. In order to find fewer, more relevant search results, the operator "AND" was used. In addition, terms related to specific rural risk factors were searched in combination with the term sarcoid*. The terms included: farm, agricultur*, water, milk, animal, pet, mo?ld, and pine. Synonyms were used with these terms when the search was too narrow. After reviewing titles and abstract, potentially relevant articles in full text were retrieved.

To avoid missing any relevant articles, the Web of Science database was used to identify additional references from the articles that were retrieved. In addition, hand-searching was used to identify studies from recent review articles.

Appendix B. Specialties Excluded from Study

1. Inactive
2. Practice restricted to:

Oncology/haematological oncology/Neuro-oncology

Bone marrow, stem cell transplant

Critical care

Pediatrics

Addiction medicine, social medicine, wound care

Laboratory medicine

Obstetrics & Gynaecology

Orthopedics

Medical examiner

Clinical nutrition

Palliative care

Nephrology

GI/hepatology

Geriatrics

Sexually transmitted diseases

Appendix C. Letter and Consent Form for Specialists

UNIVERSITY OF ALBERTA
Department of Public Health Sciences
13-103 Clinical Sciences Building
Edmonton, Alberta, Canada T6G 2G3
www.phs.ualberta.ca
Tel: 780.492.6291
Fax: 780.492.9677

(date)

(address)

Dear Dr. _____:

Re: Genes and Environment in the Etiology of Pulmonary Sarcoidosis

I am writing to you on behalf of investigators from the University of Alberta and Alberta Health and Wellness who are studying sarcoidosis in Alberta, where the prevalence is suspected to be high. The etiology of sarcoidosis is not well understood but we believe that environmental exposures and gene environment interactions may be involved.

In order to study this question we need to identify a large group of patients with sarcoidosis. We aim to identify all patients with pulmonary sarcoidosis seen in Alberta by internal and pulmonary medicine specialists in the years since January 1, 1999. With your agreement Alberta Health and Wellness will search administrative records to identify patients whom you have seen and have been given a billing code of 135 (sarcoidosis), together with patients who might form a control group, also seen by you and given a respiratory diagnosis. To do this, we will need to know your practice ID number. Medical records staff employed by the University research team can then, under your guidance, visit your clinic and review these patients' charts to confirm that they are eligible for the study. We would then ask you to sign a letter to the patient (a proforma is attached) asking him/her to contact our team. Nothing further will be required from you. We would do all the work for the study but, of course, keep you informed of the results.

If you would be willing to allow Alberta Health and Wellness to identify patients seen by you since 1999, please sign and return the consent slip attached. We appreciate you may not have seen any cases at all during that time. If Alberta Health and Wellness finds this to be so we will notify you of this directly and your participation would be completed at that point. If you do not see adult patients (18-65 years) at all, it would be helpful if you would indicate this on the consent slip so that we know not to include you further.

We would be most grateful for your agreement to allow this. If you have any questions, please do feel free to contact me or one of the other members of the team at the above telephone number or address.

Many thanks for your help.

Sincerely,

Nicola Cherry, MD, PhD, FRCP, FRCP(C)
Professor and Chair

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CONSENT FOR RELEASE OF INFORMATION - PHYSICIAN

PLEASE TICK THE APPROPRIATE BOX:

EITHER: I, ***Dr.*** _____, ☐ do/ ☐ do not (please tick box) consent to Alberta Health and Wellness identifying from my patient billing information, a list of patients seen since Jan 1999 with the diagnosis of sarcoidosis (code 135) and patients with other respiratory codes to act as a comparison group. I understand that this information will be used only for the study of environmental exposures and gene environment interactions in the etiology of pulmonary sarcoidosis and that no information identifying myself or my patients will appear in any report or be released to a third party.

_____ _____

(signature) (Date)

Dr._____
(Printed Name)

If consenting, please write your Practice ID number below so that Alberta Health can identify your cases.

My Prac ID#: _____

OR: I do not see patients in the range of 18-60 years of age and have not done so in the period since January 1999 ☐

Appendix D. Chart Review Extraction Forms

UNIVERSITY OF ALBERTA

Department of Medicine
Community and Occupational Medicine Program

13-103 Clinical Sciences Building
Edmonton, Alberta, Canada T6G 2G3

www.phs.ualberta.ca

Tel: 780.492.6291
Fax: 780.492.9677

EASE PROJECT – CASES – EXTRACTION SHEET

ID No: _____

Name: _____

DOB: _____

Most recent Address: _____

City: _____

Postal Code: _____

Extraction date: _____

EASE PROJECT – CASES – EXTRACTION SHEET

Physician Name:_____ D.O.B.:_____ ID No: _____

1. Confirm diagnosis for cases:
   Is the file inconsistent with a diagnosis of sarcoidosis (i.e. is it a coding error): ☐ Yes ☐ No
   First date noted: _____

   Comments: _____

   Is this case a lung function interpretation only? ☐ Yes ☐ No
   If yes, who is the referring physician? _____

2. If consistent with sarcoidosis, is there an indication of no pulmonary involvement: ☐ Yes ☐ No
   a) Chest symptoms present? ☐ Yes ☐ No If yes, specify: _____

   _____

   b) Has patient had CXR at time of sarcoidosis? ☐ Yes ☐ No
   If yes, copy of report on file? ☐ Yes ☐ No

   Date: _____ Loc where X-ray taken:_____
   CXR normal: ☐ Yes ☐ No ☐ Unsure
   If abnormal, is x-ray consistent with sarcoidosis? ☐ Yes ☐ No ☐ Unsure
   If no, copy summary: _____

   _____

   Follow-up chest x-ray (last one)
   Copy of report on file ☐ Yes ☐ No

   Date: _____Location where X-ray taken: _____

   c) Lung Biopsy present? ☐ Yes ☐ No Date: _____
   Lung biopsy normal: ☐ Yes ☐ No ☐ Unsure
   If abnormal, is it consistent with sarcoidosis? ☐ Yes ☐ No ☐ Unsure
   Copy summary: _____

   _____

   Referring Physician on pathology report: _____

3. Other biopsy present? ☐ Yes ☐ No
   If yes, location of biopsy: _____

4. Is there any indication that patient has died: ☐ Yes ☐ No
   Date: _____

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EASE PROJECT – CONTROLS – EXTRACTION SHEET

ID No: _____

Name: _____

DOB: _____

Most recent address: _____

City: _____

Postal Code: _____

Extraction date: _____

EASE PROJECT – CONTROLS – EXTRACTION SHEET

ID No: _____

Case Number: _____

Physicians Name: _____

1. Confirm diagnosis for controls:

   Is the file inconsistent with a diagnosis reported by Alberta Health and Wellness: ☐ Yes ☐ No

   First date noted: _____

   Comments: _____

2. Is there any indication that patient has died: ☐ Yes ☐ No

   Date: _____

3. Date of Birth: _____

Appendix E. Letter, Information Sheet, and Consent Form for Subjects

Letter to case and control

(date)

(subject address)

Dear Patient Name:

Some time ago I saw you at my medical clinic because of your respiratory illness. I am now writing to you on behalf of colleagues at the University of Alberta who are investigating environmental and genetic factors that may be important in causing respiratory diseases in Alberta.

Because of your condition, researchers from the University of Alberta would like to talk to you about the study and to see if you might be willing to take part. Under the Alberta Health Information Act I cannot release your contact details directly to the University research team. I have enclosed an information sheet which gives details of the intended work of the University research team, and the part that you might play in it. I have also enclosed a consent form and a prepaid addressed envelope for you to complete and return directly to the researchers at the university.

If you do have any further questions you would like to ask the researchers before making up your mind, please do contact them toll-free at 1-866-492-6093. It is up to you whether you agree to take part or not. If you decide not to take part in the study, this will not affect the medical care you will receive.

Sincerely,

(physician)

UNIVERSITY OF ALBERTA
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Environmental Exposures and Respiratory Health in Alberta

Information sheet

Principal Investigator: Dr Nicola Cherry, Professor
Contact details: Toll free phone: 1-866-492-6093

Who is doing the study?
This study is being carried out by a group of investigators from the University of Alberta and Alberta Health and Wellness. The members of the research group all have an interest in how environmental causes may interact with genetic factors to cause respiratory disease.

Why are we doing the study?
The Alberta environment is unusual in many respects. The northerly location, weather patterns, and high proportion of rural inhabitants make it different to many other parts of Canada and the world. There is evidence that a number of respiratory diseases are associated with these types of environmental conditions, but there is little information about the occurrence of any of these diseases within Alberta. We aim to describe the occurrence of some of these diseases in Alberta, and to look at which environmental factors may be important in causing them. We also plan to see if one or more specific genes that have been associated with respiratory disease in previous research are important in Alberta.

Why have I been chosen?
During the last few months or years you have consulted a specialist physician about one of the respiratory diseases of interest to this study. This physician has agreed to send a letter and this information sheet to you so that you may decide whether you would be willing to take part in the study.

What would I have to do if I took part?
If you agree to take part we will ask you to answer some questions by telephone about the places you have lived and the jobs you have done and to collect and send us a mouthwash sample (discussed below). To help with this we will first send you a single-use bottle of mouthwash, a mouthwash collection kit, and a short form for you to complete in advance of our phone call. This will help you to put down a record of all your jobs and the places you have lived as we shall want to discuss these when we phone. This interview should take 20-30 minutes. At the same time we will also ask you to rinse your mouth with the mouthwash and return the sample to us in the packaging supplied. In recognition of the time involved in participating in this study, we will be happy to pay you $20.00 once you have returned your mouthwash sample, as a symbol of our appreciation for your help.

What will happen to my sample of mouthwash?
The mouthwash will contain a few cells shed naturally from the lining of your mouth and we can use these to see if you have the specific genes we are interested in. Because genetic information is usually considered to be very sensitive, we will take great care with these samples and the information they provide.

The samples will be kept in the Department of Medicine at the University of Alberta for five years after the analyses are complete and then destroyed. All processing and analysis of samples will be undertaken in the laboratories at the University of Alberta, and none of the specimens will be sent elsewhere. A code number will identify stored samples; your name will be linked to this code only in a file held by the principal investigator. Your sample will be tested for the specific genes that have previously been associated with respiratory diseases. Your sample will not be tested for anything else without your permission.

The results will be used by the investigators for the purposes of this study alone, and will not be included in any genetic database. The results of these tests, and even the fact you have been tested, will not be disclosed to anyone else, such as banks and insurance companies. The only exception to this is that you will be able to ask for a copy of your own results, and we will also send a copy to your physician if you ask us to do this. You may also ask that we destroy your sample at any time. Finally, although it is not planned that this research will lead to any commercially valuable discovery related to genetic testing, if it did you would not share in the financial profits of any such discovery.

Linkage to information collected by Alberta Health.
As part of the study we would also like to follow your health in the future. To do this, we need to have your agreement that your Alberta Health Number may be linked to administrative records held by Alberta Health and Wellness to provide the research team with information about any further medical consultations you may have over the years ahead.

Could any benefit come from this study?
This study is designed to identify environmental causes of respiratory disease. It may also show that the genes in which we are interested are important in predisposing some people to harm from these environmental factors. For those who already have disease it is unlikely that the results of this study would improve their health or treatment, but the information should help protect future generations from the agents identified. In this way the results may not only give important information about respiratory diseases in Alberta but may also have benefits to many others worldwide.

Could any harm come to me for taking part in this study?
It is very unlikely that you will come to any harm. All we are asking you to do is to answer some questions over the phone, and to use a widely available, standard mouthwash. The mouthwash is not considered hazardous in normal use and can be bought in many pharmacies and supermarkets for everyday use.

Whether or not you participate in this study will not affect your medical care in any way. Your doctor will still continue to see you and treat you in the way he or she thinks best for your condition. You will be free to withdraw from the study at any time if you wish.

What about confidentiality?
The information you give will be used only for the purposes of this study. It will be stored securely at the University of Alberta. It will only be seen by the research team and will not be passed to any one else without your written permission. Neither your name nor any other identifying information will be published or presented in any report of the results. All the study data will be kept for a period of at least five years after the study is completed before being destroyed, and will be kept securely throughout this period.

Where can I find out more?
If you have any questions you would like to ask before sending back the consent form please phone us on the toll free help line at 1-866-492-6093, if it is after office hours please leave a voice message and we will get back to you within few days of receiving your message, or write to the above address.

What do I do next?
If you are willing to take part in this study please sign the enclosed consent form and return it to us in the pre-stamped envelope provided.

Whom do I contact if I have concerns about the way the study is being conducted?
If you have any concerns or complaints about how this study is being conducted you may contact the Health Research Ethics Board office at the University of Alberta at 780-492-9724.

UNIVERSITY OF ALBERTA

Department of Public Health Sciences

Occupational Health Program

13-103 Clinical Sciences Building
Edmonton, Alberta, Canada T6G 2G3

www.phs.ualberta.ca

Tel: 780.492.6291
Fax: 780.492.9677

CONSENT TO PARTICIPATE IN STUDY

I have read the information sheet, 'Environmental Exposures and Respiratory Health in Alberta'.

I ☐ am/ ☐ am not **(please tick box)** willing to participate in the University of Alberta study described in the information sheet. I understand that I will be contacted by telephone to participate in a questionnaire survey, and will also be asked to use and return a sample of mouthwash. I also agree that my Alberta Health number may be linked to administrative databases held by Alberta Health to allow the investigators to follow the progress of my illness after my interview.

My preferred time to be telephoned would be (please circle your preferred time):

Morning **Afternoon** **Evening** **Any time**

Other (please specify): _____

What is the best phone number to contact you on at this time? _____

_____
(print name)

_____
(address, town, province, postal code)

_____
(home phone number, if different to above) Other phone number (cell/work phone)

_____
(e-mail address – if available)

_____ _____
(signature) (date)

Letter to case and control

(date)

(patient address)

Dear Patient Name:

Some time ago I saw you at my medical clinic because of your respiratory illness. I am now writing to you on behalf of colleagues at the University of Alberta who are investigating environmental and genetic factors that may be important in causing respiratory diseases in Alberta.

Because of your condition, the researchers from the University of Alberta and University of Calgary would like to talk to you about the study and to see if you might be willing to take part. Under the Alberta Health Information Act I cannot release your contact details directly to the University research team. I have enclosed an information sheet which gives details of the intended work of the University research team, and the part that you might play in it. I have also enclosed a consent form and a prepaid addressed envelope for you to complete and return directly to the researchers at the university.

If you do have any further questions you would like to ask the researchers before making up your mind, please do contact them toll-free at 1-866-492-6093. It is up to you whether you agree to take part or not. If you decide not to take part in the study, this will not affect the medical care you will receive.

Sincerely,

(physician)

UNIVERSITY OF ALBERTA
Department of Public Health Sciences
13-103 Clinical Sciences Building
Edmonton, Alberta, Canada T6G 2G3
www.phs.ualberta.ca
Tel: 780.492.6291
Fax: 780.492.9677
UNIVERSITY OF CALGARY

TITLE: Environmental exposures and gene-environment interactions in the etiology of pulmonary sarcoidosis.

SPONSOR: AHFMR

INVESTIGATORS: Nicola Cherry, Robert Cowie, Jeremy Beach, Igor Burstyn, Xing Fang Li, A. Senthilselvan, Donald Schopflocher, Lawrence Svenson

This consent form is only part of the process of informed consent. It should give you a basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. If you have any questions you would like to ask before sending back the consent form please phone us on the toll free help line at 1-866-492-6093 or write to the above address. Take the time to read this carefully. If you are willing to take part in this study please sign the enclosed consent form (page 3) and return it to us in the pre-stamped envelope provided. If you agree to participate, we will return a copy of the signed consent form for your records signed and witnessed by our investigator/delegate together with the research material.

BACKGROUND/WHAT IS THE PURPOSE OF THE STUDY?

The Alberta environment is unusual in many respects. The northerly location, weather patterns, and high proportion of rural inhabitants make it different to many other parts of Canada and the world. There is evidence that a number of respiratory diseases are associated with these types of environmental conditions, but there is little information about the occurrence of any of these diseases within Alberta.

We aim to describe the occurrence of some diseases in Alberta, and to look at which environmental factors may be important in causing them. We also plan to see if one or more specific genes that have been associated with respiratory disease in previous research are important in Alberta.

WHAT WOULD I HAVE TO DO?

If you agree to take part we will ask you to answer some questions by telephone about the places you have lived and the jobs you have done and to collect and send us a mouthwash sample (discussed below). To help with this we will first send you a single-use bottle of mouthwash, a mouthwash collection kit, and a short form for you to complete in advance of our phone call. This will help you to put down a record of all your jobs and the places you have lived as we shall want to discuss these when we phone. This interview should take 20-30 minutes. At the same time we will also ask you to rinse your mouth with the mouthwash and return the sample to us in the packaging supplied.

WHAT ARE THE RISKS?

It is very unlikely that you will come to any harm. All we are asking you to do is to answer some questions over the phone, and to use a widely available, standard mouthwash. The mouthwash is not considered hazardous in normal use and can be bought in many pharmacies and supermarkets for everyday use.

Whether or not you participate in this study will not affect your medical care in any way. Your doctor will still continue to see you and treat you in the way he or she thinks best for your condition. You will be free to withdraw from the study at any time if you wish.

WILL I BENEFIT IF I TAKE PART?

This study is designed to identify environmental causes of respiratory disease. It may also show that the genes in which we are interested are important in predisposing some people to harm from these environmental factors. For those who already have disease it is unlikely that the results of this study would improve their health or treatment, but the information should help protect future generations from the agents identified.

In this way the results may not only give important information about respiratory diseases in Alberta but may also have benefits to many others worldwide.

If you agree to participate in this study there may or may not be a direct medical benefit to you. Your disease may be improved during the study but there is no guarantee that this research will help you. The information we get from this study may help us to provide better treatment in the future for patients with sarcoidosis.

DO I HAVE TO PARTICIPATE?

No, this is simply a request that you consider participating in this study. During the last few months or years you have consulted a specialist physician about one of the respiratory diseases of interest to this study. This physician has agreed to send a letter and this information sheet to you so that you may decide whether you would be willing to take part in the study.

Whether or not you participate in this study will not affect your medical care in any way. Your doctor will still continue to see you and treat you in the way he or she thinks best for your condition. You will be free to withdraw from the study at any time if you wish.

WHAT ELSE DOES MY PARTICIPATION INVOLVE?

If you agree to take part we will ask you to answer some questions by telephone about the places you have lived and the jobs you have done and to collect and send us a mouthwash sample (discussed below). To help with this we will first send you a single-use bottle of mouthwash, a mouthwash collection kit, and a short form for you to complete in advance of our phone call. This will help you to put down a record of all your jobs and the places you have lived as we shall want to discuss these when we phone. This interview should take 20-30 minutes. At the same time we will also ask you to rinse your mouth with the mouthwash and return the sample to us in the packaging supplied.

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not be paid for participating. However, you should not have to pay anything to participate either. The package we send out if you agree to participate should contain all the required materials and includes return postage.

WILL MY RECORDS BY KEPT PRIVATE?

The information you give will be used only for the purposes of this study. It will be stored securely at the University of Alberta. It will only be seen by the research team and will not be passed to any one else without your written permission.

Neither your name nor any other identifying information will be published or presented in any report of the results. All the study data will be kept for a period of at least five years after the study is completed before being destroyed, and will be kept securely throughout this period.

IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

It is very unlikely that you will come to any harm. All we are asking you to do is to answer some questions over the phone, and to use a widely available, standard mouthwash. The mouthwash is not considered hazardous in normal use and can be bought in many pharmacies and supermarkets for everyday use.

In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by the University of Alberta, Alberta Health and Wellness, the University of Calgary, the Calgary Health Region or the Researchers. You still have all your legal rights. Nothing said in the consent form alters your right to seek damages.

SIGNATURES

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigations, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. If you have further questions concerning matters related to this research, please contact:

Dr. Robert Cowie (403) 220-8981

OR

Dr. Nicola Cherry (780) 492-6291

If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary at (403) 220-3782.

_____	_____
Participant's Name	Signature and Date
_____	_____
Investigator/Delegate's Name	Signature and Date
_____	_____
Witness' Name	Signature and Date

The University of Calgary Conjoint Health Research Board has approved this research study.

A signed copy of this consent form will be sent to you to keep for your records and reference.

Appendix F. Package for Study Participants

EASE MAILOUT QUESTIONNAIRE

Please fill in the tables below before we telephone as our interviewer will go through them with you.

Start with where you are currently living and end with the place your mother was living when you were born.

Domicile Number	City, town or village	Province	Country	Postal code (if known)	What year did you start living there?	What year did you stop living there?	Was this a working farm? (Yes/No)
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							

Please fill in the table below, giving details of every job starting with the most recent, that you have done since leaving school.

No	**Job title (what you did)**	**Industry (what they did)**	When did you start? (month/year)	When did you leave? (month/year)	How many hours/week did you perform this job?
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

Finally, please read through the list of industries below and tick a box for every industry you have work in, Again, the interviewer will go through this list with you.

Industry	
Mining	☐ Yes ☐ No
Oil and Gas	☐ Yes ☐ No
Construction	☐ Yes ☐ No
Pulp and paper industry	☐ Yes ☐ No
Chemical industry	☐ Yes ☐ No
Ceramics, stone, clay, glass or concrete	☐ Yes ☐ No
Metal industry	☐ Yes ☐ No
Manufacturing of heating equipment	☐ Yes ☐ No
Manufacturing of industrial machinery	☐ Yes ☐ No
Manufacturing of computer equipment	☐ Yes ☐ No
Manufacturing of semi-conductors and related devices	☐ Yes ☐ No
Manufacturing of electrical equipment	☐ Yes ☐ No
Repairing of electrical equipment	☐ Yes ☐ No
Manufacturing of automotive electrical equipment	☐ Yes ☐ No
Repairing/rebuilding of automotive electrical equipment	☐ Yes ☐ No
Manufacturing/rebuilding of non-electrical vehicle parts	☐ Yes ☐ No
Manufacturing/rebuilding of truck trailers	☐ Yes ☐ No
Ship building	☐ Yes ☐ No
Ship repair	☐ Yes ☐ No
Manufacturing of parts/components for guided missiles or space vehicles	☐ Yes ☐ No
Manufacturing of dental equipment/supplies	☐ Yes ☐ No
Manufacturing of jewelry/precious metal goods	☐ Yes ☐ No
Repairing of jewelry/precious metal goods	☐ Yes ☐ No
Metal working	☐ Yes ☐ No
Manufacturing of nuclear weapons	☐ Yes ☐ No
Recycling	☐ Yes ☐ No
Manufacturing fluorescent lamps	☐ Yes ☐ No
Armed forces	☐ Yes ☐ No
Lumber/wood products	☐ Yes ☐ No
Farming or other agricultural work	☐ Yes ☐ No
Firefighting	☐ Yes ☐ No
Slaughterhouse or meat-packing	☐ Yes ☐ No
Animal handler/veterinarian	☐ Yes ☐ No
Health care sector	☐ Yes ☐ No

Appendix G. Ethics Approval

213 Heritage Medical Research Centre
University of Alberta, Edmonton, Alberta T6G 2S2
p.780.492.9724 (Biomedical Panel)
p.780.492.0302 (Health Panel)
p.780.492.0459
p.780.492.0839
f.780.492.7808

ETHICS APPROVAL FORM

Date: May 2008

Name of Principal Investigator(s): Dr. Nicola Cherry

Department: Medicine

Title: Environmental exposures and gene-environment interactions in the etiology of pulmonary sarcoidosis (phase 2)

The Health Research Ethics Board (Biomedical Panel) has reviewed the file on this project for which all documentation is currently up to date. The research has been found to be acceptable within the limitations of human experimentation.

Specific Comments:

This is the annual re-approval and is valid for one year. Next year, a few weeks prior to its expiration, a Progress Report will be sent to you for completion. If no major issues are identified, your approval will be renewed for another year.

For studies where investigators must obtain informed consent, signed copies of the consent form must be retained, as should all study related documents, so as to be available to the HREB on request. They should be kept for the duration of the project and for at least seven years following its completion. In the case of clinical trials approved under Division 5 of the Food and Drug regulations of Health Canada, study records must be retained for 25 years.

S.K.M. Kimber, MD, FRCPC
Chair, Health Research Ethics Board
Biomedical Panel

Issue #5817

FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

2006-03-06

OFFICE OF MEDICAL BIOETHICS
Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1
Telephone: (403) 220-7990
Fax: (403) 283-8524
Email: omb@ucalgary.ca

Dr. R.L. Cowie
Department of Medicine
University of Calgary
Calgary, Alberta

Dear Dr. Cowie:

RE: Environmental Exposures and Gene-Environment Interactions in the Etiology of Pulmonary Sarcoidosis

Grant ID: 18884

The above-named research, including the Clinical Research Proposal, the Consent Form (Version 1.0, dated December 21, 2005), the Letter to Participating Subjects (Version 1.0, dated December 21, 2005), the Letter to Patient and Control (Version 1.0, dated December 21, 2005), the Consent for Release of Information – Physician sign off, the Consent for Release of Information – Physician letter, the Ease Mail-out Questionnaire, the Ease Telephone Questionnaire (Revised Version dated September 9, 2005), the Beryllium Exposure Questionnaire (Revised Version dated February 9, 2005), the Occupational Exposure Questionnaire has been granted ethical approval by the Conjoint Health Research Ethics Board of the Faculties of Medicine, Nursing and Kinesiology, University of Calgary, and the Affiliated Teaching Institutions. The Board conforms to the Tri-Council Guidelines, ICH Guidelines and amendments to regulations of the Food and Drug Act re clinical trials, including membership and requirements for a quorum.

You and your co-investigators are not members of the CHREB and did not participate in review or voting on this study.

Please note that this approval is subject to the following conditions:
(1) appropriate procedures for consent for access to identified health information has been approved;
(2) a copy of the informed consent form must have been given to each research subject, if required for this study;
(3) a Progress Report must be submitted by 2007-03-06, containing the following information:
   i) the number of subjects recruited;
   ii) a description of any protocol modification;
   iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
   iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
   v) a copy of the current informed consent form;
   vi) the expected date of termination of this project.
(4) a Final Report must be submitted at the termination of the project.

Please accept the Board's best wishes for success in your research.
Yours sincerely,

Glenys Godlovitch, BA(Hons), LLB, PhD

Chair, Conjoint Health Research Ethics Board

GG/sg
c.c. Adult Research Committee Dr. J. Conly (information) Research Services Office of Information & Privacy Commissioner

Appendix H. EASE Questionnaire

ID No.: _____

EASE TELEPHONE QUESTIONNAIRE

Name of Participant: _____

Address: _____

_____

Telephone Number: (_____) _____

****

Name of Interviewer: _____

Date of Contact	Time of Contact	Outcome of Contact

DATE OF INTERVIEW: _____

TIME INTERVIEW STARTED: _____

TIME INTERVIEW ENDED: _____

ID No.: _____

OCCUPATIONAL EXPOSURE HISTORY QUESTIONNAIRE – EASE

Hello Mr/Mrs_____. My name is _____ and I am calling from the University of Alberta about the study of environmental factors and respiratory disease. You sent back the form agreeing to take part in the study and suggested this might be a good time to phone.

1. May I go ahead and first check your date of birth?

   Date of Birth: [__][__] [__][__] [__][__][__][__]
   day month year

2. Have you received the letter and tables we previously mailed? Could you get these out now.
   First I'd like to find out something about where you have lived since you were born. For each place I'd like to know the name of the city, town, village or settlement in which you lived and, if you know it, the postal code. Let's start with where you are currently living and end with the place your mother was living when you were born.
   [Interviewer: after completing each line ask "Where did you live next?"]
   If under 3 months at a residence, do not record

Domicile Number	City, town or village	Province	Country	Postal code	What year did you		Was this a working farm? (Yes/No)
					start living there?	stop living there?	
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							

ID No.: _____

Domicile Questionnaire **Domicile Number [1]**

Lets first talk about the place you are living now.
Interviewer: You may tick more than one box if applicable.

D1 First can you tell me about the water supply. Is it:

- ☐ Piped water from the utility company
- ☐ Spring water
- ☐ Well water
- ☐ Other (e.g. river) _____
  (Interviewer write in)

D2 How do you heat this place? Is it:

- ☐ Natural gas
- ☐ Fuel oil
- ☐ Electricity
- ☐ Kerosene
- ☐ Coal
- ☐ Wood
- ☐ Something else _____
  (Interviewer write in)

D3 What fuel is used for cooking? Is it:

- ☐ Natural gas
- ☐ Fuel oil
- ☐ Electricity
- ☐ Kerosene
- ☐ Coal
- ☐ Wood
- ☐ Something else _____
  (Interviewer write in)

D4 Do you have any heating stoves or fireplaces in this place (do not include electrical)?

		How many were there?	What did they burn?	How often were they used?
Heating Stove	☐ Yes ☐ No		☐ Wood ☐ Coal ☐ Gas ☐ Other (please specify)	☐ Everyday in winter ☐ Every week in winter ☐ Occasionally
Fireplace	☐ Yes ☐ No		☐ Wood ☐ Coal ☐ Gas ☐ Other (please specify)	☐ Everyday in winter ☐ Every week in winter ☐ Occasionally

ID No.: _____

Domicile Number [1]

D5 Do you ever have a wood fire, wood pit or BBQ outside? ☐ Yes ☐ No

If yes,

Wood fire/wood pit		☐ Everyday in summer ☐ Every week in summer ☐ Occasionally ☐ Other (e.g. everyday year round)
BBQ	What do you burn? ☐ Wood ☐ Charcoal ☐ Gas ☐ Other (please specify)	☐ Everyday in summer ☐ Every week in summer ☐ Occasionally ☐ Other (e.g. everyday year round)

D6 Do you usually drink milk?

☐ Yes
☐ No

If yes, was it:

☐ Bought in a store
☐ Direct from a local farm
☐ Other _____
(Interviewer write in)

D7 Do you keep any animals or birds (other than farm animals) in this place?

☐ Yes
☐ No

If yes, did you have:

		If yes, how many
Cats	☐ Yes ☐ No	
Dogs	☐ Yes ☐ No	
Horses	☐ Yes ☐ No	
Cage birds	☐ Yes ☐ No	
Other _____ *(Interviewer write in)*	☐ Yes ☐ No	

D8a Has there been any renovation done that arose from water damage?

☐ Yes
☐ No
☐ Uncertain

D8b Do you ever see mold grow anywhere on the inside of the dwelling?

- ☐ Yes
- ☐ No
- ☐ Uncertain

D8c Does any part of the house smell moldy?

- ☐ Yes
- ☐ No
- ☐ Uncertain

D9a Is this place:

- ☐ close to other homes
- ☐ is it way off by itself?

D9b How close is the nearest household to you?

- ☐ less than 20 meters
- ☐ 20-200 meters
- ☐ greater than 200 meters

D10a Is the place:

- ☐ surrounded by trees
- ☐ is the nearest woodland a long way off?

D10b Is the nearest tract of trees (say 20 or more)?

- ☐ less than 20 meters
- ☐ 20-200 meters
- ☐ greater than 200 meters

D10c What sort of trees are the ones closest to you?

- ☐ Mainly evergreens (e.g., pine, spruce)
- ☐ Mainly trees that lose their leaves in winter (e.g., poplar)
- ☐ Mixed

Interviewer: ***Only ask the following questions for working farm residences (if on page 2, question 2, Column 8 = yes – go to DF1; if no – go to next Domicile Number (take new sheet))***

DF1 While you are living on this farm, do you help with the farm work or just live there?

- ☐ Worked on the farm as an adult
- ☐ Worked on the farm as a child
- ☐ Just lived there

DF2a Do you grow grain commercially on this farm?

- ☐ Yes
- ☐ No

If yes, what grain do you grow?

_____

DF2b Do you grow fruits and vegetables on this farm?

☐ Yes
☐ No

If yes, what fruits/vegetables do you grow?
(Interviewer: If for own consumption only, indicate this below)

_____

DF3 On this farm do you keep:

		If yes, how many on average
Cattle	☐ Yes ☐ No	
Pigs	☐ Yes ☐ No	
Chickens/Turkeys	☐ Yes ☐ No	
Sheep	☐ Yes ☐ No	
Horses	☐ Yes ☐ No	
Other _____ ***(Interviewer write in)***	☐ Yes ☐ No	

DF4 If kept any animals, do you recall any disease outbreak amongst the animals?

☐ Yes
☐ No

If yes, which of the animals?

☐ Cattle
☐ Pigs
☐ Chickens/Turkeys
☐ Sheep
☐ Horses
☐ Other _____
(Interviewer write in)

How often does this happen?

☐ Once only
☐ More than once

If so, what was the illness and what animals were affected? ***(interviewer write in verbatim)***

_____

_____

_____

ID No.: _____

Education history

3. Did you attend secondary school?

☐ Yes
☐ No

If no, go to question 4.

If yes, was it in North America?

☐ Yes
☐ No

If yes, what is the highest grade you completed in secondary school?

_____

If no, how old were you when you left secondary education?

_____

Did you go onto college or university?

☐ Yes
☐ No

If yes,
How many years of college or university did you complete?

Full time _____

Part time _____

Employment history

4. Lets now talk about your work,
Are you now in paid employment for yourself or somebody else?

☐ Yes
☐ No

If no,
Have you ever been in paid employment for yourself or somebody else?

☐ Yes
☐ No

If no,
What have you been doing since you left school? ***(interviewer write in verbatim)***

_____

_____

_____

ID No.: _____

5a. Could you now look at the employment table previously mailed to you.
Would you tell me about every job, starting with the most recent, that you have done since leaving school.

Job number	What is the job title? (what did you do)	What industry was it? (what did they do)	When did you start? (month/year)	When did you leave? (month/year)

(Interviewer check for any date gaps and write in the explanation – unemployed, student)

_____

_____

_____

5b. In addition to the employment above, did you do any part-time or volunteer work?

_____

_____

_____

ID No.: _____

6. Now I want to check through the list of jobs and industries that we sent you and asked you to think about before this interview. Do you have it with you? I'll go through it quickly. Did you ever work in: ***(Interviewer: If numerous job numbers for each industry, complete a separate industry questionnaire page for each job)***

Industry		Job number from Question 5	Industry questionnaire Page:
Mining	☐ Yes ☐ No		1
Oil and Gas	☐ Yes ☐ No		2
Construction	☐ Yes ☐ No		3
Pulp and paper industry	☐ Yes ☐ No		4
Chemical industry	☐ Yes ☐ No		5
Ceramics, stone, clay, glass or concrete	☐ Yes ☐ No		6
Metal industry	☐ Yes ☐ No		7
Manufacturing of heating equipment	☐ Yes ☐ No		8
Manufacturing of industrial machinery	☐ Yes ☐ No		9-10
Manufacturing of computer equipment	☐ Yes ☐ No		11
Manufacturing of semi-conductors and related devices	☐ Yes ☐ No		12
Manufacturing of electrical equipment	☐ Yes ☐ No		13
Repairing of electrical equipment	☐ Yes ☐ No		14
Manufacturing of automotive electrical equipment	☐ Yes ☐ No		15
Repairing/rebuilding of automotive electrical equipment	☐ Yes ☐ No		16
Manufacturing/rebuilding of non-electrical vehicle parts	☐ Yes ☐ No		17
Manufacturing/rebuilding of truck trailers	☐ Yes ☐ No		18
Ship building	☐ Yes ☐ No		19
Ship repair	☐ Yes ☐ No		20
Manufacturing of parts/components for guided missiles or space vehicles	☐ Yes ☐ No		21
Manufacturing of dental equipment/supplies	☐ Yes ☐ No		22
Manufacturing of jewelry/precious metal goods	☐ Yes ☐ No		23
Repairing of jewelry/precious metal goods	☐ Yes ☐ No		24
Metal working	☐ Yes ☐ No		25
Manufacturing of nuclear weapons	☐ Yes ☐ No		26
Recycling	☐ Yes ☐ No		27
Manufacturing fluorescent lamps	☐ Yes ☐ No		28
Armed forces	☐ Yes ☐ No		29

ID No.: _____

Industry		Job number from Question 5	Industry questionnaire Page:
Lumber/wood products	☐ Yes ☐ No		30
Farming or other agricultural work	☐ Yes ☐ No		31
Firefighting	☐ Yes ☐ No		32
Slaughterhouse or meat-packing	☐ Yes ☐ No		33
Animal handler/veterinarian	☐ Yes ☐ No		34
Health care sector	☐ Yes ☐ No		35

7. For the some of the above jobs I need to ask you a few extra questions.
(Interviewer – complete industry questionnaire pages where you indicated yes to that particular industry)

8. Finally just to be sure I've got everything, in any of your jobs we have already talked about, did you carry out any of the following tasks:

Job Task			Job number from Question 5
Welding	☐ Yes ☐ No		
Pesticide application (insecticide, herbicide, seed treatment)	☐ Yes ☐ No		
Metal working (grinding, cutting, machining)	☐ Yes ☐ No		
Furnace work	☐ Yes ☐ No	What did it burn?	
Fire fighting	☐ Yes ☐ No	What types of fires did you fight?	
Handling of animals or animal waste	☐ Yes ☐ No		

Hobbies

Have you ever engaged in hobbies that involves any of the following:

		What year did you start?	What year did you end?	How many minutes a week did you spend on this, on average over those years?
Making jewelry with precious metals or gems?	☐ Yes ☐ No			
Making or repairing or electronic devices, including computers?	☐ Yes ☐ No			
Welding?	☐ Yes ☐ No			
Soldering?	☐ Yes ☐ No			
Car repair or rebuilding?	☐ Yes ☐ No			
Handling semi-conductor chips?	☐ Yes ☐ No			

Are there any other hobbies that your involved with where you have exposure to metals or chemicals? Please specify

_____

_____

ID No.: _____

Smoking Questionnaire

Now I need to ask you a few questions about your smoking history

S1 Have you ever smoked tobacco or tobacco products?

☐ Yes
☐ No

If no, go to H1 (page 17)

If yes, did you smoke:

☐ Cigarettes
☐ Pipe
☐ Cigars

If only smoked pipe and cigars, go to H1 (page 17)
If smoked cigarettes, go to S2.

S2 Have you ever smoked at least one cigarette a day for as long as a year?

☐ Yes
☐ No

If no, go to H1 (page 17)
If yes,

S3 If you have ever smoked cigarettes, at what age did you start smoking at least one cigarette a day?

_____ age in years

S4 Do you now smoke at least one cigarette a day?

☐ Yes
☐ No

If no, how old were you when you last smoked as much as one cigarette a day?

_____ age in years

S5 What is the **MOST** cigarettes a day that you have ever smoked on a regular basis?

_____ cigarettes/day

For how many years did you smoke this much?

_____ years

S6 How many cigarettes a day do/did you **USUALLY** smoke?

_____ cigarettes/day

ID No.: _____

Health Questionnaire

That's nearly all the questions, I just need to ask you about your health, and particularly about diseases of the lung.

H1 As a child or adolescent or since you have grown up did you suffer from:

		How old were you when you first had this diagnosis?
Asthma	☐ Yes ☐ No	
Hayfever/allergic rhinitis	☐ Yes ☐ No	
Eczema/dermatitis	☐ Yes ☐ No	
Acne	☐ Yes ☐ No	
Any other allergies (please specify)	☐ Yes ☐ No	

H2 As allergies are sometimes related to breastfeeding, were you breastfed?

☐ Yes
☐ No
☐ Unsure

H3 Have you ever been diagnosed with:

		How old were you when this was first diagnosed?
Tuberculosis	☐ Yes ☐ No	
Farmer's lung, grain handlers lung, or similar (please specify)	☐ Yes ☐ No	
Sarcoidosis	☐ Yes ☐ No	
Histoplasmosis	☐ Yes ☐ No	

ID No.: _____

H4 Has anyone in your family or living in your household at any time been diagnosed with:

		If yes, what was their relation to you? (eg. father, sister, wife, husband, son/daughter)
Tuberculosis	☐ Yes ☐ No	
Farmer's lung, grain handlers lung, or similar (please specify)	☐ Yes ☐ No	
Sarcoidosis	☐ Yes ☐ No	
Histoplasmosis	☐ Yes ☐ No	
Asthma	☐ Yes ☐ No	
Hayfever/allergic rhinitis	☐ Yes ☐ No	
Eczema/dermatitis	☐ Yes ☐ No	

H5 Do you have any serious medical condition that we haven't yet discussed?

☐ Yes
☐ No

If yes, what condition is that:

_____

H6 Finally, as people from different backgrounds are more at risk of some diseases, may I ask how you define your ethnicity. Would you say you were:

☐ White
☐ Aboriginal
☐ Black
☐ Asian
☐ Other _____
(Interviewer write verbatim)

H7 There is also an interest in a condition called chronic beryllium disease. Has any physician suggested you might have had this disease?

☐ Yes
☐ No
☐ Do not remember/not sure

ID No.: _____

Thank you – that's the end of the questionnaire.

When we have the results, would you like to receive a copy of the results?

☐ Yes
☐ No

We may want to ask a few more questions, could we contact you again later?

☐ Yes
☐ No

Can we now talk about the mouthwash sample, about how to collect it and what you should do to send it back to the university.