Physician Diagnosed Allergic Rhinitis in Manitoba: 1985–1998

By

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A Thesis

Submitted to the Faculty of Graduate Studies in the Partial Fulfilment of the Requirements for the Degree of

Master of Science

Department of Community Health Sciences
University of Manitoba
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Abstract

Introduction. Allergic disorders are a global concern of increasing magnitude. Insufficient clinical definition of allergic diseases is a main reason for inadequacy of epidemiological data, making accurate assessment of time trends in populations difficult. A worldwide increase is noticed in prevalence of asthma-like symptoms and asthma diagnoses, especially among children, but the data for other allergic disorders is less consistent. Though the common nature of allergic disorders is universally recognised, there is a limited knowledge about their exact relationships and changes in these relationships with time. The term "atopy" was first introduced to define the common allergic nature of asthma, allergic rhinitis (AR) and eczema. The lack of standard clinical identification of atopy, however, has led to further categorisation of asthma as atopic and non-atopic and resulted in conflicting evidence about trends in atopy and in atopic proportion of asthma. Other allergic disorders have seen much less research effort and consequently, less is known about their epidemiology.

Objectives. The main aim of this study was to contribute to epidemiological knowledge about two allergic diseases – AR and asthma, using Manitoba Health database of physicians' diagnoses. The study examined time trends in health care utilisation for AR in Manitoba and compared them with time trends in utilisation for asthma during the same period, controlling for urban/rural place of residence, age and gender.

Methods. Claims for provincial residents submitted by physicians to Manitoba Health (MH) between 1985 and 1998 with diagnoses of asthma (ICD-9 493) and AR (ICD-9 477) were extracted from the MH Data repository. Two main outcome measures, annual prevalence (APU) and annual incidence (AIU) of utilisation, were calculated for the total provincial population, and separately for gender, age group, area of residence, and for income quintile in Winnipeg. In addition, aggregate statistics and frequency of utilisation over 14 years and pattern of utilisation for patients with diagnoses recorded in 1991 were analysed.

Results.

- About 14% of the total Manitoba population had diagnosis of AR during the study period, each person with AR being seen twice on average. A little over 17% of the population were diagnosed with asthma and the average asthmatic saw a physician almost 6 times. On average, AR patients made 288 visits and asthma patients made 864 visits per 1,000 diagnosed per year.
- Over 14 years of the study, about 32% of AR patients had a concurrent asthma diagnosis and about 26% of asthmatics were diagnosed with AR at the same time. Co-existence of AR and asthma resulted in increased utilisation for each condition and averaged in 1,113 visits per 1,000 diagnosed per year.
- There were no gender differences in frequency of utilisation for either AR or asthma and utilisation per patient declined with time in all diagnostic groups.
- The APU and AIU of AR varied by region of residence, by age and by gender. They were consistently higher in women compared to men aged 15 to 65, and in urban residents compared to rural up to 45 years of age.
- Trends in utilisation for AR differed from those for asthma. While APU of asthma almost tripled during the study period, APU of AR increased only 24%. APU and AIU for asthma were much higher than APU and AIU for AR in children, and these differences increased with time. In adults, the differences were smaller and changed little with time. Most of the asthma increase occurred in Winnipeg children and in people without diagnosis of AR.

Conclusions. Asthma and AR affected comparable proportions of the Manitoba population, but diagnosis of asthma resulted in much higher utilisation. In addition, time trends in utilisation for AR differed strikingly from trends for asthma, particularly in the youngest age groups. Asthma seems to manifest itself earlier in life than previously and that creates an additional burden on the provincial health care system. Coexistence of AR and asthma in the same person resulted in increased utilisation for each of the conditions. The results also suggest that the relationship of physician diagnosed asthma with underlying atopy in children, as indexed by the diagnosis of AR, may be changing with time.

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LIST OF ABBREVIATIONS

95% CI	- 95 percent Confidence Interval
AD	- Atopic Dermatitis
AIU	- Annual Incidence of Utilisation
APU	- Annual Prevalence of Utilisation
AR	- Allergic Rhinitis
C-M-H	- Cochran-Mantel-Haenszel statistics (odds ratios)
DP	- Disease Prevalence
ECRHS	- European Community Respiratory Health Survey
ETS	- Environmental Tobacco Smoke
ICD-9CM	- International Classification of Diseases, Clinical Modification, version 9
IgE	- Serum Immunoglobulin E
ISAAC	- International Study of Asthma and Allergy in Children
MH	- Manitoba Health
NHANES	- National Health and Nutrition Examination Survey (US)
OR	- Odds Ratio
PAR	- Perennial Allergic Rhinitis
PDAR	- Physician Diagnosed Allergic Rhinitis
PEI	- Prince Edward Island
PHIN	- Personal Health Identification Number
RSV	- Respiratory Syncytial Virus
Q1-Q5	- Quintiles (1 to 5) representing ranking by neighbourhood family income
PAR	- Perennial Allergic Rhinitis
SAR	- Seasonal Allergic Rhinitis
SPT	- Skin Prick Test
UK	- United Kingdom
US	- United States

1. Introduction

1.1. Rationale

Despite numerous scientific advances that have improved the understanding of the mechanisms and pathophysiology of allergic diseases and have resulted in various new treatments, allergic diseases such as asthma, allergic rhinitis (AR) and eczema continue to be a global health problem. Asthma is the most severe of these disorders and has been most extensively studied. There is little doubt that the prevalence of asthma symptoms and asthma diagnoses have increased in the last 2-3 decades, especially in younger people [1] [2] [3] [4], but the reasons behind this increase are unclear. Is symptomatic asthma a different disease now than it was 20 years ago? Is it diagnosed more readily then before? Does it manifest itself earlier in life then it did in previous decades? These questions are still lacking definitive answers.

Allergic rhinitis is a less serious disease than asthma and partly because of this, even fewer data are available regarding its epidemiology and trends in populations [5]. However, there is some evidence that AR is becoming increasingly common [6] [7] [8]. By some estimates, allergic rhinitis affects about 20 percent of population worldwide, causes numerous physician visits and has economic implications in terms of treatment costs and lost productivity [9] [10] [11]. While symptoms may be mild in many people, a significant number have disability. In many populations AR patients outnumber asthma patients and high proportion of new patients have co-existing upper and lower airway diseases [11] [12]. Nasal inflammation may adversely affect asthma and intranasal anti-inflammatory treatment may have a beneficial effect on asthma [13]. For all these reasons allergic rhinitis is recognised as an important health problem and has attracted renewed interest of medical researchers.

1.2. Objectives

Recognition of many common features of AR and asthma have led to their consideration as expressions of inflammation in one common airway as opposed to their classification as distinct and separate entities [13] [14]. Various studies have shown that allergic rhinitis is a significant risk factor for the development of subsequent asthma in both children and adults [15], and patients with both conditions tend to have more severe asthma than asthmatics without AR [16]. Many therapies originally indicated for either allergic rhinitis or asthma are undergoing reassessment to explore their potential utility in both diseases [13]. To effectively implement the results of these assessments, it is important to know the epidemiological similarities and differences of the two conditions to devise the best strategies in dealing with their impact on populations.

An important obstacle to a better understanding of the epidemiology of allergic rhinitis is the absence of a standardised and validated method for identifying the condition. This is a serious problem when comparing results of cross-sectional prevalence studies that employ different methods (questionnaires). At present the most carefully evaluated questionnaire for detecting AR among members of the general population is that used by International Studies of Asthma and Allergies in Children (ISAAC) [17]. These studies however, are limited to school-aged children, though the disease affects all age groups. Very few studies have examined AR prevalence concurrently with asthma prevalence at more than one point in time [2] [4] [6] [18]. Administrative data, while not a perfect tool for measuring the real prevalence of the diseases, offers an advantage of a standardised method that allows comparisons over extended periods of time and also gives insights into the severity of the disease and its burden on the health care system [19] [20].

In this thesis we propose to analyse available administrative data from Manitoba Health Insurance Plan (Manitoba Health Database) to address the following objectives:

- To assess the trends in utilisation of physician resources for allergic rhinitis in the Canadian province of Manitoba from 1985 to 1998;
- To compare these trends to the trends in utilisation for asthma during the same period;
- In addition to describing trends in utilisation in different population groups, this study aimed to test the hypothesis that the relationship of physician-diagnosed asthma with atopy did not change over time. If that was the case, then changes in utilisation for asthma should parallel changes in prevalence of atopy, manifested by changes in utilisation for AR [1].

[1] Clinicians and epidemiologists often use hay fever (AR) as a marker of atopy [4].

2. Literature review – allergic rhinitis (AR)

4.1. Definition and Symptoms

Most commonly, rhinitis is classified into three main categories: allergic rhinitis (seasonal or perennial), infectious rhinitis (acute or chronic), and other (structural, vasomotor, hormonal or non-allergic rhinitis with eosinophilia) [21]:

1. Allergic Rhinitis
   - Seasonal
   - Perennial
2. Infectious Rhinitis
   - Acute
   - Chronic
3. Non-allergic, Noninfectious Rhinitis
   - Structural
   - Vasomotor
   - Hormonal
   - NARES (non-allergic rhinitis with eosinophilia)

Allergic, or IgE-mediated rhinitis (AR), which is the focus of the present study, refers to the antigen-induced, antibody-mediated, hypersensitivity reaction that occurs in the nose. The symptoms include intense itching in the nose and the roof of the mouth, nasal congestion, rhinorrhea (runny nose), and sneezing [22]. Allergic rhinitis may be seasonal or perennial in nature. The seasonal form of allergic rhinitis is caused mostly by allergens released during tree, grass or weed pollination. The synonyms for seasonal allergic rhinitis include pollinosis and hay fever, although the later is frequently used to refer to any type of AR independent of its pattern. The perennial (year-round) form of allergic rhinitis is caused mostly by allergies to animal dander, dust mites or mould spores, with or without associated pollen

exposure. Non-specific triggers such as cold air or strong odours can also trigger the symptoms of AR [21].

The reaction to allergens is usually immediate (early phase). However, it can sometimes be delayed (late phase), occurring hours after the exposure. The entire set of symptoms typically occurs in the early-phase reaction, but nasal congestion alone predominates in the late-phase reaction. The late-phase reaction is typical for chronic allergic rhinitis, with hyper-secretion and congestion as the most prominent symptoms [23]. Itchy, watery, swollen eyes are common accompanying symptoms of AR and primary symptoms of allergic conjunctivitis [24]. Some of the prevalence studies incorporate these symptoms into assessment of the prevalence of allergic rhinoconjunctivitis [25] [26].

4.2. Diagnosis

The International classification of diseases (9th revision) defines AR by the code 477 with the following sub-groups:

477.1 – due to pollen (pollinosis)

477.2 – due to other causes

477.3 – unspecified cause [27].

AR is frequently underdiagnosed because many people affected do not require physician services due to the mild form of the disease and/or availability of over-the counter medications [28]. It can be also confused with other conditions with similar symptoms, such as vasomotor rhinitis (ICD-9CM "472") characterised by chronic nasal congestion without the palate itch, or mislabelled as persistent colds or sinus problems (ICD-9CM "473)" [27]. Appropriate history and a physical examination are often necessary for making the diagnosis of AR, as there is no "gold-standard" test. Measurement of total serum IgE levels can be misleading, because there is a considerable normal range in adults. Many patients with allergic rhinitis will have a normal total IgE level but raised levels of specific IgE to one or more aeroallergens [5]. Skin prick tests (SPT) are objective tests with good specificity although

seasonal changes and some medications can affect the results [29]. Besides, SPTs can be a nuisance and are ineffective in detection of uncommon specific allergens. Nasal challenge testing may be of benefit for patients with an unclear history and negative skin prick/serological tests but there is no standardised method for performing these tests. Skin prick testing, nasal smears for eosinophils, or tests of total or specific IgE all improve sensitivity in diagnosing allergic rhinitis, although between 28 and 60 percent of patients with AR have no evidence of allergy by skin prick testing or measurement of specific IgE [30].

4.3. Etiology

The etiology of allergy in general and allergic rhinitis in particular is not well understood. The current general theory is that the development of allergic disease requires two conditions: the atopic familial predisposition to develop allergy and exposure of the sensitised person to the allergen. Familial aggregation of allergy has been recognised for years [31] [32] [33]. Although it is clear that the genetics of allergic diseases are complex and do not conform to simple Mendelian patterns, candidate genetic loci for atopy have been isolated [34]. Studies in several family cohorts in England have suggested that allergic rhinitis is a dominant trait, and that the gene for the specific IgE responses resides in chromosome-11 [35].

Inhaled airborne allergens, which may be present outdoors or indoors, are the main causes of allergic rhinitis. These include tree and grass pollens, moulds, dust mites, cockroaches, and animal dander [36]. Patients can become sensitive to one or several allergens. Although it is well established that exposure to allergen is necessary for the development of sensitivity and symptoms, it is not known why allergic individuals become sensitive to certain allergens and not others given similar levels of exposure. The threshold of reactivity to each allergen also appears to vary greatly from one patient to another; certain individuals react to small doses, and others tolerate a much larger amount before developing symptoms [36]. The individuals with different atopy-related genotypes have different

sensitivities to environmental exposures, though the exact pattern for gene-environmental interaction involved in the etiology of allergy is yet to be determined [37] [38].

The large number of people affected worldwide and large differences from one community to another suggest that environmental factors play a major role in the development of allergic diseases. It is believed that risk factors that were unknown several decades ago have become relevant in connection with changes in nutrition, environmental exposure, or lifestyle, while some protective factors that were related to a more traditional lifestyle in the past have been lost, which has led to a greater susceptibility to atopic diseases [39] [40]. Environmental factors most extensively studied for their association with allergy can be categorised into the following groups:

Pregnancy/Labour/Birth. Several perinatal and neonatal factors have been identified as associated with the risk of developing atopic illness. Obstetric and labour complications and increased head circumference at birth may increase the risk of allergic disorders among children [41] [42]. Conversely, many cases of pre-term birth are thought to be the result of bacterial infections during pregnancy [43]. The observation that low birth weight infants have a lower prevalence of atopic sensitisation could therefore fit into hypothesis that some prenatal and perinatal bacterial infections can act as potential modulators of atopic manifestations [44]. Some studies have shown that people born during pollination season have increased risk of developing allergy [45], while others found no influence of month of birth in that regard [46].

Childhood infections. There is increasing evidence to indicate that early childhood infections may influence the subsequent sensitisation to allergens [47]. Elimination of previously frequent childhood infections, improved hygiene and a semi-sterile environment may all facilitate atopy. Some studies found that respiratory allergy is less frequent in people heavily exposed to orofecal and foodborne microbes [48] and in those who had measles [49] or hepatitis A [50]. Conversely, some viral infections, particularly those caused by respiratory syncytial virus (RSV), seem to promote the subsequent development of childhood wheezing illness, asthma, and atopy [51] [52]. Although not all studies have

found that RSV increases the risk of allergy, these findings suggest that the effects of infections on the subsequent risk of allergic disease may depend on the pathogen involved. Studies in children who had attended day care centres during infancy support this concept [51] [53] [54].

Family size. Growing evidence indicates that sibship size contributes to the expression of atopy in families [55] [56] [57]. Children born into families with several, particularly older, siblings have been found to have a reduced risk of allergic sensitisation at school age [56]. As in the case of early infections, the "hygiene hypothesis" or alteration of immunoregulation by the action of microbial antigens, attained through increased exposure in the families with many children is the most widely accepted for the explanation of this effect [55].

Domestic environment. Housing characteristics can play a role in the development of allergic conditions through facilitating exposure to increased levels of indoor allergens such as house dust mites, fungi or animal dander, and also through the use of hazardous construction materials [58]. Wall-to-wall carpeting, house humidifiers and some heating options can create conditions favourable for allergic sensitisation. From a number of cross-sectional studies conducted in both children and adults, it has become apparent that there is a close association between allergen exposure in the domestic environment and sensitisation to that specific allergen [59] [60].

Pet ownership. While an early life exposure to cat or dog seems to increase the risk of sensitisation to animal allergens during the first few years of life [59], it may offer a protective effect against developing any sensitisation in later life [60]. The effect is similar to that of the presence of siblings at home [55] - [57] or childhood infections [47] – [50]. Custovic et al have suggested that the difference in effects between early and late childhood might reflect the maturation of the immune response from initial sensitisation to later tolerance [61]. Conversely, Remes et al found that pet ownership did not have any effect on atopic status of individuals though the incidence of asthma symptoms was reduced in those who owned a dog or a cat as a child [62]. This last finding does not fit into any of the previous immunologic models.

Air pollution. Air pollution caused by vehicles' exhaust or industrial fumes was suspected to be responsible for upward trends in allergies. However, no consistent evidence was found to suggest that exposure to air pollution increased the incidence of allergic diseases, although pollutants may trigger exacerbations and enhance allergen responses [63]. A strong association between allergic rhinitis caused by cedar pollen allergy and exposure to heavy traffic was reported from Japan [64], and increased traffic density was found to be a risk factor for asthma and AR in childhood in a German study [65]. However, other investigators were unable to show any relationship between traffic exposure and the prevalence of hay fever or asthma [66]. Also, several studies in children and adults have shown that the prevalence of hay fever and atopy were all significantly lower in the polluted cities of East Germany compared to West German cities [67] [68]. Likewise, the prevalence of atopic sensitisation and asthma was lower in schoolchildren living in the more polluted eastern part of the Baltic area compared with western Sweden with lower levels of air pollution [69] [70]. These findings are more consistent with the theory that air pollution is a trigger of asthma exacerbations, but not a cause of atopy in childhood [71].

Environmental tobacco smoke exposure (ETS). Tobacco smoking is a well-known secondary risk factor for asthma. It increases the severity and the frequency of exacerbations in those who have established disease [72]. However, an extensive review did not support a positive association of allergic sensitisation with parental smoking, either prenatally or postnatally [73]. The same research group found that although environmental smoke increased the risk of respiratory symptoms in children and promoted the development of clinical symptoms among already sensitised subjects, it was not associated with an increased prevalence of atopy [74] [75].

Urban residence and Farm Environment. Some studies have shown that urban residence and urban place of birth are independent risk factors for AR and asthma [76] [77] [78]. The observed increased risk of asthma in urban residents is often attributed to increased traffic density [66] [78]. However, not all studies were able to demonstrate urban-rural differences in the prevalence of allergic symptoms and a relationship with air pollution [76] [79]. A Danish study of general practices found

increased rates of consultations for AR in urban areas, but they were not always symptom-related and the possibility of utilisation bias was not ruled out [80]. No difference was found between urban and rural populations regarding the prevalence of symptoms in Sweden [81] and increased prevalence of atopy was found in rural Ethiopians [82]. Recent results from studies of farming environments added another possible explanation to previously observed differences between urban and rural prevalence of allergic diseases. Studies from several countries have shown that the prevalence of symptoms of AR and of allergic sensitisation was much lower among offspring of farmers than among other children in the same rural areas [83] [84] [85] [86] [87]. This protection was not limited to a specific allergen and exposure to farm animals was the characteristic most strongly linked to the effect [84]. The role of endotoxin exposure as another possible mechanism for this protective effect has been considered in the literature, since highest endotoxin concentrations were found in the environments of farming families and also in dust samples from kitchen floors and mattresses in rural areas [88] [89] [90]. When non-farming rural population was compared to urban population, no difference in the prevalence of atopic disorders was found [83].

Nutrition. It has been suggested that changes in dietary habits in Western societies over the last decades may be related to the increase in the prevalence of allergy [91]. In some prospective studies breast-feeding was found to have a beneficial effect on the incidence of food allergy, eczema, and wheezing in the first years of life [92]. But other studies were not able to reproduce these findings [93] and no consistent protective effect of breast-feeding on the subsequent development of childhood asthma was shown. A benefit from hypoallergenic feeding formulas to at-risk infants with a family background of atopic disease was demonstrated by some studies [94] [95], but this effect seems to be transient [96]. Food allergens are less important in the etiology of allergic rhinitis, but cannot be completely ignored, especially in children [97] [98].

Socio-Economic Status. Several studies in Germany, UK and Italy suggested that high socio-economic status is a potential risk factor for early sensitisation and manifestation of allergic disease in populations of western industrialised countries [99] [100] [101] [102]. A gradient between affluent and poor

regions in the developing world was also shown [103]. These findings however, have not been reproduced in all regions, particularly not in inner-city areas of the United States, where low social stratum has repeatedly been associated with increased asthma morbidity [104]. No correlation between a positive skin test and level of education or income was seen in the Danish population study [80]. In several UK and US studies the prevalence of physicians' diagnoses in children was affected by socio-economic status, but no influence of income on the prevalence of the disease (symptoms) was found [28] [101]. Socio-economic status is most likely a surrogate index for lifestyle characteristics and not a risk factor per se. This measure is assessed differently in different studies and that can explain the inconsistency of the findings.

Occupation. Occupational rhinitis refers to nasal response to airborne substances in the workplace, which may be allergic or non-allergic, e.g., laboratory animal antigen, grain, wood dust, and chemicals. More than 240 agents in the workplace have been shown to cause occupational allergy and the list is growing as new materials and processes are introduced [105]. The prevalence of rhinitis caused by occupational factors is estimated to be between 5% to 15% in workers [21]. High-risk occupations are identified in industries involving exposure to highly active allergens, such as animal products, chemicals, latex and flour [106].

Other factors. Several studies focusing on differences between the former socialist countries and Western European societies reported lower prevalence rates for atopy in the East [68] - [71]. These findings were particularly striking in areas with small genetic differences, such as East and West Germany, where it was found that lifestyle mainly influences the development of atopy in the first years of life [107]. In a recent Swedish study, the prevalence of atopy in children from anthroposophic[1] families was found to be lower than that in children from other families, which led the authors to the conclusion that lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood [108]. The intestinal microflora might be a major source of microbial stimulation of the immune system in early

[1] Anthroposophy is a spiritual view of the human being developed by Austrian philosopher Rudolf Steiner. Anthroposophically Extended Medicine (AEM) is an expansion of conventional medicine well established in Western Europe and has gained recognition In the US, Canada, South America and Eastern Europe.

childhood. The results of a comparative study of Estonian and Swedish children demonstrated that in Estonia the typical microflora includes more lactobacilli and fewer clostridia, which are associated with a lower prevalence of atopic disease [109] [110].

There are many other lifestyle-related factors that have relevance to atopic manifestations in children [40]. The exact mechanisms through which environmental factors might be able to influence the development of allergies are not yet known. A widely considered theory proposes that modern vaccinations, fear of germs and increased hygiene are depriving the immune system of input upon which it is dependent and leads to increased incidence of allergies [50] [55]. Rook and Stanford summarised this theory in a review article entitled "Give us this day our daily germs" [111]. But it is not entirely clear which germs, at what time and under which circumstances. Moreover, results from some studies challenge this hypothesis [49]. Studies of the role of environmental factors are also hindered by the fact that individuals with different atopy-related genotypes will have different sensitivities to environmental exposure [37] [38].

4.4. Epidemiology

Prevalence

Although allergic rhinitis is very common, data regarding its epidemiology is limited and often contradictory [112] [113]. For feasibility reasons, large population studies of AR do not always include allergy testing and the absence of standard definition and methods makes it difficult to interpret and compare the results. Exceptions include European Community Respiratory Health Survey (ECRHS) and International Study of Asthma and Allergy in Children (ISAAC). Phase I of ISAAC studies used a standardised questionnaire as their instrument and provided data about worldwide variations in the prevalence of allergic rhinitis in school-aged children. The ISAAC module on AR included 6 questions and allowed comparisons for both prevalence and severity of AR symptoms in children aged 6-7 and 13-14 years. Rhinitis was described as a problem with sneezing or a runny/blocked nose when a child

did not have a cold or the flu. Additional questions were asked about rhinitis associated with itchy-watery eyes, and about history of hay fever [17]. Across 56 different countries, 156 centres including two Canadian cities, participated in the first phase of this study between 1995 and 1997 [114]. A summary of the results is reproduced in Appendix 1. The reported overall lifetime prevalence of AR in 6-7 year old children varied from 2.0% (Akola, India) to 64% (Cuernavaca, Mexico). For 13-14 years old the figures were from 4.2% (Jima, Ethiopia) to 80.5% (Asuncion, Paraguay). The lowest rates of rhinitis prevalence were found in parts of Eastern Europe, and in South and Central Asia. High rates of prevalence were reported from many centres from different parts of the world, with consistently high numbers found in Australia, New Zealand, and North and South America. There were wide variations observed within many countries, including Australia, Brazil, China, India and France. India's figures for rhinitis ever in 6-7 year old children, for example, varied from 2% to 28%.

ECRHS, a standardised study of respiratory symptoms in adults, was carried out between 1993 and 1995 by 48 centres in 22 countries. The summary of the results has been recently published [115]. Community-based samples of 3,000 to 4,000 people aged 20-44 years were randomly selected in each site and interviewed by mail questionnaire. The primary focus of this study was on asthma and asthma-like symptoms and nasal allergies were assessed by a single question "Do you have nasal allergies? (Yes/No)", which left room for interpretation about its time frame. Random sub-samples of 15-20% were extensively interviewed in person and underwent laboratory testing [116]. Six Canadian sites also participated in this study [117]. A summary of the results, including Canadian data, is reproduced in Appendix 2. The ECRHS reported prevalence of nasal allergies in adults aged 20-44 years varied from 9.5% (Algiers, Algeria) to 40.9% (Melbourne, Australia) [115]. Canadian ECRHS data showed variation by site, increasing from east to west: from 25% (PEI) to 36% (Vancouver). In Winnipeg 28% of those surveyed reported having nasal allergies [117].

For 15 countries, in which both ECRHS and ISAAC surveys were undertaken, there was generally a good agreement between the results of these two studies. For self-reported asthma, 74% of country level and 36% of centre level of variation in ECRHS study was explained by variation in ISAAC study.

For hay fever these numbers were 61% and 73%, and for eczema 41% and 50%, respectively [118]. These findings add support to the validity of the two studies.

Results from other cross-sectional studies are more difficult to interpret and compare because of methodological differences. Some studies have measured current prevalence (i.e. symptoms in the last 12 or 24 months) while others measured history or cumulative prevalence (symptoms ever) or did not explicitly indicate the time frame. To improve specificity, many studies included questions on physician diagnosed AR and/or incorporated some form of physical examination or laboratory testing of sub-samples of both symptomatic and asymptomatic individuals [28] [119]. The largest population study of this kind was the National Health and Nutrition Examination Survey (NHANES II) in the United States, where skin test reactivity was determined on a sample population of over 12,000 individuals 12 to 74 years old at 64 sampling sites in the US from 1976 to 1980 [119]. This study estimated the prevalence of AR to be around 20%.

Where available, administrative data such as insurance claims or data from general practices was used to assess time trends in the prevalence or incidence of AR [19] [20] [28] [80] [120]. Reliance on records of doctors' diagnoses rarely results in incorrect labelling of subjects as rhinitic, but underdiagnosis is common [28]. Patients with mild disease and those with atypical clinical presentation often go undetected. Thus, this definition has a good specificity but low sensitivity. One study found that the previous diagnosis of AR had a specificity 94% and sensitivity 34% in identifying the current disease [5]. Another study determined that for the lifetime physician's diagnosis of AR (PD AR) the specificity was 98% and the sensitivity was 52% [86].

Appendix 3 shows the summary of results from various epidemiological studies of general populations (identified by "Medline" search, 1970-2001). The reported overall prevalence of AR in these studies (allowing for differences in methodology and selection of study participants) varied from 4.5% (Singapore, ages 20-74) [121] to 55% (US, ages 3-54) [122]. A Canadian study published in 1970 reported 19% prevalence for the history of AR in male Ontario physicians [123]. In 1974 a study of the

entire 10,000-person population of Tecumseh (US), showed that annual prevalence of AR was 7.8% in males and 8.2% in females [124]. The cumulative prevalence was about 10% for both genders, and seasonal allergic rhinitis was almost twice as common as perennial allergic rhinitis. More recent U.S. figures suggest a16-20% prevalence rate [119] [125]. Many Asian countries, such as Japan, Turkey and Arabic Emirates, also reported high rates for AR [126] [127] [128]. A national Korean study reported one of the lowest rates in the world [76] though the recent ISAAC study in this country found high rates of AR in children (Appendix 1). Fewer data were available for South America [129], but ISAAC studies there reported the highest rates of AR in children (Appendix 1).

Several studies have estimated the prevalence of seasonal allergic rhinitis, because a good assessment of this can be achieved by questionnaire. The reported prevalence of seasonal AR varied from 1.6 % (China, ages12-20) [130] to 41.5% (US, cumulative at age 40) [131]. Less information was available about the prevalence of perennial rhinitis, but studies that focused on this form of AR also reported wide variations, from 1.1% (Korean national survey) [76] to 20.4% (US, NHANES, ages 12-74) [119]. A British study estimated that 13% of adult's population had perennial AR, 8% had both seasonal and perennial AR, and 3% had only seasonal AR [132].

Incidence

Allergic rhinitis can occur for the first time in people of any age and either gender, but predominantly it is a disease first occurring in childhood [19] [80]. The 1974 Tecumseh study showed an annual incidence rate of allergic rhinitis 0.5% during infancy and 4-5% among children ages 5-9 [124]. Incidence continued to rise from 9% during adolescence to 15-16% after adolescence. Incidence remained constant in the young adults, and then gradually declined during the middle years and among the elderly. Perennial allergic rhinitis can occur very early, even in the neonate [133]. Studies from freshmen at Brown University (US) showed the mean onset of perennial allergic rhinitis and hay fever at 9.1 and 10.6 years, respectively [131]. A recent multi-centre prospective birth cohort study investigated annual incidence of sensitisation to inhalant allergens during the first 6 years of life [97]. The incidence of

sensitisation to inhalant allergens increased with age from 1.5% at 1 year to 8% at 6 years. Prevalence of allergic sensitisation to at least one allergen increased to 26% at 6 years of age.

Natural Course.

Once acquired, allergic rhinitis usually persists for many years. A Swedish study of teenagers assessed 4 years apart found that the incidence rate per year was 1% [26] [134]. Among those who already acquired the disease the remission (absence of symptoms) rate/year was 22%, and the relapse (re-occurrence) rate/year was 11%. In another Swedish study, incidence of allergic rhinitis was fairly constant during childhood and cessation of symptoms was uncommon [135]. In a follow-up of the Danish study, about 10% of patients were free of symptoms after 8 years of observation [6]. Data collected in Tecumseh after a 4-year interval indicated that remission of AR occurred in 5% of females and in 10% of males and was also influenced by the duration of the disease, so that people with earlier onset had a higher remission rates [124] [136]. This study also showed that perennial rhinitis was less likely to disappear than other types of AR. In former Brown University students (male to female ratio 2:1) who completed a 23-year follow-up questionnaire inquiring about their history of allergies and asthma, improvement decreased with increasing age of onset, from 85% of those with onset at 1-5 years of age, to 39% of those with onset at 20 years and later. A total of 55% had noted improvement; of these 23% reported being symptom free. Of the remaining 45%, the AR was unchanged in 33% and worse in 9% [137]. Thus over a long period of time, AR symptoms may improve in the majority of individuals, especially for those with early age of onset, but few individuals become symptom-free.

Reasons for variation in epidemiological data.

There are many factors that can potentially affect the results of epidemiological studies, and explain at least some of the differences reported by various studies.

♦ **Climate/Geography.** Some differences can be explained by the differences in climate, as the prevalence of AR is typically higher in dry inland areas compared to damp coastal regions (Australia: 31% vs. 21% [138], US: 55% in dry desert vs. 16% on average [25] [119]). The type and relative potency of common pollens and the overall aeroallergen burden also vary with geography. Ragweed pollen, the most common cause of seasonal AR in North America, is considered to be a more potent allergen than the grass and tree pollens associated with hay fever in Europe [21]. The influence of climate, pollen distribution, or a combination of both on the prevalence of AR has been demonstrated in several studies [139] [140] [141]. Not all of the variation, however, can be explained by these factors. Some studies showed quite marked differences between regions with similar climate and pollen prevalence [114] [115] [142].

♦ **Gender & age.** More male children suffer from allergic rhinitis before adolescence, whereas females are more often affected among adults [19] [80] [143]. The natural course of the disease is also dependent on the age of onset and on gender, so that "current disease" vs. "history of the disease" can differ in participants. Some differences in results of epidemiological studies can be explained by different age-gender composition of study populations.

♦ **Ethnicity/Migration.** Racial differences have been reported in some populations, though not in all. In Britain, the prevalence of AR among men consulting general practitioners was found to be 90% higher among West Indians and 92% higher among Asians than among the native British [144]. AR was more prevalent in whites than in blacks in NHANES survey [119], but no difference was found between white and non-white employees of a light industrial plant in the US [145]. Although genetic factors may contribute to racial differences [146], migration studies suggest that environmental factors play a more important role. Immigrants appear to have a greater prevalence and later onset of AR than native populations [147] [148] [149]. Most studies do not report the ethnic composition of the population or their place of origin, and some populations may be more homogeneous than others.

♦ **Urban/Farming environment.** As was discussed in chapter 2.4, some rural environments show lower rates of allergic disorders and lower consultation rates for these disorders [76] - [78] [80] [83] - [87]. Thus the level of urbanisation of the study population and urban vs. rural place of birth could account for some of the differences seen in studies.

Time trends

Most of the studies done in the late 1980s and in the 1990s reported higher prevalences of AR than studies in the 1970s and early 1980s (Appendix 3). To what extent this phenomenon is due to increased awareness of allergic conditions among general populations and medical practitioners is not always clear [3] [134] [150] [151]. Examination of Swedish army recruits showed that the prevalence of hay fever rose from 4.4% in 1971 to 8.4% in 1981, without evidence of changes in individual physicians' diagnoses [152]. Surveys of British general practices between 1970-1980 and 1981-1992 found increases in consultation rates for AR during both these periods [19] [153]. A Tucson longitudinal study (US) found that the prevalence of AR and the prevalence of skin test reactivity both increased 11% between 1979 and 1987 [154]. Conversely, some of the studies found no differences in the prevalence of AR between different time periods studied [18], or found an increase of self-reported hay fever but no change in number of people with atopy defined as a positive skin test [151], while at least one study noticed a decrease in the prevalence of allergic rhinitis among children [128].

3. STUDY DESIGN & METHODS

3.1. Database

The province of Manitoba (Canada) has a universally accessible health care system and all permanent residents of the province are registered with the Manitoba Health Insurance Plan. This plan is administered by the Manitoba Health Services Commission (MHSC). MHSC registry contains data such as personal health insurance number (PHIN), date of birth, gender and residential postal code. An electronic version of this registry is available for research purposes. This version is updated every 6 months, with dates of the start of the coverage and the end of the coverage noted. The absence of names and addresses in this research registry and the use of scrambled rather than real PHIN numbers safeguard confidentiality of the subjects, prohibiting personal identification. This form of registry was used to identify the study population. Information about coverage was used in the calculation of the number of person-years of observations and the date of birth was used for age calculations. The validity of the information contained in research registry files has been established [155].

Fee for service was the predominant method of payment for physician services in the Province during the study period. These payments depended upon submission of claims containing the following information:

- patient's identification number (PHIN)
- diagnosis
- date of service
- type of service
- year of birth
- gender
- residential postal code.

All contacts for medical services can be ascribed to individual residents through unique PHIN numbers. The reliability and validity of the diagnoses and personal information recorded in medical claims have been established [156] [157].

Between 1985 and 1998 diagnoses were coded according to the Ninth Revision of the International Classification of Diseases (ICD-9CM). From this Manitoba Health database we selected medical claims with diagnostic code "477" for allergic rhinitis and diagnostic code "493" for asthma with tariffs corresponding to the examinations by a physician (tariffs "8500" through "8599") and with dates of services from 1985 to1998. For AR, almost all services were provided on an outpatient basis. For asthma, both inpatient and outpatient services were included. The medical claims data was linked with the population registry files for each of the calendar years, which also contained the age, gender and postal code of all Manitobans.

3.2. Definitions

Age. Patients' age and population ages were calculated as of December 31 of each year of the study. Age was further stratified into 5 year groups, from 0-4 to 55-59 for calculation of age-sex adjusted rates. People aged 60 and more were considered as one group in the analysis. For age specific rates age was stratified into 6 groups: 0-4, 5-9, 10-14, 15-19, 20-54 and 55+.

Area of residence. The Province is comprised of one major city (Winnipeg) and the remainder of the province, which is largely rural, with about a dozen of towns with populations between 5,000 and 30,000. In this study utilisation patterns for Winnipeg residents (about 630,000 residents) were compared with those residing outside Winnipeg (about 500,000 residents). Area assignments were based on the postal codes from claims in a given year. For the small proportion of study subjects who changed their place of the residence during the same calendar year, information from the first claim

was used. For convenience henceforth Winnipeg is termed urban and the rest of the province is termed rural, though it contained some medium-size towns (Brandon, Thomson, Dauphin etc.)

Socio-economic status. Residents of Winnipeg were divided into 5 groups of similar size based on mean household income for enumeration areas derived from Canadian Census data available for the years of the study. Enumeration areas were ranked from poorest to wealthiest and then grouped into 5 quintiles. Each Winnipeg resident was linked to a census enumeration area by residential postal code and for each resident a quintile income rank was assigned, with Q1 being the poorest and Q5 being the richest. Income quintiles were studied only in Winnipeg, because in rural Manitoba family incomes vary widely within small geographic areas [158].

Main outcomes. Main outcomes studied were

- Allergic Rhinitis – ICD-9 CM code "477"
- Asthma – ICD-9 CM code "493".

Outcome Measures. Incidence and prevalence are two basic measures of disease occurrence in populations over a given period. The choice of the time period is arbitrary, but a calendar year is one of the common preferences, resulting in a calculation of the annual prevalence and annual incidence. Annual prevalence of the disease is defined as a proportion of population who had the disease during a calendar year. Annual incidence of the disease is a number of new cases in a calendar year per population at risk (those who do not yet have the disease). Because it is not always plausible to determine the population at risk, for large populations the total population is usually also used as the denominator for calculating the annual incidence, as well as for calculating the annual prevalence [159].

The use of administrative data does not allow for the measurement of the real incidence or prevalence of the disease, since only those who go to see a physician and are given the diagnosis could be detected as cases. Use of physician diagnosis is a specific but less sensitive method for detecting the disease occurrence in the population [28] [86]. However, the annual prevalence and the

annual incidence of the disease can be approximated by annual prevalence and annual incidence of utilisation for this disease. Assessment of trends in utilisation of health care resources for the conditions of interest over time can give an insight into the changes in real incidence and prevalence in the population and contains valuable information for health care planners [160].

In this thesis annual prevalence and annual incidence of utilisation of physician resources were the measurements of choice in assessing trends for AR and asthma in the Province.

1. Annual prevalence of utilisation (APU). APU was defined as a number of people with a given diagnosis in each of the calendar years (from 1985 to 1998), per 1,000 population.
2. Annual incidence of utilisation (AIU). AIU was defined as a number of people with a given diagnosis in each of the calendar years who did not have that diagnosis (claims) in prior years, per 1,000 population.

Total annual incidence of utilisation was calculated in two ways:

- AIU_1 - based on the data from 5 preceding years: the event was assumed to be new if there was no event (claim with the same diagnostic code) in the 5 previous years.
- AIU_2, based on all available data (at least 5 prior years), for years 1990 to 1998, was also calculated, to assess the sensitivity of this outcome.

The AIU_1 and AIU_2 for AR and asthma are shown in figure 3-1. As expected, AIU_1 exceeded AIU_2, the difference increasing with time, as data from more years became incorporated in calculation of AIU_2. However, these differences were trivial. AIU_1 was higher than AIU_2 between 1995 and 1998 by 10-14% for AR and by 8-12% for asthma. Because no utilisation data was available for years prior to 1985, the true incidence of utilisation could not be calculated in people born prior to this year. Though AIU_2 offered a better approximation of the true incidence in utilisation in years 1995 to 1998, AIU_1 allowed for a better analysis of time trends, since it considered the same time frame in each of the years. Therefore, AIU_1 was used to compare trends for AR and asthma between 1990 and 1998, keeping in mind that it somewhat overestimated true annual incidence of utilisation by including

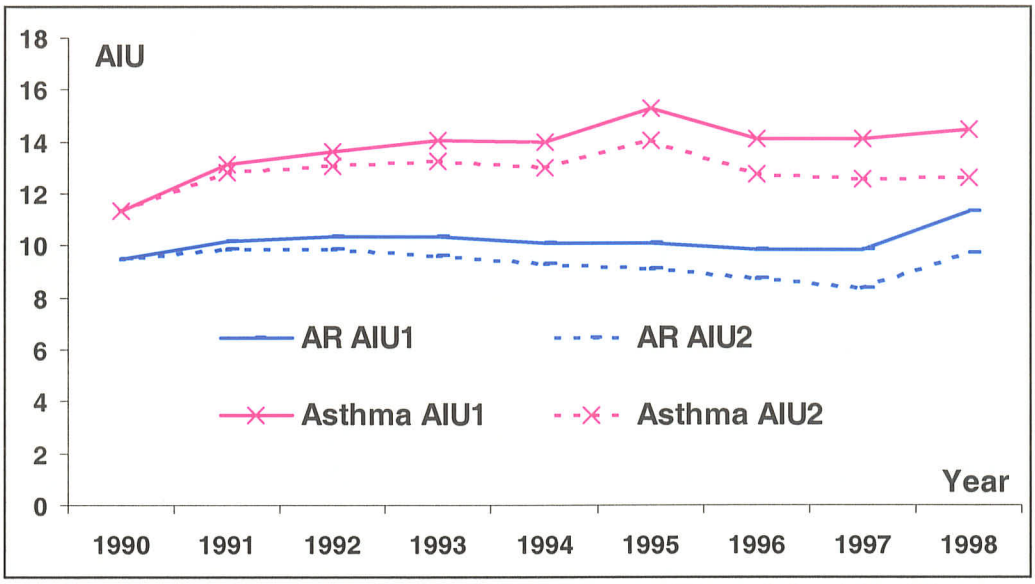

Figure 3-1. **AIU for AR and asthma measured in two ways, per 1,000 population. 1990-1998.**

people who had a diagnosis more that five years previously. From now on this measure is referred to as annual incidence of utilisation, or AIU, without the index.

3.3. Study Population

All residents of the province covered by Universal Provincial Health Insurance at any time between 1985 and 1998 were subjects of the study. This comprised the total population of the province of Manitoba, with the exception of those covered under a Federal Health Plan (such as military personnel and their family members) and those who recently moved into the Province and were still covered by another province's insurance plan.

Table 3-1 shows the population of Manitoba, from 1985 to 1998 by gender and age groups.

MALE													
Year/Age	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60+
1985	42,484	42,070	43,275	44,647	51,961	51,247	46,163	41,012	31,315	26,182	24,968	24,523	81,558
1986	42,864	42,232	42,920	44,296	50,185	52,066	47,270	41,746	33,313	26,767	24,816	24,256	82,081
1987	42,804	42,367	42,438	44,390	48,101	52,223	48,338	42,112	35,423	27,538	24,501	24,412	82,729
1988	42,788	42,854	42,214	44,033	46,038	52,705	48,779	42,799	37,010	28,399	24,698	24,109	83,466
1989	43,165	43,098	41,690	43,825	44,177	52,311	49,283	43,879	38,422	29,583	24,660	23,956	84,009
1990	43,197	43,158	41,495	43,055	42,975	50,444	49,826	44,675	39,659	30,292	25,090	23,662	84,494
1991	42,910	43,378	41,488	42,558	42,453	48,135	50,130	45,479	40,258	32,032	25,546	23,539	85,367
1992	42,545	43,095	41,442	41,732	42,093	45,306	49,556	46,076	40,248	33,948	26,231	23,215	86,147
1993	42,937	42,827	41,774	41,162	41,629	43,152	49,584	46,411	40,775	35,386	27,003	23,390	86,164
1994	42,450	43,429	42,402	41,009	42,050	42,033	49,859	47,372	42,128	36,963	28,377	23,490	87,215
1995	42,023	43,683	42,555	40,868	41,038	40,945	48,164	47,846	43,060	38,222	29,088	23,920	87,475
1996	41,044	43,615	42,700	40,785	40,157	39,929	45,806	48,073	43,895	38,923	30,763	24,239	87,471
1997	40,312	43,604	42,825	41,079	39,542	39,810	43,702	48,088	44,798	39,218	32,721	25,039	87,804
1998	38,690	43,450	42,537	41,186	38,748	38,812	41,214	48,010	45,096	39,677	34,211	25,837	88,603
FEMALE													
Year/Age	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60+
1985	40,196	39,734	41,255	43,227	51,435	49,947	45,850	40,539	30,640	25,791	24,828	25,563	103,876
1986	40,494	40,024	40,449	42,948	49,590	50,587	46,711	41,322	32,523	26,352	24,575	25,203	105,040
1987	40,571	40,080	40,123	42,683	47,499	50,978	47,378	41,599	34,612	27,319	24,305	25,113	106,294
1988	40,749	40,426	40,102	42,196	45,271	51,570	47,880	42,320	36,314	28,271	24,637	24,311	107,725
1989	41,171	40,537	39,809	41,527	43,680	51,105	47,891	43,753	37,799	29,170	24,701	24,157	108,713
1990	41,153	40,816	39,416	40,885	42,358	49,656	48,245	44,540	39,360	29,752	25,019	23,888	109,581
1991	41,130	41,007	39,498	40,160	41,880	47,785	48,801	45,357	40,058	31,549	25,581	23,660	110,667
1992	40,803	40,909	39,175	39,520	41,354	45,044	48,686	45,789	40,224	33,374	26,423	23,447	111,623
1993	41,036	40,818	39,285	39,265	40,601	42,579	48,910	45,937	40,865	34,946	27,250	23,703	111,850
1994	40,584	41,525	39,754	39,360	40,662	41,799	49,178	46,568	42,471	36,757	28,291	23,835	113,090
1995	40,320	41,588	40,125	38,953	40,249	40,768	47,951	46,994	43,403	38,359	28,905	24,244	113,235
1996	39,263	41,729	40,220	38,872	39,029	39,913	45,900	47,323	44,108	38,917	30,582	24,663	113,127
1997	38,300	41,856	40,469	38,958	38,692	39,727	43,803	47,580	44,808	39,246	32,415	25,540	113,241
1998	36,824	41,403	40,307	38,892	38,168	38,761	41,258	47,559	44,936	39,890	34,038	26,271	113,932

Table 3-1. **Population of Manitoba by year, gender and age group.**

3.4. Statistical analysis

Crude rates of APU and AIU were calculated for each of the years of the study, for the whole Province and separately for each gender, age group, and area and in Winnipeg for each income quintile. Age-gender standardised rates of APU and AIU were calculated for comparisons between years, between areas and between income quintiles. Adjustment of rates of APU and AIU by age and gender would not really be necessary for the whole Province, for year to year comparisons, since the age-gender structure of the provincial population did not change during the study period. However, urban and rural areas and different income quintiles could have different age-gender population structures, therefore the age-gender adjustment was used to facilitate comparisons between years,

between areas and between quintiles. The total Manitoba population in 1991 was used as a reference population for the calculation of directly standardised rates [161].

Linear regression models were used to test time trends for standardised rates of AR and asthma APU and AIU for the total Province, for each gender, area of residence, and in Winnipeg for each income quintile. Interaction terms were used to test if trends differed by gender, area or income quintile [162]. Linear regression models were also used to test time trends of APU and AIU for AR and asthma, separately for each age group. Interaction terms in these models were used to test if trends of AR differed from trends of asthma. Cochran-Mantel-Haenszel (C-M-H) statistics were used to calculate odds ratios for gender effect in each of the years [163].

To assess the extent of utilisation for allergic AR and asthma for the total population of the Province over the study period and to facilitate comparisons between trends of AR and asthma, total number of people diagnosed with allergic rhinitis and/or asthma at least once during 14 years (1985 through 1998) were enumerated. Total number of visits made for AR and/or asthma and total number of patient-years of observation during the study period were also calculated. The date of the first diagnosis during 1985 -1998 period was used as the start point and the date of the end of insurance coverage or December 31, 1998, whichever earliest, was used as the end point for the patient-years calculation.

Frequency of utilisation per diagnosed patient was assessed by dividing the total number of visits made for each diagnosis during the study period by the total number of people with that diagnosis during that time. The average number of visits made per 1,000 diagnosed patients per year of observation was also calculated.

The same figures were computed for three separate consecutive intervals during the study: 1985 to 1988, 1989 to 1993 and 1994 to 1998.

4. RESULTS

4.1. Annual Prevalence of Utilisation (APU)

Total (age-gender adjusted)

The total annual prevalence of utilisation for AR and asthma adjusted for age and gender to the 1991 reference population is shown in figure 4-1.

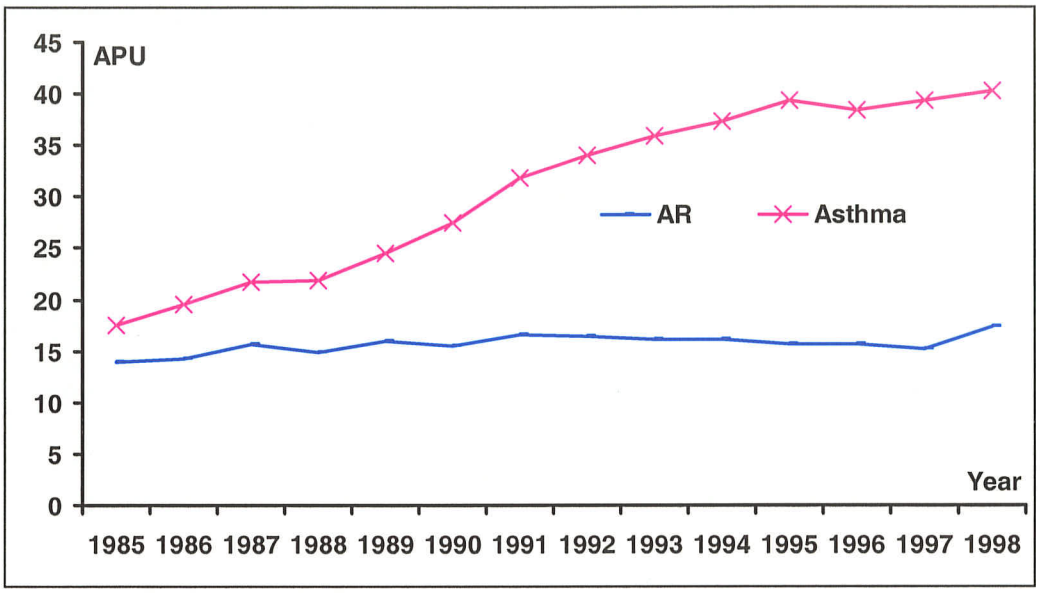

Figure 4-1. Age-gender adjusted APU for AR and asthma, per 1,000 population. 1985-1998.

Because age-gender distribution of the provincial population was stable over the years of the study, adjusted rates were only marginally different from crude rates. The APU of AR fluctuated during the study period between 13.9 and 17.4 per 1,000 population, with an overall statistically significant trend of average increase of 0.14 cases [95% CI: 0.04-0.23] per 1,000 population per year (p=0.012). The biggest increase occurred from 1985 to 1987 (average increase 0.8 cases per 1,000 population per year) and the smallest - from 1994 to 1998 (average increase 0.08 cases per 1,000 population per year).

The APU of AR was similar to APU of asthma at the beginning of the study period (13.9. vs. 17.5 per 1,000 population, respectively). However, the increase in APU of asthma was much greater, averaging 1.93 [95% CI: 1.68-2.18] cases per 1,000 population per year ($p<0.0001$). This resulted in a more than 2-fold difference between APU AR and asthma (17.4 vs. 40.2 per 1,000 population, respectively) at the end of the study period. For asthma APU, a period from 1988 to 1992 had the highest rate of increase (average increase 3.2 cases per 1,000 population per year), and a period at the end (1993 to 1998) had the smallest rate of increase (average increase 0.76 cases per 1,000 population per year). Overall, trend in AR APU did not parallel trend in asthma APU.

Gender

Gender differences in the annual prevalence of utilisation for AR and asthma are shown in figure 4-2.

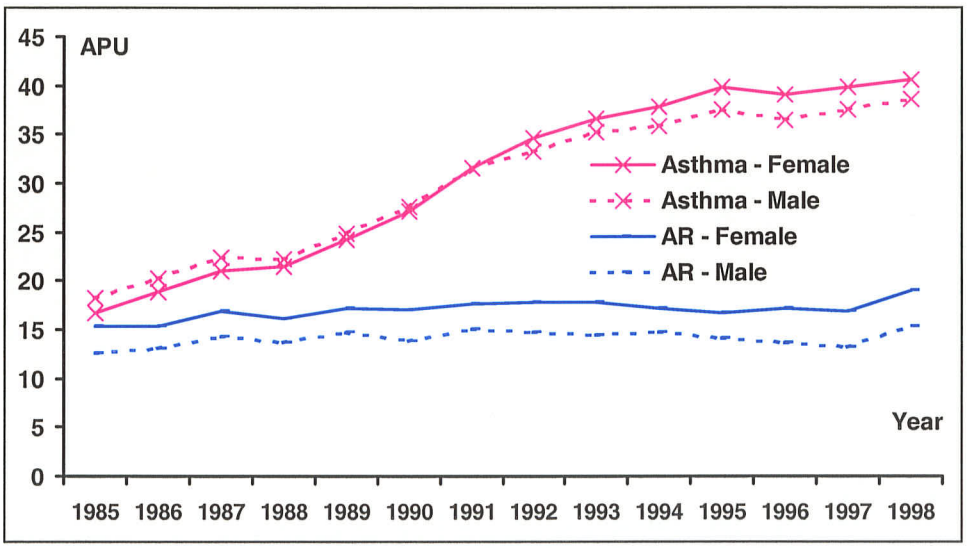

Figure 4-2. APU for AR and asthma by gender, per 1,000 population. 1985-1998.

For AR male and female trends were similar, though the trend for females was statistically significant ($p=0.01$, average increase of 0.14 [95% CI: 0.04-0.18] cases per 1,000 population per year), while the trend for males was not. APU of AR was always higher in females ($p<0.001$), with female to male ratio varying from 1.15 [95% CI: 1.12-1.18] in 1989 to 1.23 [95% CI: 1.19-1.27] in 1998 (C-M-H). The gender-year interaction term was not significant, indicating that the trends of AR APU in males and females were not different.

Asthma APU increased significantly with time in both genders ($p < 0.001$), with average increases of 1.71 cases [95% CI: 1.47-1.95] and 2.07 cases [95% CI: 1.79-2.34] per 1,000 population per year (males and females, respectively). For asthma, the gender difference was not consistent. The prevalence was lower in females between 1985 and 1988 with odds ratios from 0.92 [95% CI: 0.89-0.94] to 0.96 [95% CI: 0.94-0.98]. (C-M-H). There was no gender difference in asthma APU from 1989 to1991 and it was higher in females after 1991, with odds ratios from 1.04 [95% CI: 1.02-1.06] in 1992 and 1993 to 1.7 [95% CI: 1.5-1.10] in 1996 (C-M-H). There was no difference between male and female trends for asthma determined by interaction term.

Age

Distributions of the annual prevalence of utilisation for AR and asthma by age at the beginning and at the end of the study period are shown in figure 4-3.

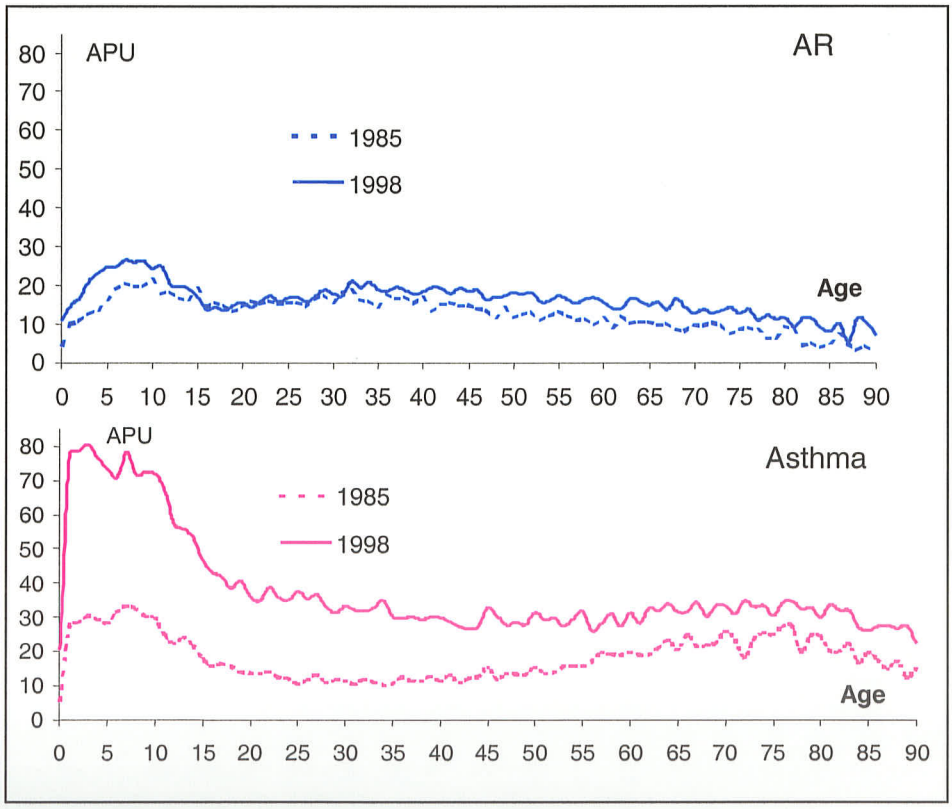

Figure 4-3. APU for AR and asthma by age, per 1,000 population. 1985 and 1998.

Age patterns were analogous in intermediate years. The age distribution of APU of AR had two apparent peaks: the larger one at ages 5 to 10, and a smaller peak at ages 30 to 45. Lower rates of APU were encountered in both the youngest and oldest age groups. APU of AR increased with time in children and in adults over 30 and did not change in those aged 15 to 30.

The annual prevalence of utilisation for asthma had a different age distribution: asthma APU was highest in children aged 2 to 11 and lowest in adults aged 20 to 50. Asthma APU increased with time the most in children and the least in those aged 60 or more. At the beginning of the study, AR APU was lower than asthma APU only in children less than 15 and in those aged 55 or more, while rates for AR and asthma APU in people 15 to 54 were similar.

Figure 4-4 shows time trends in APU of AR and asthma separately for 6 different age groups. APU of AR increased significantly in children 0 to 4 ($p = 0.03$, an average increase 0.25 cases [95% CI: 0.08 - 0.42] per 1,000 population per year) and in adults over 55 ($p < 0.0001$, average increase 0.14 cases [95% CI: 0.03-0.21] per 1,000 population per year). Other age groups had similar trends, though they were not statistically significant.

Asthma APU increased significantly in every age group, most strikingly in people younger than 20 years of age. Average increases in order of age group were 3.90 cases [95% CI: 3.22-4.57], 3.73 cases [95% CI: 3.06-4.40], 2.98 cases [95% CI: 2.50-3.45], and 2.44 cases [95% CI: 1.97-2.92], per 1,000 population per year. In adults aged 20 and over, asthma APU increased steadily but less strikingly with time. Average increases in asthma APU for these groups were 1.56 cases [95% CI: 1.46-1.67] for 20-54 years old and 0.79 cases [95% CI: 0.65-0.93] per 1,000 population per year, for 55 years of age and older.

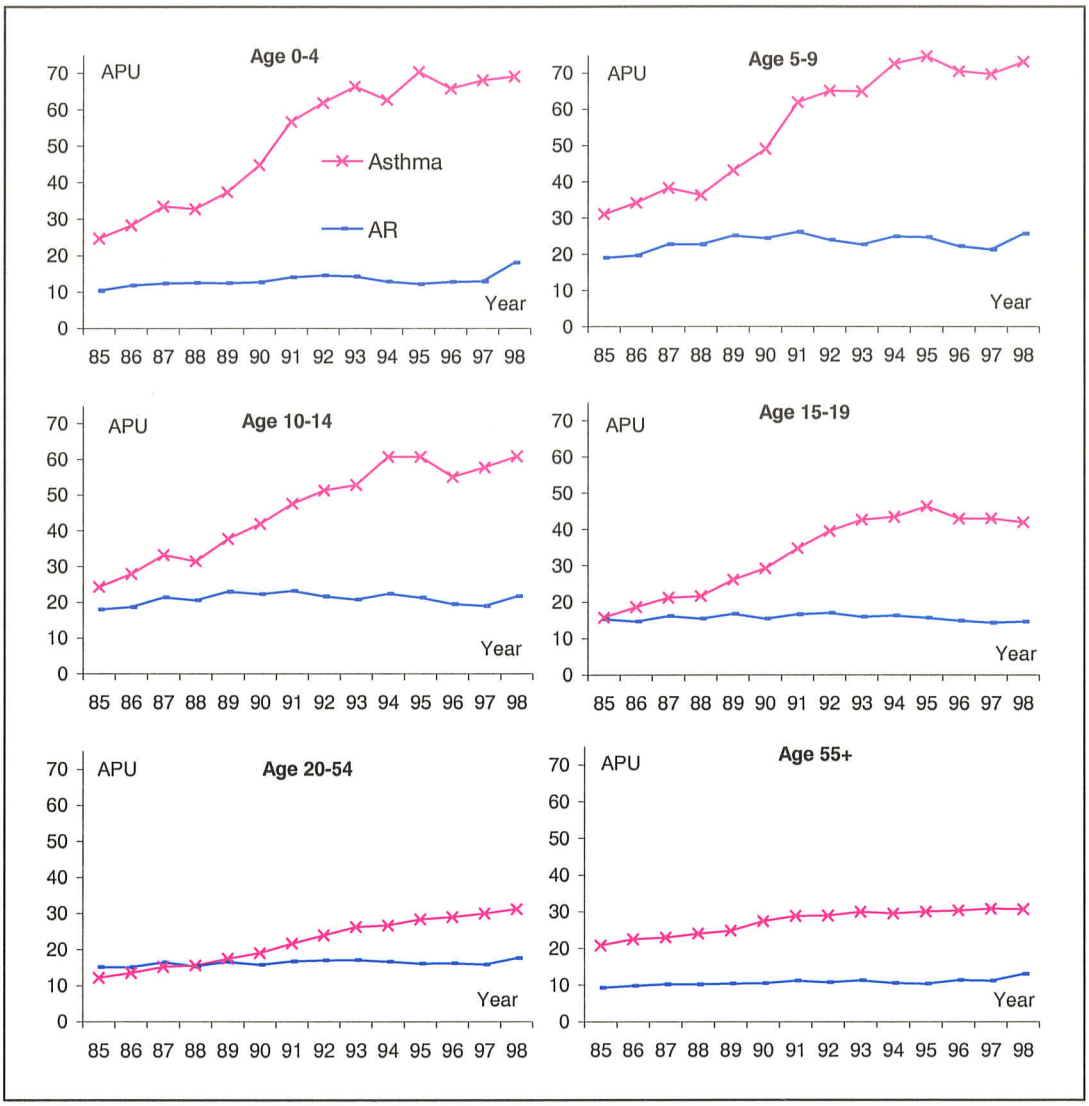

Figure 4-4. APU for AR and asthma by age group, per, 1000 population. 1985-1998.

For all age groups trends in asthma APU were statistically different from those for AR APU when tested by interaction terms ($p < 0.05$) though the difference was not obvious in elderly.

Age and gender

The annual prevalence of utilisation for AR is shown as a function of gender and age group in figure 4-5. The years shown are 1985, 1990 and 1998 – beginning, middle and end of the study period. In each of the years of the study, AR APU in females had two similar peaks – at ages 5-9 and at

ages 30-40. The first peak was smaller than the second peak in earlier years of the study, equal to it in the middle and exceeded it at the end of the study. For males, there was only one obvious peak –

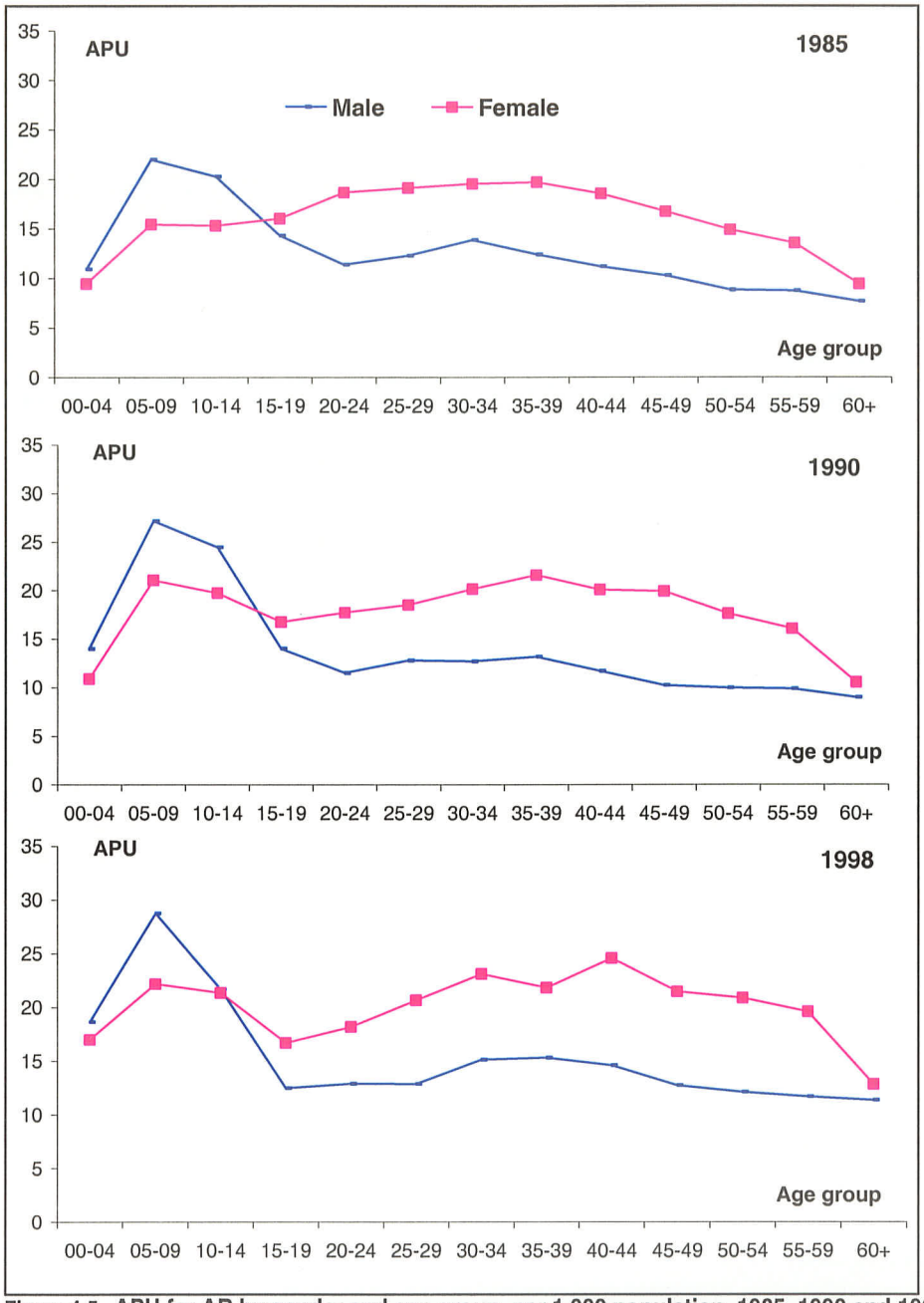

Figure 4-5. APU for AR by gender and age group, per 1,000 population. 1985, 1990 and 1998.

at ages 5 to 9. AR APU was always higher in young boys (< 10 year old) than in girls and higher in women than in men. The age at which the crossover occurred shifted with time towards younger ages, from 15-19 years old in 1985 to 10-14 years old in 1998. Gender differences in AR APU increased with time more noticeably in adults than children.

The annual prevalence of utilisation for asthma is shown as a function of gender and age group in figure 4-6. Again, the years shown are 1985, 1990 and 1998.

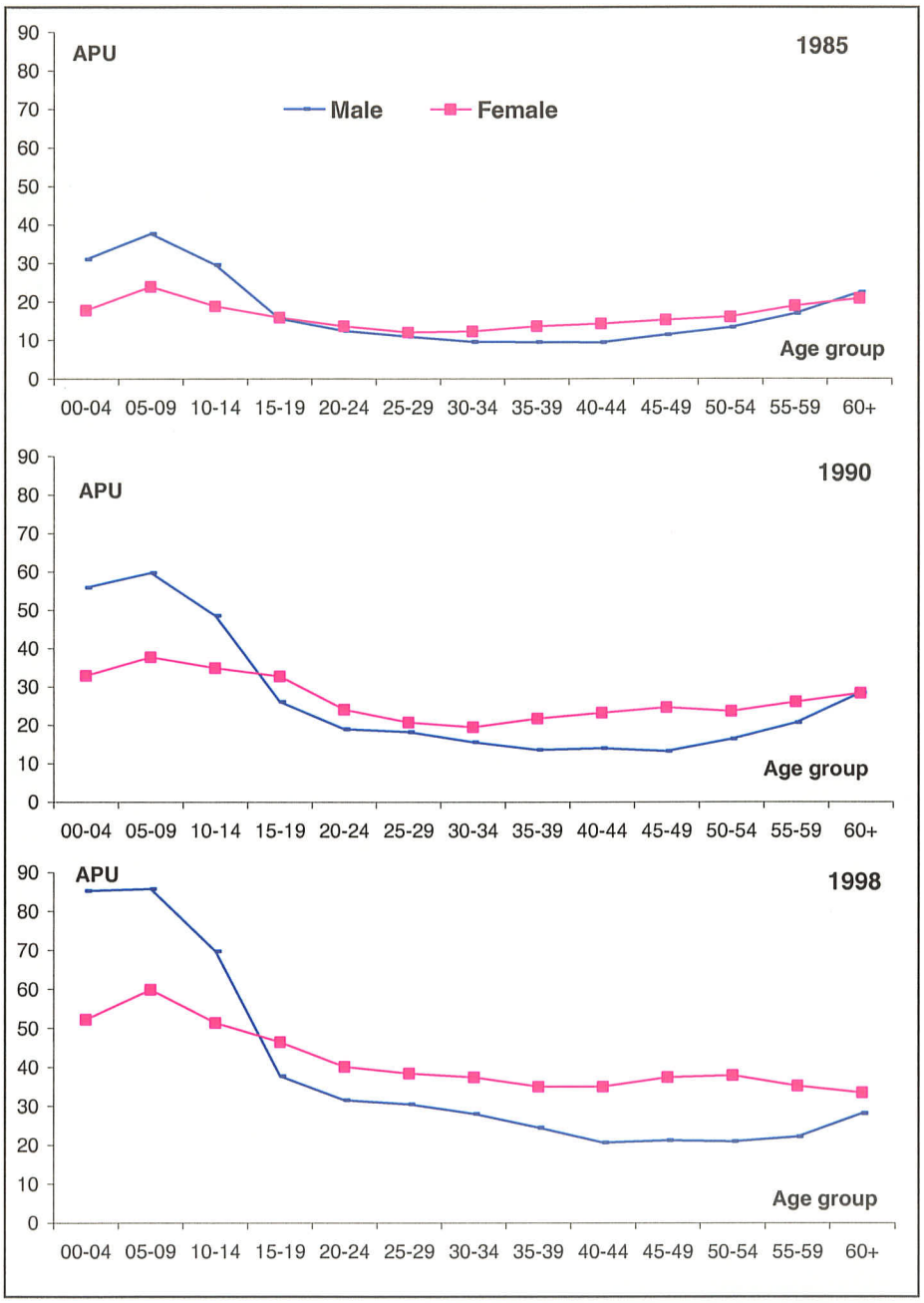

Figure 4-6. APU for asthma by gender and age group, per 1,000 population. 1985, 1990 and 1998.

In each of the years of the study, asthma APU in males was highest in the 3 youngest age groups. In females the peak in younger ages was more pronounced in the later years of the study, while the distribution by age in earlier years was near flat. Asthma APU was higher in boys than in girls and

higher in women than in men. As in AR APU, the age at which the crossover occurred shifted with time towards younger ages, but less noticeably so.

Area (by age and gender)

APU for AR and asthma in 1991 according to urban and rural place of residence and age are shown in figure 4-7, separately for males (a) and females (b).

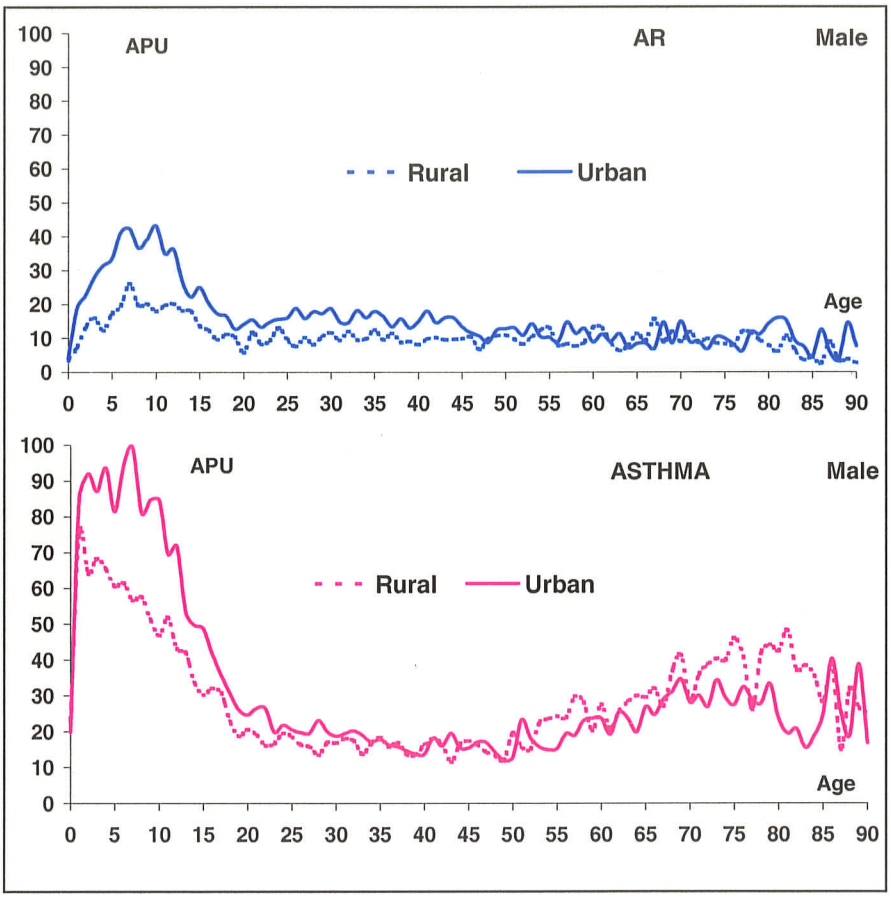

Figure 4-7(a). APU for AR and asthma by area and age in males, per 1,000 population. 1991.

Both AR and asthma APU in both males and females were higher in the urban area for children and younger adults. For AR, residence differences disappeared after the age of 45 for both genders. For asthma, residence differences disappeared in both males and females after the age of 30. Males over 60 in the rural area had slightly higher rates of asthma APU then their urban counterparts.

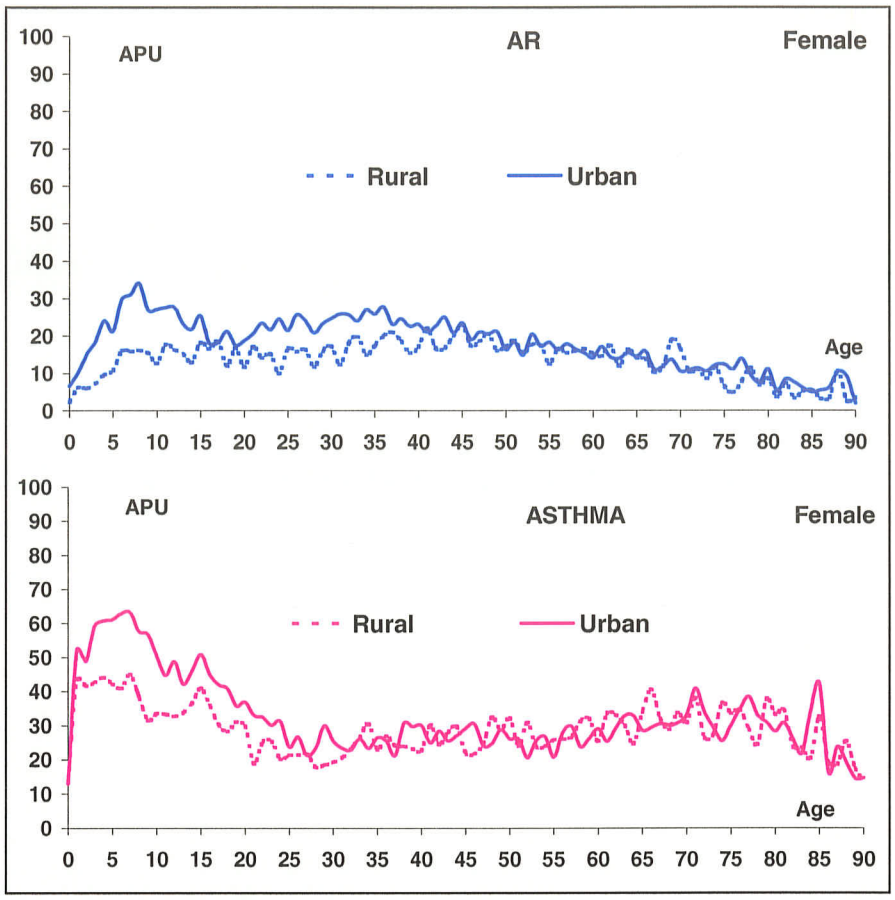

Figure 4-7(b). APU for AR and asthma by area and age in females, per 1,000 population. 1991.

Other years showed similar patterns of distribution, although area differences seen in children and young adults increased with time for both genders.

Area (age-gender adjusted)

Age and gender adjusted rates of APU for AR and asthma according to residence (urban vs. rural) are shown as function of time in figure 4-8. APU of allergic rhinitis increased significantly with time in the urban area ($p=0.002$), with an average increase of 0.25 cases [95% CI: 0.15-0.35] per 1,000 population per year, and did not increase in the rural area. For asthma, both rural and urban rates of APU increased significantly ($p<0.0001$). Between 1985 and 1998, urban rates of asthma APU increased on average by of 2.26 cases [95% CI: 2.02-2.50] per 1,000 population per year while rural rates increased by 1.52 cases [95% CI: 1.24-1.80] per 1,000 population per year. Both AR and asthma APU were

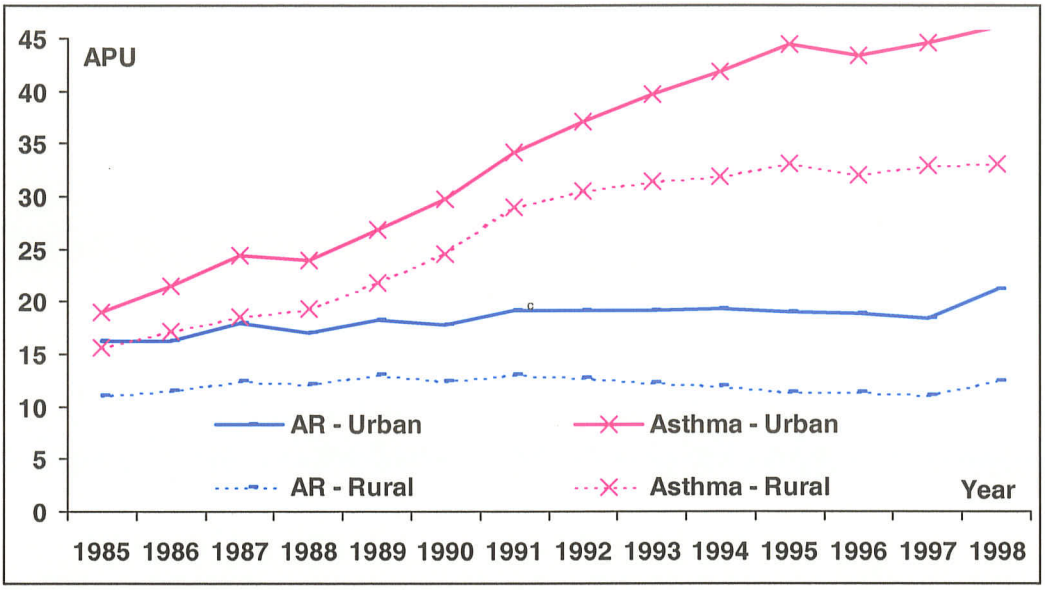

Figure 4-8. Age-gender adjusted APU for AR and asthma by area of residence, per 1,000 population. 1985-1998.

higher in urban area at all times during the study period and regional differences increased with time for both conditions (area-year interaction terms significant, $p<0.001$).

Income (Winnipeg, age-gender adjusted)

The age/gender-adjusted rates of AR and asthma APU as a function of income quintile in Winnipeg are shown in figure 4-9. At the beginning of the study, the rates of AR APU were smaller in lower income groups. These quintile differences disappeared by 1995 because rates of AR APU did not change in quintile 5 and increased in other quintiles, with poorer groups having a bigger increase. Average increases for AR APU between 1985 and 1998 for each of the quintiles were Q1: 0.63 cases [95% CI: 0.62-0.64], Q2: 0.35 cases [95% CI: 0.24-0.46], Q3: 0.22 cases [95% CI: 0.12-0.32] and Q4: 0.17 cases [95% CI: 0.05-0.29] per 1,000 population per year, respectively. The year-income interaction term was significant ($p<0.0001$), indicating that AR APU changed differently in different income groups.

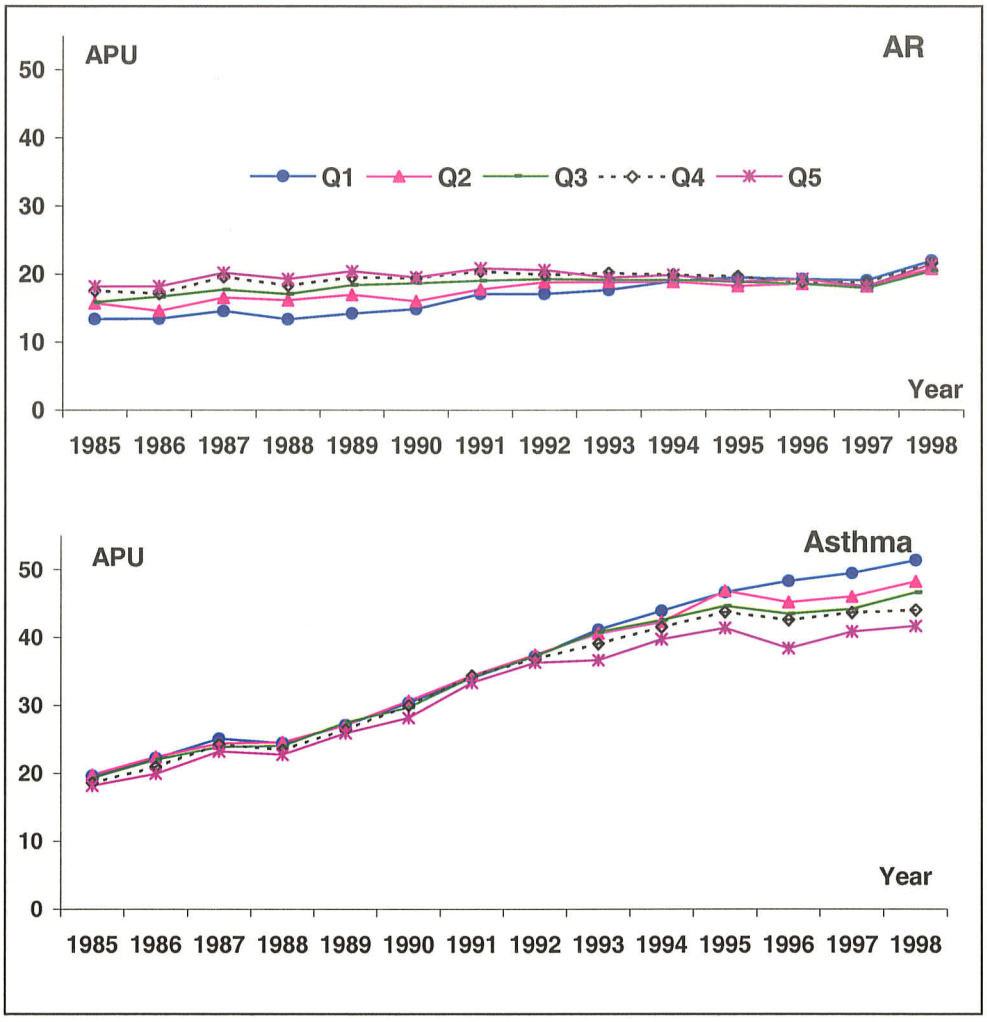

Figure 4-9. Age-gender adjusted APU for AR and asthma by income quintile, per 1,000 population. Winnipeg, 1985-1998.

For asthma APU, there was also a significant (p=0.0004) year-income interaction. However, in asthma APU a similar process of divergence of the quintile trends resulted in a different effect. There were no quintile differences in rates of asthma APU up to 1993. Rates of asthma APU increased with time significantly in all income groups (p<0.001), but lower quintiles had bigger increases, so that by the end of the study period asthma APU was higher in low economic quintiles. Average increases for asthma APU between 1985 and 1998 ranged from 2.63 [95% CI: 2.44-2.82] in Q1 to 1.98 cases [95% CI: 0.69-2.27] in Q5, per 1,000 population per year.

4.2. Annual Incidence of Utilisation (AIU)

Total (age-gender adjusted)

The total age-gender adjusted annual incidence of utilisation for AR and asthma is shown in figure 4-10. AIU of allergic rhinitis fluctuated with time without a significant trend. Asthma AIU increased from

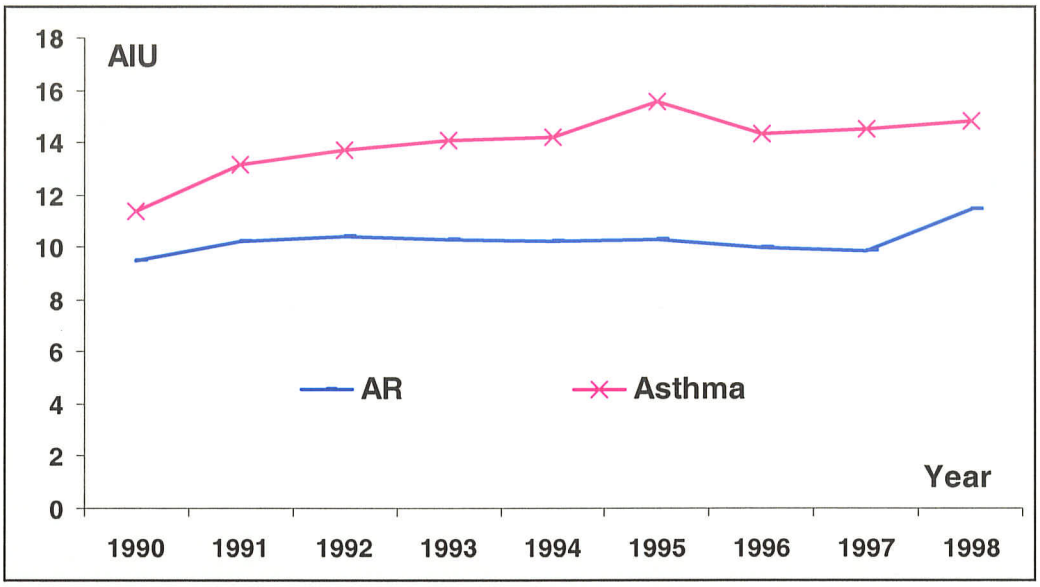

Figure 4-10. Age-gender adjusted AIU for AR and asthma, per 1,000 population. 1990-1998.

1990 to 1995 and slightly decreased after that. There was a significant overall trend (p=0.012) in asthma APU with an average increase of 0.34 cases [95% CI: 0.15-0.54] per 1,000 population per year. Asthma AIU was higher than AR AIU at all times and the difference was the biggest in 1995-1997(45%-50%) and the smallest in 1990 (20%).

Gender

Time trends for the annual incidence of utilisation for AR and asthma for both genders are shown in figure 4-11. AR AIU increased significantly with time in females (p=0.045), with an average increase of 0.15 cases [95% CI: 0.03-0.27] per 1,000 population per year. There was no significant trend for males. AR AIU was always higher in females (p<0.001) and female to male ratios were similar between 1990 and 1998 at about 1.2. The gender-year interaction term was non-significant.

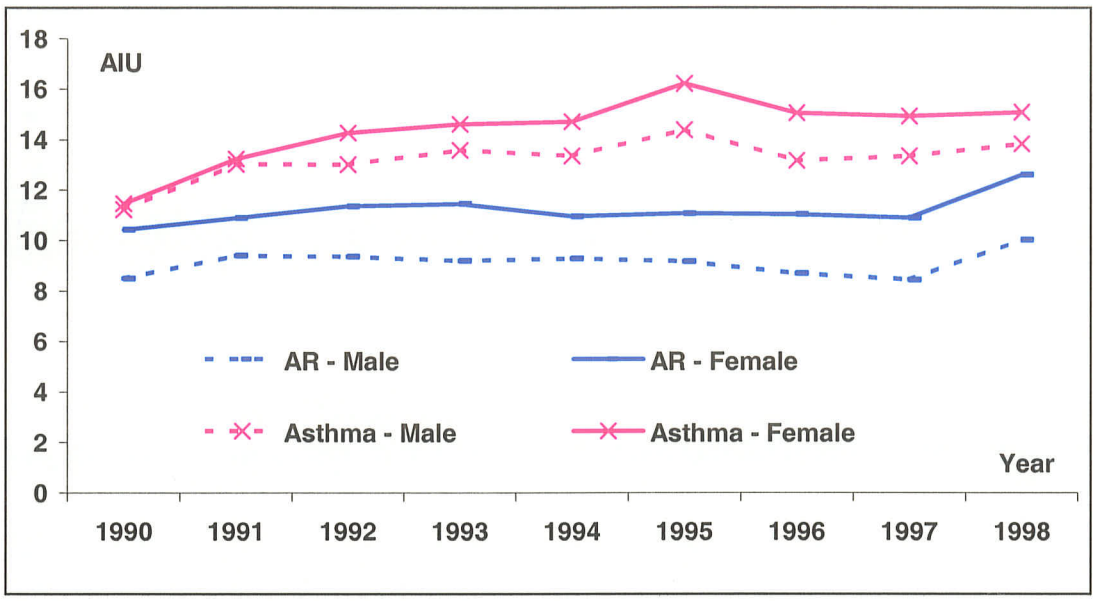

Figure 4-11. AIU for AR and asthma by gender, per 1,000 population. 1990-1998.

Most of the increase in AR AIU occurred in the last year of the study, and trend analysis was sensitive to inclusion of 1998 calendar year. When this last year was excluded from the analysis, no significant increase was found in either gender, and males even had a negative slope, though not statistically different from zero.

Asthma AIU increased significantly for both genders ($p < 0.05$) with average increases of 0.39 cases [95% CI: 0.15-0.63] and 0.22 cases [95% CI: 0.04-0.39] per 1,000 population per year, for females and males respectively. For asthma, there was practically no difference between genders in 1990-1991, but thereafter asthma AIU was higher in females. Female to male ratios in asthma AIU during this time varied between 1.04 and 1.07, but differences did not reach 0.05 significance level for the period between 1990 and 1998 ($p=0.07$ for the gender-year interaction term).

Age

Distributions of AIU for AR and asthma by age in 1990 and in 1998 are shown in figure 4-12. The age patterns for AR AIU were similar in other years under the study. AIU for AR peaked between ages 5 and 9 and was lowest in adults aged 15 to 19 and in those older than 60. It increased with time in young children and in people over 30 and did not change in those aged 10 to 29.

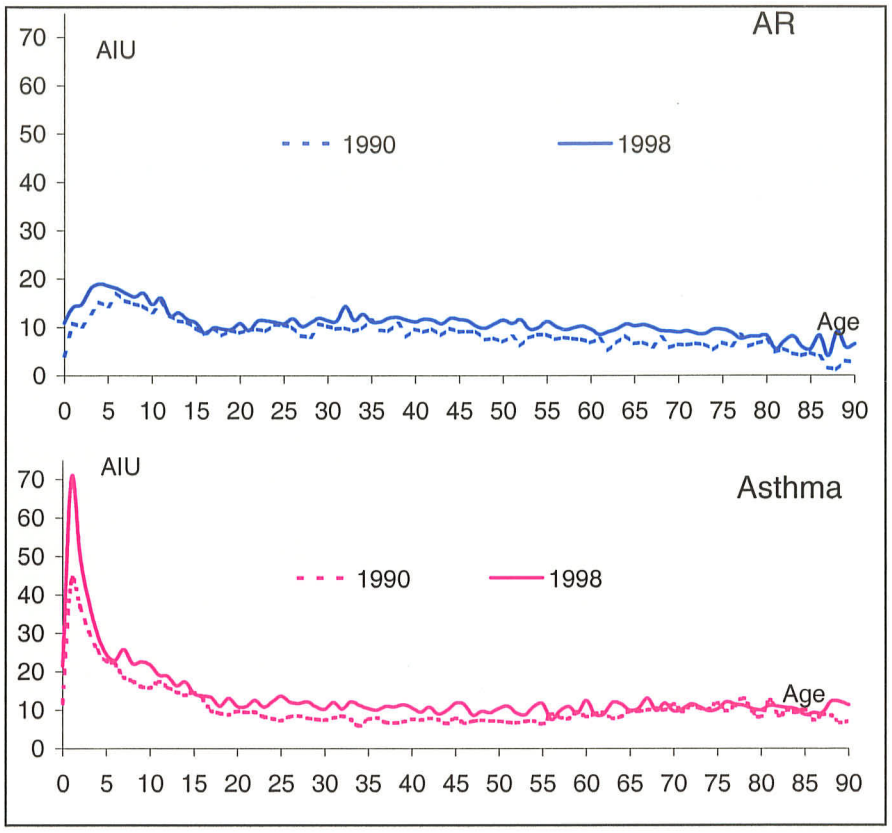

Figure 4-12. AIU for AR and asthma by age, per 1,000 population. 1991.

Annual incidence of utilisation for asthma by age had a different distribution: asthma AIU peaked between ages 1 and 2; it decreased sharply with age after that and was constant in adults over 20. The biggest increase in asthma AIU between 1990 and 1998 occurred in children aged 0 to 3, and there was no increase in asthma AIU for those aged 60 or more.

Figure 4-13 shows time trends for AR and asthma AIU for different age groups. AR had significant trend only in those aged 55+. For ages 0 to 4 AR AIU was 3 to 4 times lower than asthma AIU at all

times between 1990 and 1998. Asthma had a significant trend in this group with an average increase of 1.05 cases [95% CI: 0.38-1.72] per 1,000 population per year. AR and asthma trends for other three groups of children were similar and not statistically significant.

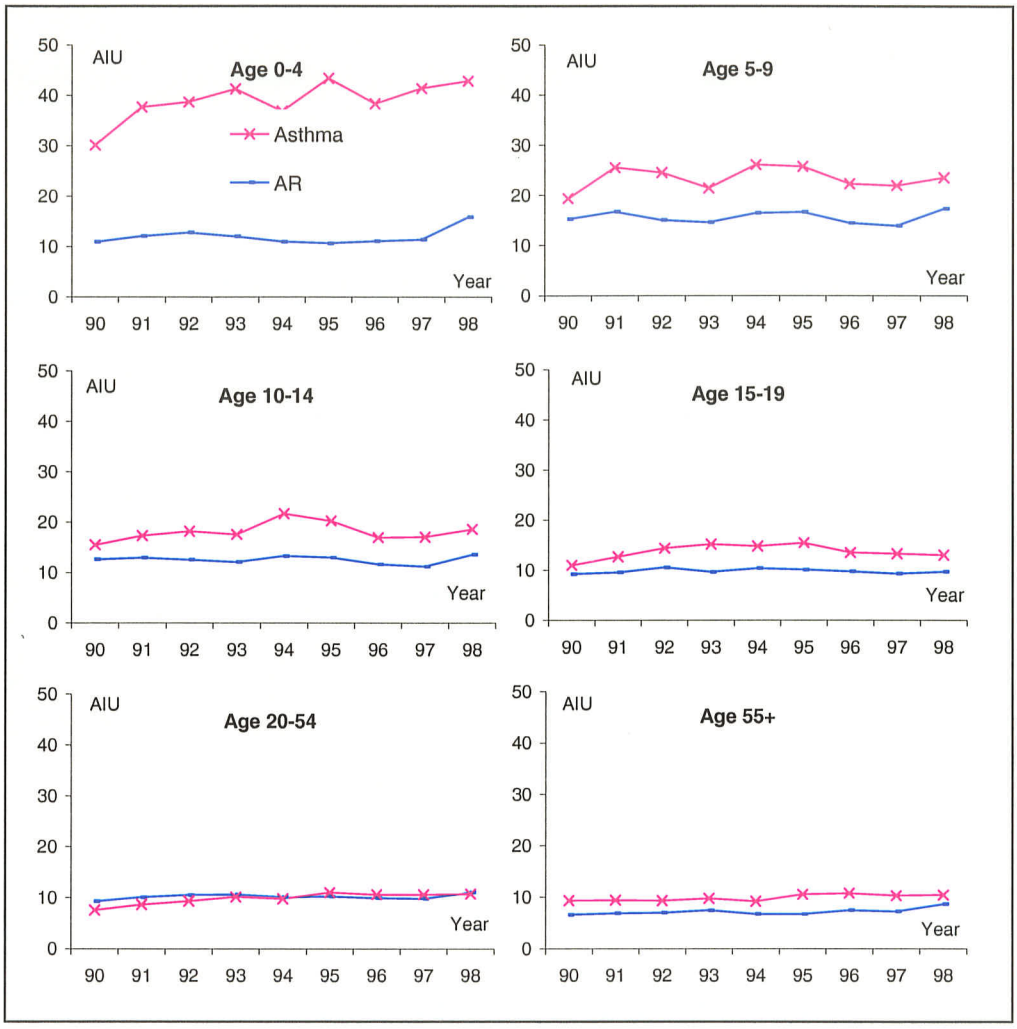

Figure 4-13. AIU for AR and asthma by age group, per 1,000 population. 1990-1998.

In adults, for both AR and asthma only those aged 55+ had statistically significant trends ($p<0.05$) and there was no difference between the two diagnoses. Average increases in this age group were essentially the same: 0.16 cases [95%CI: 0.06-0.27] and 0.18 cases [95%CI: 0.09-0.26] per 1,000 population per year, for AR and asthma respectively. In adults 20 to 54 years old AR and asthma AIU were the same and neither trend was significant.

Age and gender

The AIU for AR in males and females is shown as a function of age group in figure 4-14. Years shown are 1990 (earliest) and 1998 (latest). AR AIU in males was highest in ages 5 to 9. For males, it

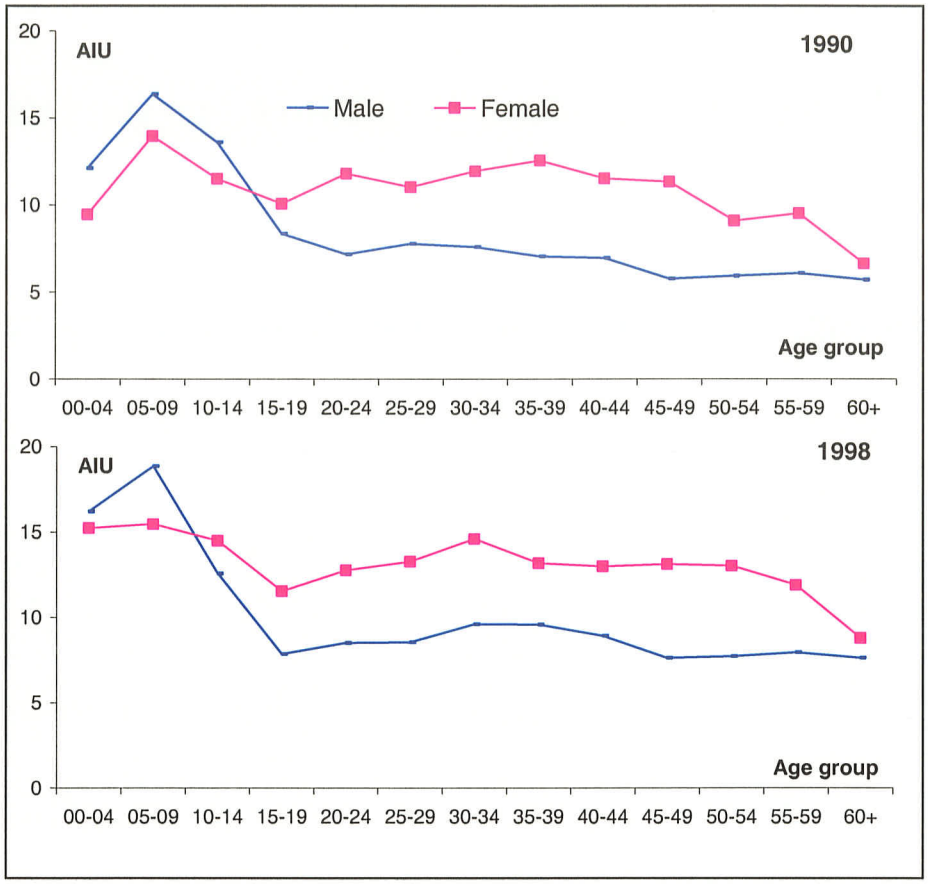

Figure 4-14. AIU for AR by gender and age group, per 1,000 population. 1990 and 1998.

did not change with time in those aged 10 to 19 and increased in people of younger and older age groups. For females, AIU for AR was similar in all age groups in all years, fluctuating between 10 and 15 per 1,000 population. The most noticeable increase occurred in females 0 to 4 year old (from 9 to 15 per 1,000 population).

The age-gender crossover shifted with time towards younger ages, from 15-19 year old in 1990 to 10 - 14 years old in 1998.

The AIU for asthma in males and females in 1990 and 1998 is shown as a function of age group in figure 4-15. Asthma AIU in males and females was highest in 0 to 4 years old and declined with age in logarithmic fashion, with males having a steeper decline. Asthma AIU was higher in boys compare to girls younger than 15 years and in woman compare to men. There were no gender difference in people aged 60 and over. The age-gender crossover in both years occurred at ages 10 to14.

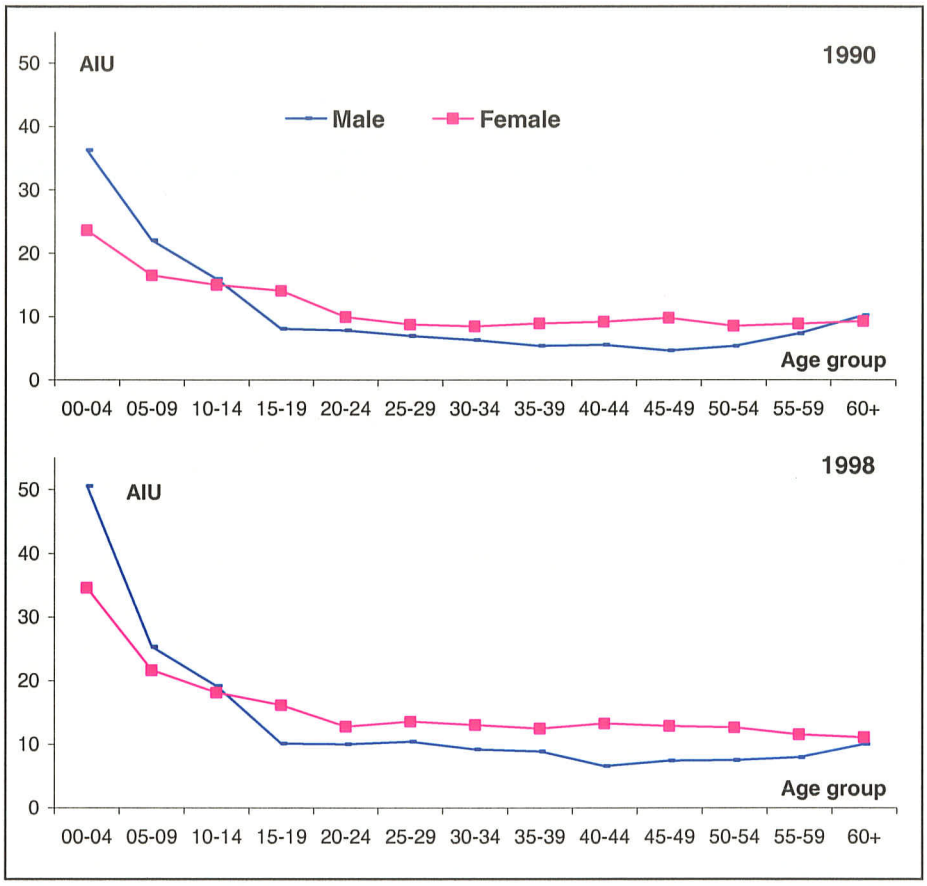

Figure 4-15. AIU for AR by gender and age group, per 1,000 population. 1990 and 1998.

Area (by gender and age)

Urban and rural AIU for AR and asthma in 1991 are shown as a function of age in figure 4-16, separately for males (a) and females (b). AR and asthma AIU were higher in the urban area in children and in young adults and for AR urban-rural differences were bigger than for asthma. For AR, there was no regional difference after the age of 45 in either gender. For asthma, regional differences

disappeared in males and females after the age of 20. Rural males aged 50 or more had slightly higher rates of asthma AIU than their urban counterparts.

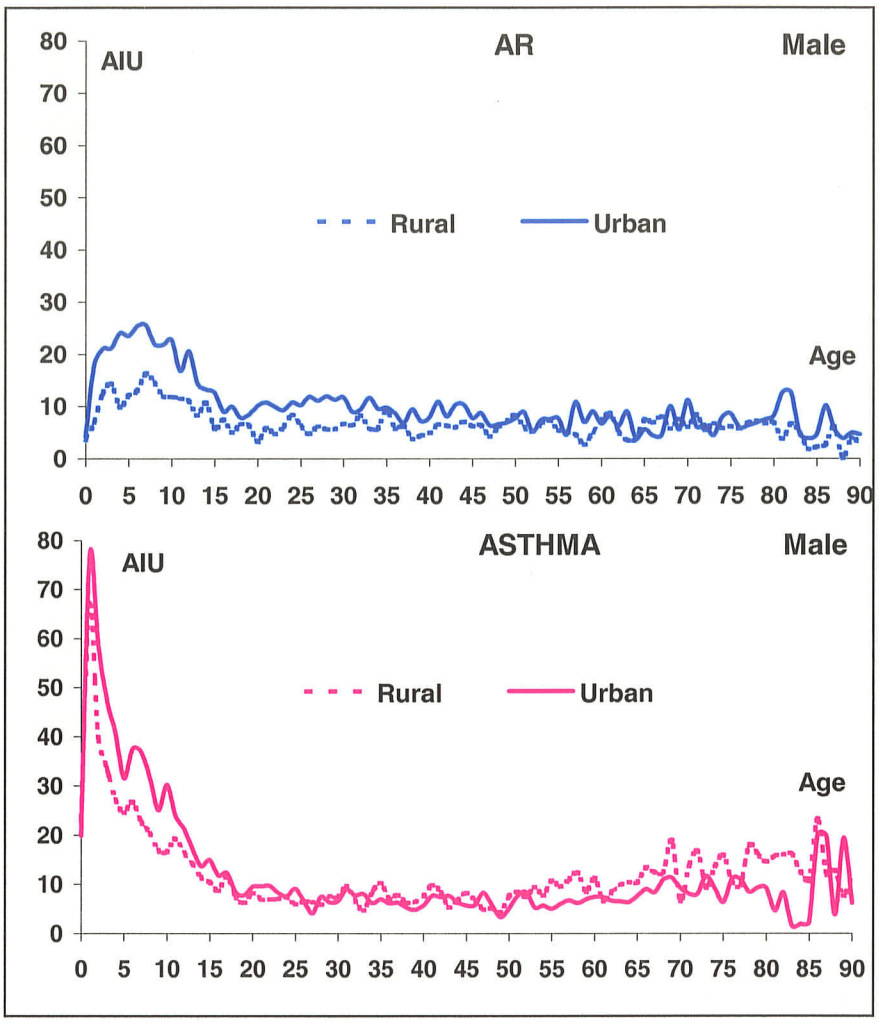

Figure 4-16(a). AIU for AR and asthma by area and age in males, per 1,000 population. 1991.

Annual incidence of utilisation in other years of the study had similar patterns, for both males and females.

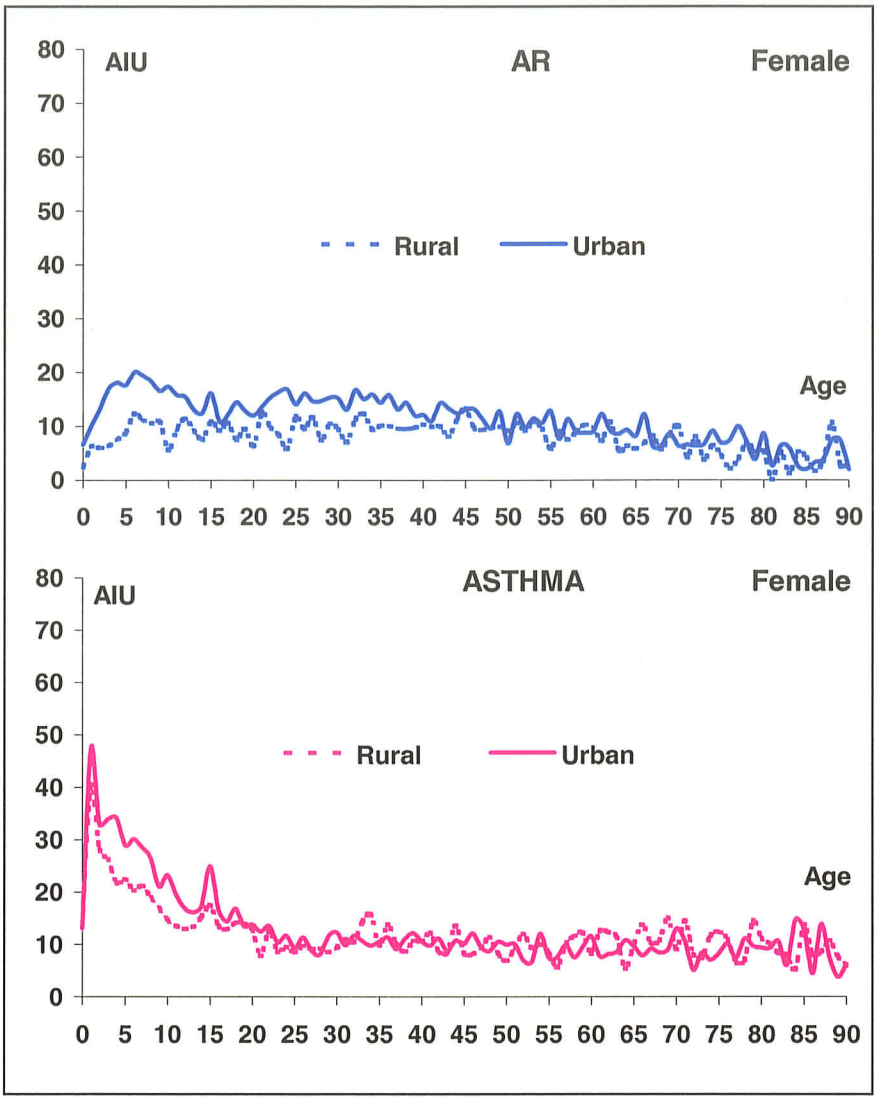

Figure 4-16(b). AIU for AR and asthma by area and age in females, per 1,000 population. 1991.

Area (age-gender adjusted)

Urban and rural age and gender adjusted AIU rates for AR and asthma are shown as a function of time in figure 4-17. Both AR and asthma AIU were higher in the urban area at all times during the study period. For AR, there were no significant increases with time in either area, and area-year interaction was also non-significant, indicating that the differences between areas were uniform.

For asthma area-year interaction was significant (p=0.02), indicating that regional trends differed significantly from each other. Asthma AIU rates in the urban area increased significantly with time

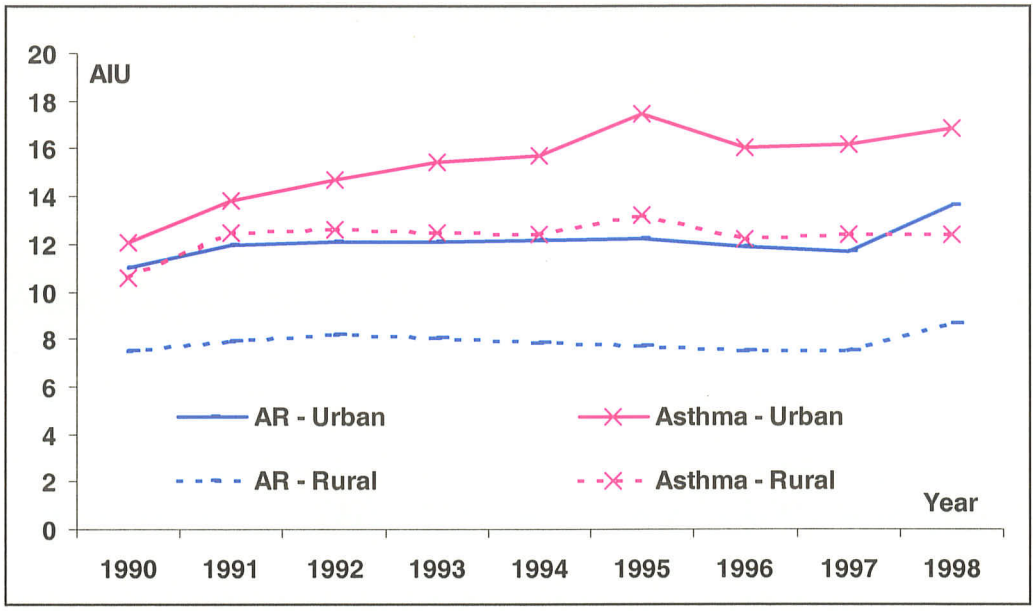

Figure 4-17. Age-gender adjusted AIU for AR and asthma by area of residence, per 1,000 population. 1990-1998.

($p<0.01$), averaging 0.52 cases [95% CI: 0.30-0.74] per 1,000 population per year, while asthma AIU in the rural area did not show a significant change with time.

Income (Winnipeg, age-gender adjusted)

The rates of AR and asthma AIU as a function of income quintile in Winnipeg are shown in figure 4-18. In 1990, AIU for AR was slightly lower in Q1 and Q2, but the differences between quintiles disappeared after 1993, because rates of AIU for AR increased significantly in Q1 ($p=0.004$) and Q2 ($p=0.036$), and did not change in Q3-Q5. The average increases in Q1 and Q2 were 0.39 cases [95% CI: 0.21-0.57] and 0.25 cases [95% CI: 0.06-0.44] per 1,000 population per year, respectively. There was a significant ($p=0.0027$) year-income quintile interaction term indicating that AR AIU changed differently in different income quintiles.

There was also a significant ($p=0.034$) year-income quintile interaction term for asthma AIU. There was no quintile difference in AIU rates from 1990 to 1993 and AIU were slightly higher in quintiles 1 to 3 after that. Rates of AIU increased significantly in all quintiles ($p<0.03$), with larger increases in lower

quintiles, ranging from 0.72 cases [95% CI: 0.52-0.92] in Q1 to 0.41 cases [95% CI: 0.14-0.68] in Q5, per 1,000 population per year.

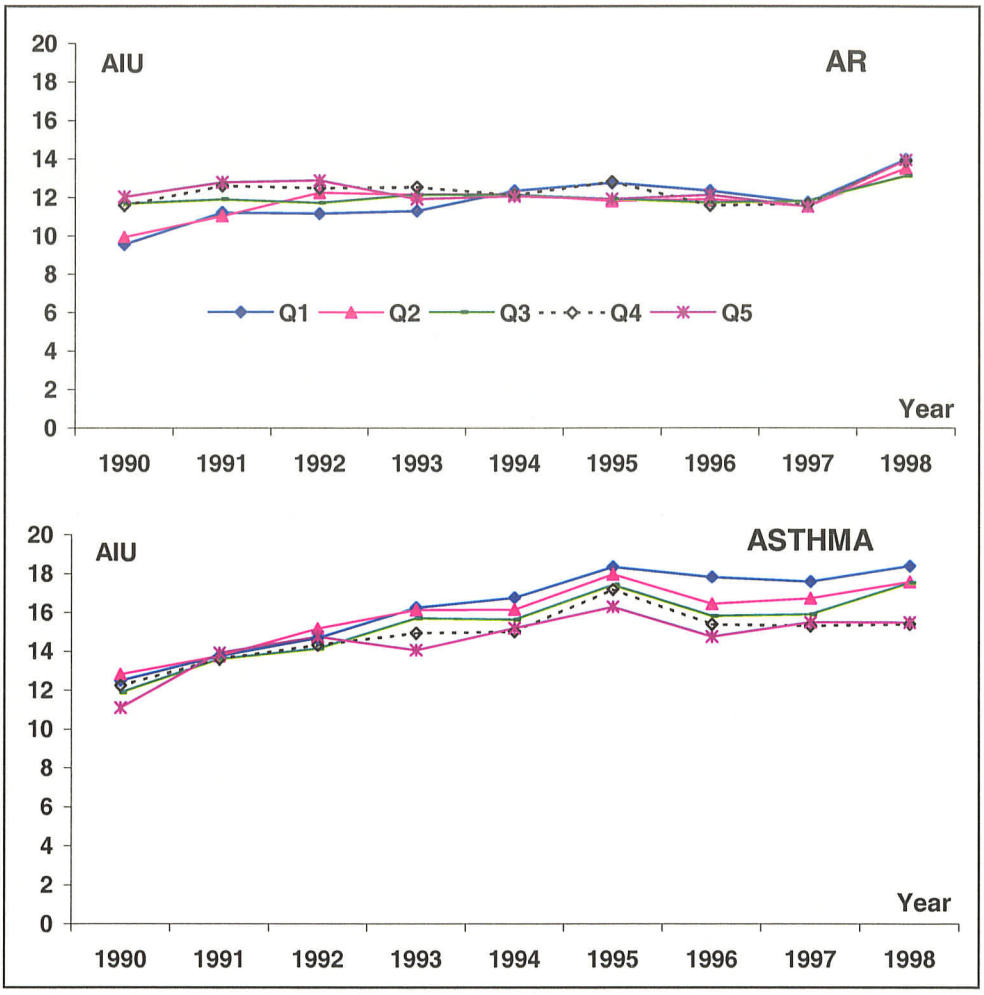

Figure 4-18. Age-gender adjusted AIU for AR and asthma, per 1,000 population. 1990-1998.

4.3. Patterns of Utilisation

Patterns of utilisation were studied in people aged 5 or more who had a physician diagnosis in 1991. Figure 4-19 shows percent of patients with a diagnosis of asthma or AR in 1991 that were seen for the same diagnosis in the years preceding or following 1991. A total of 18,069 people aged 5 or more were diagnosed with allergic rhinitis in 1991. Of these, within the 1985-1998 period of study, about 58% did

not have a prior and 58% did not have a subsequent visit for AR. Of patients with AR in 1991, 39% (7,001 people) were not seen in any prior or subsequent year and about 85% of these 7,001 people

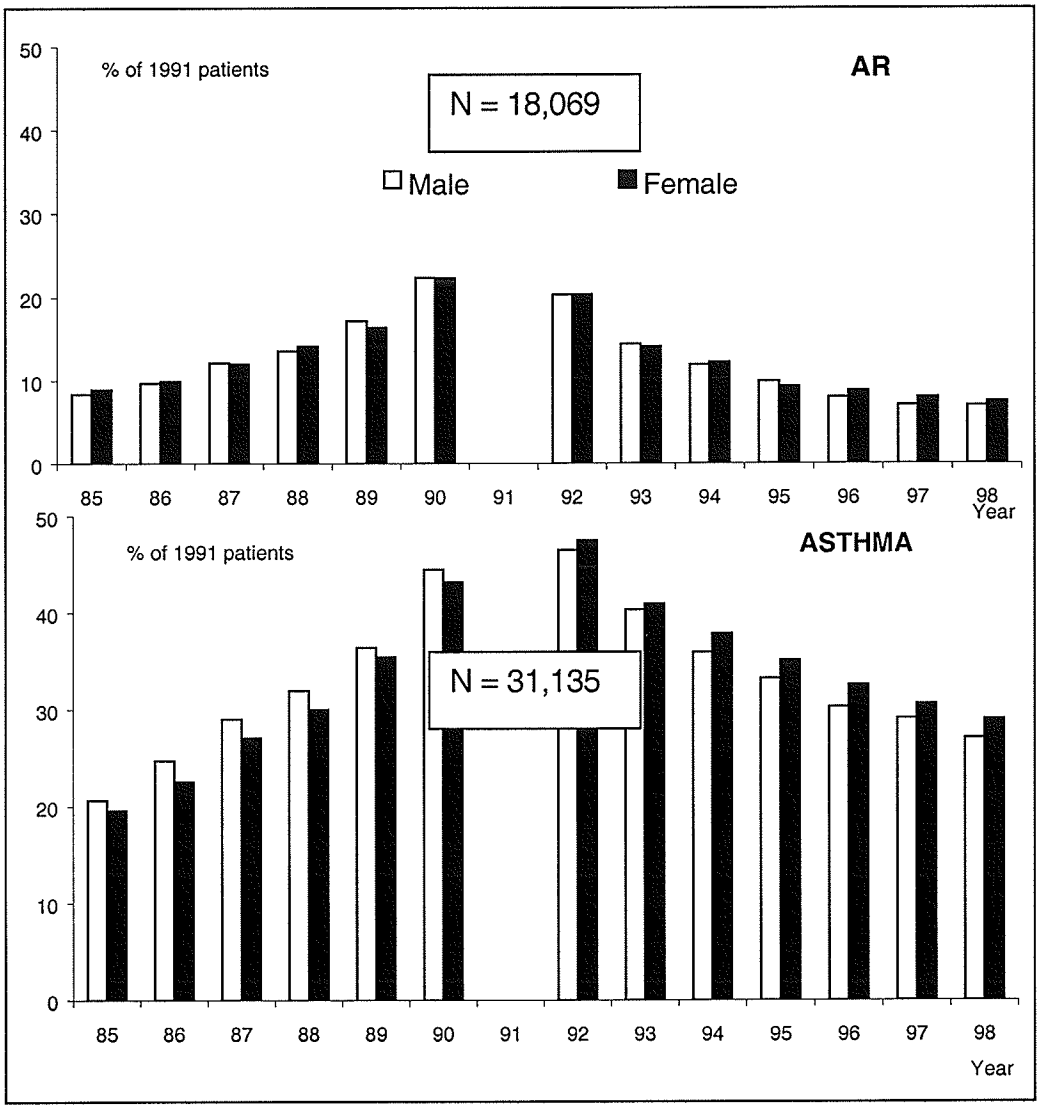

Figure 4-19. Percent of people with AR or asthma diagnoses in 1991 who were seen in other years of the study for the same diagnosis.

had only one claim in 1991 (another 12% had two claims). Of patients with AR diagnosis in 1991, 22% were also seen in the previous year and 20% in the following year. The proportion of patients seen in other years before and after 1991 decreased with the remoteness from 1991 in roughly symmetrical fashion. There was little difference between male and female patterns of utilisation for AR.

The diagnosis of asthma was associated with much higher previous and subsequent utilisation than was the case with AR. A total of 31,135 people aged 5 or more had asthma diagnosed in 1991. Of these, 37% did not have a prior and 28% did not have a subsequent diagnosis. Only about 18% of people with asthma in 1991 were not seen in any other years studied and 75% of these 5,555 people had only one claim in 1991 (another 17% had two claims). Of the patients with asthma in 1991, 44% were seen in the prior year and 47% in the following year. Slightly more females than males were newly diagnosed in 1991 (38% versus 35%), and as a result of this, males had higher utilisation rates in each of the prior years. Females conversely, had higher subsequent utilisation rates. For asthma, utilisation after the diagnosis was higher than that prior to it in both genders: 20% of all 1991 asthma patients aged 5 or more were seen in the 6th previous year as compared to 30% seen in the 6th following year.

4.4. Aggregate Utilisation (1985-1998)

To assess the extent of utilisation for allergic rhinitis and asthma for the total population of the Province over the study period, we calculated the total number of people diagnosed with AR and/or asthma at least once during 14 years (1985 through 1998). The total number of visits made for AR and/or asthma and total number of patient-years of observations during the study period were also computed. For patients with both diagnoses the first date for the earlier diagnosis was used as a starting point. For "all AR" and for "all asthma" only visits made for AR or asthma, respectively, were enumerated and the starting point was defined as the date of the first corresponding diagnosis. Results are shown in table 4-1 by diagnostic group, for males, females and the total.

Overall, about 14% of the total population of the province (estimated by the 1991 population denominator – the middle of the study period) were diagnosed at least once during the study period with allergic rhinitis and over 17% were diagnosed with asthma. Overlap of two diagnoses occurred in almost 5% of the population. Females constituted a higher fraction of all those affected by "AR only"

(10.4% females vs. 8.7% males) and in "all AR" category (15.3% females vs. 12.8% males), but there was no difference in male and female frequencies of utilisation per diagnosed patient. Males with both diagnoses had a slightly higher proportion of asthma visits (8.1 vs. 7.5 visits per patient), while females

		PATIENTS (% pop)	VISITS (visits per patient)	PATIENT-YEARS (visits per 1,000 p-y)
AR ONLY	Male	**48,537** 8.7%	**90,749** 1.9	**342,786** 265
	Female	**59,910** 10.4%	**111,792** 1.9	**420,484** 266
	Total	**108,447** 9.6%	**202,541** 1.9	**763,270** 265
ASTHMA ONLY	Male	**72,547** 13.0%	**379,395** 5.2	**475,465** 798
	Female	**73,639** 12.8%	**382,139** 5.2	**470,403** 812
	Total	**146,186** 12.9%	**761,534** 5.2	**945,868** 805
BOTH (AR + ASTHMA)	Male	**22,959** 4.1%	**243,293** 10.6 → 8.1A + 2.5AR	**214,450** 1,134
	Female	**27,873** 4.9%	**284,247** 10.2 → 7.5A + 2.7AR	**259,352** 1,096
	Total	**50,832** 4.5%	**527,540** 10.4 → 7.8A + 2.6AR	**473,802** 1,113
All AR	Male	**71,496** 12.8%	**148,611** 2.1	**522,546** 284
	Female	**87,783** 15.3%	**186,331** 2.1	**640,354** 291
	Total	**159,279** 14.0%	**334,942** 2.1	**1,162,900** 288
All Asthma	Male	**95,506** 17.1%	**564,826** 5.9	**657,086** 860
	Female	**101,512** 17.7%	**591,847** 5.8	**681,032** 869
	Total	**197,018** 17.4%	**1,156,673** 5.9	**1,338,118** 864
Note:	**Population in 1991 - males N = 560,094; females N = 574,179**			

Table 4-1. Number of people with diagnoses of AR and/or asthma and their visits, 1985-1998.

leaned a little more towards AR visits, with a similar number of total physicians' contacts per person (10.2 vs. 10.6 visits, females and males, respectively). In people with "asthma only" there was no gender difference in the fraction of the patients diagnosed (13.0% males vs. 12.8% females) and the same was true for "all asthma" (17.1% males vs. 17.7% females). There also was no difference in the frequency of utilisation between genders in any of the diagnostic categories as determined by the

average number of visits per patient or by the number of visits made per 1,000 of patient-years of observations.

The diagnosis of asthma was associated with much higher utilisation than diagnosis of AR. Patients with "AR only" averaged 265 visits per 1,000 patient-years of observations and patients with "asthma only" made 805 visits per 1,000 patient-years. The average AR patient was seen for the condition 2 times during the study period while the average asthma patient was seen for asthma almost 6 times during the same time. Co-existence of AR and asthma increased utilisation for both conditions: on average, people in this diagnostic group made 2.6 visits for AR and 7.8 visits for asthma during the study period and averaged 1,113 visits per 1,000 diagnosed patients per year of observation.

Tables 4-2 – 4-4 show the summary of utilisation for three different periods during the study – beginning (1985-1988), middle (1989-1993) and the end (1994-1998). The first period is a 4-year interval, while the second and the third periods are 5-year intervals. The data showed a consistent decline in utilisation rates per AR patient with time with some increase in a number of people affected. During 1985-88 a total of 51,756 people consulted physician for AR, which averaged about 1.15% of the total population per year. During 1989-93 this number rose to 69,811 people (1.24% of the population per year) and during 1994-98 to 72,069 people (1.28% of the population per year). Utilisation frequencies for AR patients during these 3 periods were 721, 576 and 506 visits per 1,000 diagnosed per year, respectively [1] (Tables 4-2 – 4-4). Utilisation frequencies for asthma patients during the same periods were 1,659, 1,400 and 1,159 visits per 1,000 diagnosed per year, respectively, while the number of people diagnosed with asthma increased from 54,917 to 96,728 to 123,209, the biggest increase occurring between the first and the second intervals.

[1] Note that number of visits per 1,000 patient-years of observation is higher in each of the three periods than in overall 14-years period. This fact results from the shorter periods of observations for those with early diagnosis.

		PATIENTS (% pop)	VISITS (visits per patient)	PATIENT-YEARS (visits per 1,000 p-y)
AR ONLY	Male	**18,521**	**31,723**	**46,978**
		3.3%	1.7	675
	Female	**23,114**	**40,573**	**58,903**
		4.0%	1.8	689
	Total	**41,635**	**72,296**	**105,881**
		3.7%	1.7	683
ASTHMA ONLY	Male	**23,084**	**94,562**	**61,842**
		4.1%	4.1	1,529
	Female	**21,712**	**95,520**	**57,538**
		3.8%	4.4	1,660
	Total	**44,796**	**190,082**	**119,380**
		3.9%	4.2	1,592
BOTH (AR + ASTHMA)	Male	**4,881**	**38,790**	**15,820**
		0.9%	7.9 →5.7A + 2.2AR	2,452
	Female	**5,240**	**40,870**	**16,985**
		0.9%	7.8 → 5.3A + 2.5AR	2,406
	Total	**10,121**	**79,660**	**32,805**
		0.9%	7.9 → 5.5A + 2.4AR	2,428
All AR	Male	**23,402**	**42,665**	**60,275**
		4.2%	1.8	708
	Female	**28,354**	**53,700**	**73,426**
		4.9%	1.9	731
	Total	**51,756**	**96,365**	**133,701**
		4.6%	1.9	721
All Asthma	Male	**27,965**	**122,409**	**75,761**
		5.0%	4.4	1,616
	Female	**26,952**	**123,264**	**72,282**
		4.7%	4.6	1,705
	Total	**54,917**	**245,673**	**148,043**
		4.8%	4.5	1,659
Note:	**Population in 1991 - males N = 560,094; females N = 574,179**			

Table 4-2. Number of people with diagnoses of AR and/or asthma and their visits, 1985-1988.

		PATIENTS (% pop)	VISITS (visits per patient)	PATIENT-YEARS (visits per 1,000 p-y)
AR ONLY	Male	**23,218** 4.1%	**38,744** 1.7	**71,072** 545
	Female	**29,247** 5.1%	**48,560** 1.7	**88,868** 546
	Total	**52,465** 4.6%	**87,304** 1.7	**159,940** 546
ASTHMA ONLY	Male	**39,262** 7.0%	**165,694** 4.2	**122,898** 1,348
	Female	**40,120** 7.0%	**168,750** 4.2	**123,781** 1,363
	Total	**79,382** 7.0%	**334,444** 4.2	**246,679** 1,356
BOTH (AR + ASTHMA)	Male	**8,012** 1.4%	**61,136** 7.6 → 5.5A + 2.1AR	**31,629** 1,933
	Female	**9,334** 1.6%	**69,080** 7.4 → 5.1A + 2.3AR	**36,513** 1,892
	Total	**17,346** 1.5%	**130,216** 7.5 → 5.3A + 2.2AR	**68,142** 1,911
All AR	Male	**31,230** 5.6%	**55,473** 1.8	**97,651** 568
	Female	**38,581** 6.7%	**69,692** 1.8	**119,825** 582
	Total	**69,811** 6.2%	**125,165** 1.8	**217,476** 576
All Asthma	Male	**47,274** 8.4%	**210,101** 4.4	**150,003** 1,401
	Female	**49,454** 8.6%	**216,698** 4.4	**154,746** 1,400
	Total	**96,728** 8.5%	**426,799** 4.4	**304,749** 1,400
Note:	**Population in 1991 - males N = 560,094; females N = 574,179**			

Table 4-3. **Number of people with diagnoses of AR and/or asthma and their visits, 1989-1993.**

		PATIENTS (% pop)	VISITS (visits per patient)	PATIENT-YEARS (visits per 1,000 p-y)
AR ONLY	Male	**23,533**	**36,461**	**72,744**
		4.2%	1.5	501
	Female	**29,935**	**45,118**	**91,164**
		5.2%	1.5	495
	Total	**53,468**	**81,579**	**163,908**
		4.7%	1.5	498
ASTHMA ONLY	Male	**49,953**	**193,579**	**168,313**
		8.9%	3.9	1,150
	Female	**54,655**	**204,993**	**183,662**
		9.5%	3.8	1,116
	Total	**104,608**	**398,572**	**351,975**
		9.2%	3.8	1,132
BOTH (AR + ASTHMA)	Male	**8,176**	**52,762**	**33,259**
		1.5%	6.4 → 4.7A + 1.7AR	1,586
	Female	**10,425**	**64,700**	**41,767**
		1.8%	6.1 → 4.5A + 1.7AR	1,549
	Total	**18,601**	**117,462**	**75,026**
		1.6%	6.3 → 4.6A + 1.7AR	1,566
All AR	Male	**31,709**	**50,475**	**99,422**
		5.7%	1.6	508
	Female	**40,360**	**62,937**	**124,750**
		7.0%	1.6	505
	Total	**72,069**	**113,412**	**224,172**
		6.4%	1.6	506
All Asthma	Male	**58,129**	**232,327**	**197,478**
		10.4%	4.0	1,176
	Female	**65,080**	**251,874**	**220,127**
		11.3%	3.9	1,144
	Total	**123,209**	**484,201**	**417,605**
		10.9%	3.9	1,159
Note:	**Population in 1991 - males N = 560,094; females N = 574,179**			

Table 4-4. Number of people with diagnoses of AR and/or asthma and their visits, 1994-1998.

4.5. Summary of the results

In summary, similar proportions of Manitoba population were given diagnosis of AR and asthma between 1985 and 1998, but asthma diagnosis resulted in much higher utilisation. Overall increase in asthma was also much bigger than increase in AR and asthma trends did not parallel trends of AR (Figures 4-1, 4-10, Tables 4-1 to 4-4).

The number of people consulting physician for "AR only" or for "AR plus asthma" increased little with time. The biggest increase occurred in the diagnostic group "asthma only" (Tables 4-2 to 4-4). Asthma had different rates of increase during the study, with the biggest increase occurring between 1988 and 1992 and the smallest increase at the end of the study, from 1994 to 1998 (Figures 4-1, 4-10).

Allergic rhinitis was more prevalent in females than in males and gender differences did not change with time. There were no significant gender differences in asthma APU or AIU (Figures 4-2, 4-11, Tables 4-1 to 4-4).

Different age groups were affected differently (Figures 4-4, 4-13). Both diseases increased with time most in 0 to 4 years old children. The divergence between asthma and AR was also biggest in youngest children and there were no differences in trends of AIU for two diagnoses in adults. Only in adult age group 55+ there were significant trends in AIU, and the rates of increase were the same for AR and asthma for these ages. Other age groups did not have significant trends for either of the diseases, but this could be because the years of the biggest increase in APU could not be incorporated into the calculation of AIU (Figures 4-1, 4-11).

APU and AIU for AR and asthma were always higher in Winnipeg. (Figures 4-8, 4-17). When different age groups were compared, the difference was only evident in children and young adults and no difference was present in elderly (Figures 4-7(a), 4-7(b), 4-16(a), 4-16(b)). For AR, the differences in children increased with time, because AR APU in rural area did not change and AR APU in Winnipeg

showed a significant increase. For asthma, both APU trends were significant, and differences between urban and rural areas also increased with time. For AIU, only urban asthma increased significantly, while rural asthma or urban and rural AR did not change with time.

Income groups in Winnipeg were not equally affected – the APU and AIU increased more in poorer then in richer quintiles, for both AR and asthma (Figures 4-9, 4-18). These trends resulted in appearance of quintile differences in asthma and disappearance of quintile differences in AR at the end of the study period.

Asthma and AR patients had different utilisation patterns. Average AR patient was seen only 2 times during the study period and AR patients made on average 288 visits per 1,000 diagnosed per year. Average asthmatic was seen almost 6 times, and asthma patients made 864 visits per 1,000 diagnosed per year.

Co-existence of AR and asthma in the same patients increased frequency of utilisation for each condition. Utilisation per patient declined with time similarly in all diagnostic groups and there was no gender difference in frequency of utilisation, either for AR or for asthma (Tables 4-1 to 4-4).

5. Discussion

5.1. Allergic rhinitis and asthma

Allergic rhinitis and asthma are two allergic diseases, and their similarities have been extensively reported [13] - [15]. The most common underlying characteristic of these diseases is atopy. Unfortunately, agreement on the definitions of terms such as allergies, asthma, atopy, hay fever, skin test reactivity, or bronchial hyper-reactivity is not achieved. The general agreement is that there is no agreement on the definitions of many of these terms [164].

The term atopy was initially introduced by Coca and Cooke [165] in 1923 in order to identify a subgroup of clinical allergies involving reactive or skin-sensitising antibodies that were subject to hereditary influences. It has been redefined over the years in various ways. Some researchers use the term to refer to all allergic phenomena, regardless of the demonstration of a specific antibody, whereas others have restricted the term to those involving an allergen-specific, skin-sensitising IgE antibody [166].

IgE-mediated mechanisms have been assumed to play a role in the pathogenesis of some asthmatics (termed atopic, or extrinsic), because their exposure to "extrinsic" allergens to which they are sensitised results in exacerbation of the disease. This does not necessarily imply a role for IgE-mediated mechanisms in asthma pathogenesis, as distinct from exacerbation, and IgE-mediated mechanisms do not unavoidably result in asthma because many highly sensitised atopic individuals never develop the disease. Other asthmatics, who are not apparently sensitised to environmental allergens and in whom IgE-mediated mechanisms are not obvious, have been labelled non-atopic or intrinsic [167]. It is now generally accepted that this term is used to describe a group of asthmatics who are skin-prick test negative to extracts of aeroallergens and whose serum total IgE concentrations are

within the normal range [166]. It has also been shown that atopic and non-atopic asthma are remarkably similar in many aspects [168] [169].

In summary, although IgE-mediated mechanisms may clearly be important in allergen-induced, short-term exacerbations of asthma in atopic individuals, their role in the pathogenesis of chronic disease, in both atopic and non-atopic subjects, is less certain. Several reports in recent decades indicated that the fraction of asthmatics without apparent clinical atopic manifestations was increasing with time [3] [4]. Although an atopic nature of the disease can not be clearly demonstrated in some patients with allergic rhinitis (AR) or atopic dermatitis (AD), these two diagnoses are more strongly associated with IgE-mediated mechanisms than asthma and there were no reports of changes in these associations with time.

Recently, an increasing number of epidemiological studies, which did not perform clinical tests in studies populations, used the diagnoses of AD or AR as approximations of atopy to study asthma outcomes, asthma phenotypes, or asthma trends in populations. In the absence of more definitive clinical markers, asthma is more often defined as atopic if it occurs in conjunction with another allergic disorder, such as AR or AD, and labelled as non-atopic if there is no evidence of suchlike allergic manifestations [3] [4] [170].

5.2. Use of utilisation data

It has been shown that utilisation data can be used to estimate the real prevalence of chronic diseases such as asthma or allergic rhinitis, providing that certain assumptions are true [160]. The prevalence of the disease (**DP**) in population can be expressed through 2 components (Equation (1)):

$$DP = L^{(+)}D^{(+)} + L^{(-)}D^{(+)} \qquad (1)$$

where **L** denotes the label (physician's diagnosis) and **D** denotes the disease. The first component of this equation $L^{(+)}D^{(+)}$ represents a treated disease, and the second component $L^{(-)}D^{(+)}$ represents untreated disease. The prevalence of the diagnosis, or label ($L^{(+)}$), is also generally comprised of the two components (Equation 2):

$$L^{(+)} = L^{(+)}D^{(+)} + L^{(+)}D^{(-)} \qquad (2)$$

The first component in this equation $L^{(+)}D^{(+)}$ represents a true diagnosis, and the second component $L^{(+)}D^{(-)}$ represents a false diagnosis, or label without a disease.

Mulloly et al [160] introduced a conceptual framework within which cumulative treated prevalence in a medical care system can be related to source prevalence. The main assumptions for this framework include

- Stability of the source population size;
- Negligible disease-specific death rates;
- Constant incidence and remission rates;
- Constant immigration and termination of coverage rates.

This framework is also sensitive to the time interval analysed, and in a given reference it was based on a 5-year interval, which seams to be a reasonable compromise when considering conditions such as AR and asthma. We saw in our study, that average asthma patient was treated a little less than once in 2 years, while AR patient was only seen on average once in 7 years (Table 4-1).

It is more difficult to relate time trends in utilisation to the prevalence of chronic diseases, as the assumptions may not hold the test of the time. Given many uncertainties in defining cases of diseases such as asthma or AR, for which there is no universal agreement concerning the diagnosis and no definitive testing for the disease, definitive inferences about the trends of disease prevalence **DP** in the

population can not be reached from utilisation data alone. For our population there were no data available on the prevalence of the symptoms at more than one point at time. Valid inferences can be achieved only about cumulative prevalence of the treated disease over the total study period.

As mentioned previously, the absence of standardisation in definition of allergic disease such as AR and asthma makes the components of equations (1) and (2) volatile, and they can change differently with time. For example the increase in the component $\mathbf{L^{(+)}D^{(+)}}$ of the equation (1) (diagnosed disease) can be brought about mostly by the decrease of the second component $\mathbf{L^{(-)}D^{(+)}}$ (undiagnosed disease), as the definition of the disease itself evolves with time. A true increase in the prevalence of the disease in the population (**DP**) is also a possibility. False diagnoses $\mathbf{L^{(+)}D^{(-)}}$ might also represent a bigger or smaller proportion of the total label $\mathbf{L^{(+)}}$ over time.

In this thesis we are only assessing changes in the total label $\mathbf{L^{(+)}}$ (equation (2)). Even if we could assume that the second component of this equation (diagnosis without disease $\mathbf{L^{(+)}D^{(-)}}$) was much smaller than the first component, nonetheless it would be impossible to deduce from utilisation data alone if the change in the total label $\mathbf{L^{(+)}}$ had resulted from the decrease of the second component of equation (1) $\mathbf{L^{(-)}D^{(+)}}$ or from the increase in the actual prevalence of the disease **DP**.

In the case of asthma and other allergic disorders the combination of both effects is likely to be present. Many studies of asthma-like symptoms found a real increase in their prevalence in general populations in the last decades [2] - [5], but a possibility of diagnostic exchange and of increased diagnostic detection of allergic diseases, especially for asthma was also demonstrated [3] [4].

It has been argued that the increase in asthma label could be at least partially due to the increase in the false diagnosis of early childhood wheezers as asthmatics [171], but this argument boils down to the question as to what is and what isn't asthma. Wheezy bronchitis and asthma may differ in their natural history and heritability, but several studies have shown that early childhood wheezers or those with

diagnosis of bronchiolitis also have an increased risk of developing asthma, independently of allergic sensitisation [172] [173]. Study of Manitoba children confirmed that the diagnosis of asthma given during the first year of life was the factor most strongly associated with asthma diagnosis during the $5^{th} - 6^{th}$ year of life [174]. As there is no universal agreement on asthma diagnosis, in this thesis we will consider a broad definition of asthma and assume that the proportion of false diagnoses was negligible in terms of the total population studied. This assumption is supported by a recent study that compared the agreement between survey data and administrative database used in our study for asthma diagnosis in 20-44 year old Manitobans. The study found that the absence of asthma symptoms on questionnaire virtually excluded the probability of being seen by a physician for asthma [175].

An obstacle in comparing utilisation data for AR and asthma is that, though they share many similarities, they differ significantly in terms of the proportions of affected individuals seeking medical attention for their symptoms. This thesis can only compare the proportions that see a physician for symptoms of AR and/or asthma. Because many people affected by AR do not require physician services and because the symptoms of allergic rhinitis may be mislabelled as persistent colds or sinus problems, AR is likely to be under-diagnosed [28]. The fact that various medications for AR are readily available over the counter, while asthma medications are dispensed only on a prescription basis, probably contributes to the fact that diagnosis of asthma results in increased intensity (frequency) of utilisation, compare to that of AR.

The analysis of the cumulative data shows that, though similar proportions of Manitoba population were given labels of AR and asthma (14% and 17%, respectively) at any time during the study period, the frequency of utilisation for these conditions varied significantly. The average AR patient was seen 2 times during 14 years of the study, while average asthma patient was seen 6 times during the same time (Table 4-1). Almost 60% of all AR patients with a diagnosis in 1991 were never seen in the following 7 years, while this was true for less than 30% of all 1991 asthma patients (Figure 4-19). The comparison between annual prevalences of utilisation for the two conditions is therefore problematic. We believe, however, that the focus of this thesis on time trends rather than on year to year

comparisons does not invalidate the use of this measure. One only needs to keep in mind that the measure of APU underestimates the cumulative prevalence of the diagnosed AR ($\mathbf{L}^{(+)}\mathbf{D}^{(+)}$) in the population to a greater degree than is the case for asthma.

Annual incidence of utilisation (AIU) represents a better measurement for comparing the two diagnoses, as it only counts new (or previously uncounted) cases and to some degree adjusts for differences in the frequencies of utilisation between conditions. The drawback is that it could only be calculated for the most recent years 1990-1998, leaving out the periods of the biggest increases in asthma APU (from 1988 to 1990) and AR APU (from 1985 to 1988). The most striking divergence between the two diagnoses occurred in the two youngest age groups, for which the APU and AIU are closely related (most prevalent cases are incident cases). This fact adds to the validity of APU use in trend comparisons and supports the argument that differences seen in trends of APU reflect real differences in the prevalence of the diagnoses in the population studied. The analysis of the three separate time periods within 14 years of the study (Tables 4-2 - 4-4) also showed that the total number of people with asthma diagnoses in each of the three consecutive periods increased more than the total number of people with AR diagnosis.

On the other hand, frequencies of utilisation (per diagnosed patient) declined with time consistently in each of these periods for both diagnoses. That means that the measure of APU probably underestimated the prevalence of the diseases in our population more in later periods than in did in earlier. The effect of diagnostic suppression can also be present in our study, since only one diagnostic code per visit is recorded on physician's claim and asthma diagnoses might take precedence over AR since asthma is a more severe illness. However, we have no reason to believe that this phenomenon would have changed with time. Given that frequency of utilisation per patient declined for all 3 diagnostic groups ("AR only", "asthma only", "AR plus asthma") in similar fashion we feel that comparison of AR and asthma trends was not compromised (Tables 4-2 - 4-4).

Some inferences regarding the changes in the prevalence of the disease in the population (**DP)** can also be drawn from utilisation data, keeping in mind that the measure of APU underestimates **DP** for AR in the population to a greater degree than is the case for asthma. Because of a reduced frequency of utilisation of physician services per asthma or AR patient over the study period, the measure of APU would underestimate the real prevalence of the disease in our population more during the later periods than during earlier years of the study.

5.3. Time trends

The APU and AIU of asthma increased more than APU and AIU of AR during the study period (Figures 4-1, 4-10). The average increase in APU of allergic rhinitis during the study period was only about 0.14 cases per 1,000 population per year. There were fluctuations from year to year in this measure, and the rate of increase was higher during first 3 years of the study (0.8 cases per 1,000 population per year) and low after that (0.07 cases per 1,000 population per year). These results are not conclusive to suggest a definite increase in the prevalence of allergic rhinitis or atopy in the population. The increase in APU of AR was not greater than the general increase in rates of utilisation of physician services in the province during the study period, which averaged about 10% for period between 1980 and 1990 [[176]]. It might also indicate increased awareness of the disease among both doctors and patients [[3]] [[177]].

The lack of a significant increase in AIU of AR also argues against a true increase in the prevalence of the disease, though the years of the most increase in APU were excluded from the calculation of AIU. A British study found an increase in utilisation rates for AR between 1981 to 1992 [[19]], but no data was available for the later period. We saw some increase during earlier years, but virtually none since 1989. The evidence about trends in the prevalence of AR symptoms in populations is conflicting [[3]] - [[7]] [[18]] [[128]] [[151]]. The bulk of the previously published evidence combined with the results of our study points to the conclusion that there was probably an increase in the real prevalence of AR accompanied by the

decline in utilisation rates per AR patient. Our data showed a steady decline in utilisation rates per AR patient with time with an increase in the number of people affected. During 1985-88 a total of 51,756 people consulted a doctor for AR, which averaged about 1.15% of the total population per year. During 1989-93 this number rose to 69,811 people (~ 1.24% per population per year) and during 1994-98 to 72,069 people (~1.28% per population per year). Utilisation frequencies for AR patients during these 3 periods were 721, 576 and 506 visits per 1,000 diagnosed per year, respectively (Tables 4-2 - 4-4).

The overall trend of AR APU did not parallel the trend of asthma APU. The increase in APU of asthma was much greater than the increase in AR APU, averaging almost 2 cases per 1,000 population per year, and at the end of the study period asthma APU more than 2-fold higher than AR APU (40.2 vs. 17.4, per 1,000 population). An earlier study of the same population during 1980-1990 had already noticed this phenomenon [176], and trends for asthma in our population correspond well with the recent CDC report about self-reported asthma trends in US [178].

We can argue that given the observed trends for AR, the increase in the prevalence of atopy in Manitoba population between 1985 and 1998, (measured indirectly by the APU of AR), was about 20-30%. In contrast, the increase in asthma APU was about 130%. Only some of this increase in asthma however, could have been caused by the increase in the prevalence of atopy, since it was not paralleled by the similar increase in the APU of AR (Figure 4-1) or 4-5 year cumulative prevalence of allergic rhinitis (Tables 4-2 – 4-4).

The number of people consulting physician for "AR only" or for "AR plus asthma" increased little with time. The biggest increase occurred in the diagnostic group "asthma only" (Tables 4-2 to 4-4). These results are suggestive of a change in the relationship of diagnosed asthma and atopy over time in our population. Other evidence indicates that the diagnosis of asthma in more recent cohorts of children is often made without apparent symptoms of atopy [3] [170]. A study of Manitoba children noticed a decline of the fraction of asthma patients with a diagnosis of AR during the first 6 years of life, from 19.3% (1983 cohort) to 15.6% (1990 cohort) [179]. These data are in agreement with a Norwegian study, where

the fraction of asthmatics with AR declined from 30.8% in 1981 to 15.3% in 1994 [3]. Upton et al have also demonstrated that between surveys completed in 1972-76 and in 1996, asthma in adults 44-54 increased in those without, but not with hay fever [4]. The possibility that earlier detection, diagnosis and treatment of asthma prevent the development of AR symptoms cannot be ruled out. However, it seems more likely that asthma in children has become a different disease in recent years. Lower respiratory tract allergy is not preceded by upper respiratory allergies, or other atopic markers, contrary to the pattern observed previously. Indeed, some children who were allergic to mite allergens at age 11 years were reported to wheeze before they experienced the development of skin tests or serum antibodies [180].

Between 1985 and 1998, about 14% of the total provincial population required physicians' services for AR and about 17% saw a doctor for asthma. These figures are consistent with reported overall prevalence rates of these diagnoses in Western populations [21] [80] [125] [132], but are lower than the rates of reported symptoms in children [114] or adults [115] [117] [181] in many countries, including Canada. It is possible that less then half of the population with AR symptoms seeks medical attention for the condition. For asthma the figure may be only slightly higher [175] [181].

In summary, it seems that asthma is manifesting itself and is diagnosed earlier in life, than it was before, and without apparent indicators of atopy. The progressive divergence of APU of AR from APU of asthma seen in the youngest age groups was not paralleled by a similar phenomenon in adults in our study. It is not clear if the future will see a similar divergence in older age groups, as cohorts more frequently diagnosed with asthma will age. It is possible that earlier diagnosis of asthma will lead to better outcomes in later life, since earlier onset of allergic disease was associated with higher rates of remission and better outcome [135] [137]. Patients with asthma alone, without concomitant AR, and early childhood wheezers that do not demonstrate an atopic predisposition, also have better chances of become asthma-free, though they are still at increased risk when compared to non-wheezers [135] [182] [101] [172].

5.4. Possibility of the diagnostic exchange

Both AR and asthma trends had periods with different rates of increase during the study period. For AR, the biggest increase in APU occurred at the beginning of the study period from 1985 to 1987 (0.8 cases per 1,000 population per year) and was low after that (0.07 cases per 1,000 population per year) (Figure 4-1). AIU of AR in our study did not change between 1990 and 1998, with the only noticeable increase between 1997 and 1998 (Figure 4-10). This latest peak in AIU of AR between 1997 and 1998 could have been caused by the decline in rates of utilisation per AR patient. More AR cases in the most recent year could have been identified as incident, as they were not seen in the preceding 5 years.

For asthma, there were 3 periods with distinctly different rates of increase. A middle period (1988 to 1992) had the highest rate of increase (3.2 cases per 1,000 population per year), and the final period (1993 to 1998) had the smallest rate of increase (0.76 cases per 1,000 population per year). (Figure 4-1). To our knowledge, a decline in a rate of increase has not been reported elsewhere. The increase during initial years 1985 to 1987 did not differ from the 14-year average (1.9 cases per 1,000 population per year).

Asthma AIU increased from 1990 to 1995 and decreased in later years (Figure 4-10). This fact and the higher rates of increase in asthma APU between 1988 and 1992 are indicative of some changes in diagnostic criteria for asthma first occurring around 1987. A British study done prior to our study period compared data on asthma and hay fever diagnoses rates between 1970-1 and 1981-2 [[183]] and noticed increases for both AR and asthma in all age groups. Authors concluded that most of these changes did not represent changes in diagnostic criteria, with the only possible exception for asthma in age group 5-14, where some of the increased prevalence of asthma might have resulted from a reduction in the prevalence of acute bronchitis. However, a significant decrease in rates of chronic bronchitis was noticed for the study population [[183]].

During the 1980s, there was almost an universal increase in asthma awareness among caregivers, due partly to upward trends in asthma mortality rates in many industrialised countries [184], and partly to improved knowledge, reflected in the new guidelines for the diagnosis and treatment of asthma [185]. It is possible that some of the increase during that time was caused not by the increased prevalence of the disease, but by an increased frequency of the diagnosis, mostly among children. In all likelihood, both effects were present, as some children that were previously labelled as having bronchitis or bronchiolitis were given an asthma diagnosis [186], but an increase in all types of wheezing illness in childhood was also reported during that time [187].

Prior to 1988 and after 1992 the trends in asthma APU in our population were similar, suggesting that the phenomenon of diagnostic exchange has levelled off and that these trends represented a real increase in the prevalence of asthma symptoms in the population during the study period.

There was a better correspondence in trends between AR and asthma in the later years of the study, when the rates of increase for both AR and asthma APU were lowest. However, the average rate of increase for asthma APU during this period was still almost 10 times higher than the average rate of increase for AR APU (0.8 cases vs. 0.09 cases, per 1,000 population per year).

5.5. Age groups

Age distributions for AR prevalence were found to be robust in different geographical regions [19] [80] and in urban or rural area [80]. In our study the age distributions for AR APU were similar in all years studied (Figure 4-3, shown are only extreme years of the study). The highest rates of AR APU were noticed in ages 5 to14 (at about 20-30 per 1,000 population) and lowest in children 0-4 and in people 55 years and older (at about 10 per 1,000 population). There was a tendency for a faster increase in APU of AR in younger age groups and of a shift of the APU peak to earlier ages.

APU of AR increased significantly in children 0 to 4 with average increase 0.25 cases per 1,000 population per year and in adults over 55, with average increase 0.14 cases per 1,000 population per year. Though trends in AR APU for other age groups were not significant, they were similar in the magnitude of the increase, and more uniform among different ages than time trends for asthma. The annual incidence of utilisation for AR increased significantly only in those aged 55 or more, with average increase of 0.16 cases per 1,000 population per year and was accompanied by a similar increase in asthma AIU (0.18 cases per 1,000 population per year) in this group.

For asthma, the highest rates and the highest increase in rates were greatest among the three youngest age groups: (0 to 4, 5 to 9 and 10 to 14 years old). These rates of increases for asthma APU were much greater than was the case with AR APU, ranging from 3.9 cases per 1,000 population in 0-4 years old to 2.98 cases per 1,000 population in 10-14 years old. The relationship of diagnosed asthma with underlying atopy seemed to be changing most vividly for these age groups, particularly for group 0 to 4. The diagnosis of asthma in this age group was made before any symptoms of atopy could developed. For this age group the AIU of asthma in 1990-1998 was 3-4 times higher than AIU of AR.

For people ages 15-19 and 20-54 APU for both asthma and AR were very similar at the beginning of the study at about 15 per 1,000 population. The increase in APU of AR for these ages was similar to the increase in other age groups and to the overall time trend. The increase in asthma APU was not as striking as the increase in younger children, but bigger than the increase in people aged 55+ and larger than that for AR APU. It is important to notice that people aged 20 to 54 is the group for which the diagnosis of asthma is most certain [[116]]. For this group the trend in asthma APU was almost linear, without sharp changes, and different from trend for APU of AR, which did not change with time. However, there were no difference in trends of AIU for these age groups and differences seen in trends of APU were relatively small and could have resulted from different utilisation patterns for two diagnoses.

For people aged 55 and more, AR and asthma trends were almost parallel. In this age group the majority of patients were not incident cases, as incidence of allergic disease is generally very low at these ages [135] [136]. The annual incidence of utilisation (AIU) for people over 20 was less than 10 per 1,000 population, and similar for AR and asthma. The relationship between diagnosed asthma and underlying atopy seems to be the most stable in people over 55. It is interesting to notice that this was the only age group that had a significant time trend for both AR and asthma AIU ($p<0.05$). There is a limited data on AR and asthma available for these ages. Enright et al reported 12% prevalence rates for AR among people 60+ in 1994 [188]. Upton et al noticed a significant increase in both AR and asthma among adults 44-54 in the last 20 years [4], but we are not aware of any reports of the trends of AR concurrently with asthma in people over 55. It is possible that this effect in our population at least in part results from in-migration. Some studies reported that recent incoming migrants accounted for the most of noticed increase in the incidence of atopy (defined by skin-test reactivity) in people over 35 years old [154]. Migrants are also known to have a later onset of allergies than native populations [147]. The underdiagnosis and under-treatment of asthma in this age group is also a commonly reported problem [189].

In summary, trends of AR and asthma in different age-gender strata seen in our study are in good agreement with some of the trends seen in other general populations. There was a faster increase in both conditions, asthma in particular, in children. The increase was the fastest at the end of 80s and the beginning of 90s and has levelled off at the end of the study period. This is consistent with some of recent findings that also did not register increases in allergic conditions [18] [128]. The divergence between trends in AR and asthma was greatest in young children and was not apparent in adults.

5.6. Gender

Gender differences in AR and asthma prevalence are widely known and consistent in different populations [19] [80]. In general, there are more male children affected by asthma and allergic rhinitis, and reverse gender ratio is seen in adults, though the age when the switch occurs may vary from early adolescence to early adulthood. Many studies report higher prevalence of AR among females in childbearing age and overall [143]. In our study we saw a similar distribution, with a greater number of adult females given the diagnosis of AR at any time during the study.

Gender distributions for AR APU and AIU were similar in all years studied (Figures 4-2, 4-11) and female-to-male ratio was about 1.2 for both measures. Though APU and AIU of allergic rhinitis increased significantly with time in females and did not change in males, the year-gender interaction term did not reach a significant level in either of the cases. Several studies have previously demonstrated that the prevalence of atopy is similar in both genders or even higher in males [101] [190], but a higher fraction of females report symptoms or seek medical care [19] [177] [191]. This phenomenon is usually attributed to differential symptom recognition among genders [101].

For asthma, the gender difference in APU was neither consistent nor statistically significant. The prevalence was slightly lower in females between 1985 and 1989 and in males after 1991. Though there was no statistical significance for overall gender differences in asthma APU, the time period when the switch occurred and the fact that after 1991 AIU of asthma was higher in females may be indicative of an increased tendency toward diagnosing asthma in females. Previous studies have shown that asthma might be more under-diagnosed in females than it is in males [192]. This might also be due to an increase in the incidence of the disease among girls.

The age-gender crossovers for both AR and asthma APU and AIU occurred in our study at earlier ages than reported before [19] [80] [124] and in 1998 crossovers occurred at younger ages than in 1985 (1990). This was more pronounced for AR (Figures 4-5, 4-14) than for asthma (Figures 4-6, 4-15). For

both conditions the increase in the prevalence of the diagnoses was slightly higher in females in most of age groups, though the differences between male and female trends were not statistically significant. Again, this effect might be brought about by either increased diagnostic detection or by increased incidence of these diseases among females.

There was no difference in the frequency of utilisation of physicians' services between male and female patients with AR, asthma or both, in any of the time periods studied (Tables 4-1 – 4-4).

5.7. Area of residence

APU of both AR and asthma were always (at all times during the study period) higher in the urban than in the rural area (figure 4-7). When separate age groups were compared, differences were only evident for asthma in children and adolescents and for AR in children and in adults up to 50 years old. The fact that there were no differences in the APU of both asthma and AR in the oldest age group challenges the argument that these differences were caused by difference in access to health care services. There is no reason to suspect that in rural areas older groups would have a better access to health care than younger ones. These findings are in agreement with other studies that found higher prevalences of asthma and atopy in urban areas, particularly in children and young adults [[76]] - [[78]].

Urban children with asthma or AR are less likely to migrate to rural areas than their rural counterparts to the city. Thus, this does not explain the convergence of APU in adults. The fact that no differences in utilisation for either AR or asthma were found in adults over 50 years of age, supports the hypothesis that the urban environment is associated with earlier onset of symptoms and is not a direct cause of allergic disorders [[71]]. A substantial part of the rural Manitoba population is comprised of the farming community and the lower rates of allergic sensitisation found in farm children might explain some of the differences seen between two areas in our study [[83]] - [[87]].

APU of both AR and asthma increased with time more in the urban than in the rural area (significant interaction terms) (Figure 4-7). For asthma, urban and rural trends were more noticeably different than for AR, with urban-rural ratio increasing with time after 1991. Most of the increase in APU of asthma after 1991 occurred in the urban area, with the rural asthma APU increasing little between 1991 and 1998. In previous studies we noticed, that specialists, most of whom practice in Winnipeg, more readily diagnose pediatric asthma than do general practitioners [179] [193]. The overall increase in asthma APU was mostly caused by an increase in asthma APU in Winnipeg children. A similar effect was present in APU and AIU of AR, although it was much less pronounced.

5.8. Income Quintiles

Socio-economic or income status can be used as a surrogate measure for lifestyle characteristics. These characteristics may comprise dietary and other differences such as family size, smoking, domestic or workplace allergen exposure, or unknown factors. In our study the frequency of diagnoses of asthma and AR increased with time more in lower income groups than in high. This correlates with findings that lower income quintiles in Winnipeg have worse health status and higher health care needs [194]. The relatively rapid increase of asthma and AR APU in low-income quintiles may indicate true prevalence increases in these groups during the study. However, we think that the differences were most likely due to improved access to health care or increased awareness of these diseases among people in these groups. Most of the published data suggests that allergic diseases themselves don't discriminate according to income, though labelling by doctors sometimes does [28] [80] [101]. Worse control of symptoms or more severe disease in lower income groups can also account for some of differences among quintiles. Previous study of the same population has noticed that the frequency of visits to physicians and rates of hospitalisations for asthma were more common in low-income quintiles [193].

5.9. Impact on health care system

Over the 14 years of the study period similar proportions of the total provincial population sought physicians' services for AR (14%) or for asthma (17.4%). In all likelihood, many more with milder symptoms of both conditions did not seek medical services at all [175] [181]. The utilisation patterns and frequency however, differed significantly between AR and asthma. The average AR patient was seen only twice over 14 years while the average asthmatic made almost 6 visits to a doctor during the same time. The diagnosis of AR resulted on average in 288 visits per 1,000 diagnosed patients per year, while the diagnosis of asthma led to 864 visits per 1,000 diagnosed per year.

From our results it is evident that asthma diagnosis was more common than AR and required more frequent doctor's visits. In addition, asthma also caused numerous hospitalisations and emergency room visits. Considering that the number of hospitalisations per asthma patient dropped significantly during this time [193], the overall cost increase to the system caused by the increase in asthma prevalence was probably not as overwhelming as it could have been otherwise. According to the literature, the biggest increase in expenditures for allergic diseases during that time occurred in the pharmaceutical sector [195].

The increase in the number of people affected with asthma was accompanied by a decline in utilisation rates per AR patient, as was the case with asthma. Utilisation frequencies during 3 different time periods for AR patient were 721 visits in 1985-88, 576 visits in 1989-93 and 506 visits in 1994-98, per 1,000 diagnosed per year. For asthma, on average patients made 1,659 visits in 1985-88, 1,400 visits in 1989-93 and 1,159 visits in 1994-98, per 1,000 diagnosed per year (Tables 4-2 – 4-4). This fact moderated the potential impact of increased diagnostic frequencies on a provincial health care system. Or as some might argue, the decline in utilisation itself was the result of the inability of the system to accommodate the increased number of affected individuals in the same way as previously. There were some concerns about supply and distribution of physician resources in the province during the years of

the study [196] [197]. As a less severe disease, AR could have been more strongly affected by a shortage of physicians in a number of regions in the province, but the fact that the diagnostic group "AR plus asthma", which is the most severe of all, saw similar rates of decline in utilisation per patient, argues against that. In this diagnostic group the average number of visits per 1,000 diagnosed per year dropped from 2,428 visits during 1985-1988 to 1,911 during 1989-1993, and to 1,566 visits in 1994-1998 (Tables 4-2 -4-4).

Co-existence of AR and asthma increased utilisation of physicians' services for both conditions and resulted in an average of 1,113 visits per 1,000 diagnosed per year. This confirms previous findings that co-existence of AR and asthma in the same patient increases the severity of both conditions [16]. This diagnostic group clearly warrants an increased effort in medical research and development of treatment options [198]. On the positive side, the increase with time in the number of people diagnosed occurred mainly in the category of "asthma only", so that the utilisation increase was not as high as it could have been if the diagnostic group "AR plus asthma" was similarly affected. The utilisation frequencies per patient declined in similar fashion in all three diagnostic groups from the first to the second period and from the second to the third, which also reduced the potential impact of increased disease frequencies on a health care system.

5.10. Agreement with previously reported data

Our results showed a generally good agreement with previously reported data from Canada and other western countries. The proportions of the Manitoba population with diagnoses of AR or asthma are consistent with reported overall prevalence rates of these diagnoses in Western populations [21] [80] [125] [132], but are lower than the rates of reported symptoms in children [114] or adults [115] [117] [181] in many countries, including Canada. It is possible that less then half of the population with AR symptoms seeks medical attention for the condition. For asthma the figure may be only slightly higher [175] [181].

The annual adjusted utilisation prevalence rates for the diagnosis of AR in our study increased from 13.9 per 1,000 population in 1985 to 17.4 per 1,000 population in 1998. These figures fit well with reported rates of utilisation from Denmark and Britain. In 1977 study of general practices in Denmark found similar annual rate of utilisation for AR (about 15 per 1,000 population) [80]. British studies reported annual prevalence of utilisation (per 1,000 population) to be 5.1 in 1955, 10.6 in 1970,19.7 in 1981 and 22.0 in 1992 [19]. In the beginning of 1990's the reported prevalence of AR from surveys in British general populations was 24% in 16-65 years old [132] and 29% in 11-59 years old [199]. From these data we can infer that 1-year period prevalence of AR in our population was at least 20-30% if not higher, because children under 11 are also known to have high prevalence rates of AR [21] [114]. That corresponds well with the figure reported by ECRHS study in Winnipeg (28% for 20-44 years old) [117] and with figures for hay fever from ISAAC studies in Hamilton (10.7% for 6-7 year old and 27.7% for 13-14 year old) and in Saskatoon (7.2% for 6-7 year old and 12.1% for 13-14 year old) [114]. Conservative estimates in US give a similar rate of 16-20% for the overall prevalence of AR in the population [119] [125].

Age and gender curves for AR prevalence were found to be robust for different geographical regions [19] [80] and for urban and rural areas [80]. In our study the age distributions for AR APU were similar to patterns in the Tecumseh population study [124] and in general practices in Denmark [80] and Great Britain [19]. The first two studies, however, were done prior to our study period and their results resemble those of the early years of our study. There was a tendency for a faster increase in APU of AR in younger age groups and of a shift of the APU peak to earlier ages.

Asthma APU increased about 130% in our study, with a bigger increase in children. Recent report of CDC in US showed similar 15-year trends in self-reported asthma prevalence [178]. The overall reported increase between 1980 and 1994 was about 75% for all ages, with a faster increase in adults less than 34 year old and 160% increase in asthma prevalence in 0 to 4 years old children. The estimated current prevalence of asthma in US in 1994-95 was 5%, though there was a substantial variation by region. Danish study earlier reported similar rates of utilisation of physicians' resources for asthma [200].

The divergence of AR and asthma trends seen in our study corresponds to similar phenomena seen in other studies [3] [4] [170]. Many of these studies, however, also report higher rates of increase for AR in their populations. It is possible that availability of over-the-counter medications and restrain of physician's resources in the province to some extend moderated the increase in the trends of AR seen in our study.

6. Conclusions

In conclusion, similar proportions of Manitoba population were given a label of allergic rhinitis or asthma but diagnosis of asthma resulted in much higher utilisation. In addition, time trends in utilisation for AR differed strikingly from trends for asthma, particularly in the youngest age group. During the study period, asthma seemed to manifest itself earlier in life creating an additional burden on provincial health care system. Coexistence of AR and asthma in the same person resulted in increased utilisation for each of the conditions.

The results also suggest that the relationship of physician diagnosed asthma with underlying atopy in children and young adults may be changing with time. It remains a major objective of research to understand the reasons for the increase in asthma among children during recent decades, because the disease can not be effectively controlled unless the real cause of the increase is made a target for treatment. This thesis make a valuable contribution to the knowledge about epidemiology of allergic rhinitis and asthma in a total provincial population and their burden on health care system over prolonged period of time, enhancing the limited knowledge about trends for allergic diseases in Canada and adding data for international comparisons.

Our results were in generally good agreement with previously reported data from Canada and other western countries. Though utilisation rates for AR and asthma were much lower than reported prevalence of symptoms, they were similar to utilisation rates for AR and asthma reported from UK and Denmark. Asthma trends in our study were similar to those reported recently by the Center for Disease Control in US. High prevalence and significant trends in children seen in our study are consistent with results of other studies, and so are area differences. Divergence of asthma trends from AR trends in children corresponds to some of the previous reports

The limitation of the study stems from the fact that its results could not be compared to the prevalence of symptoms in population during the same time. However, using results of other studies reporting both utilisation rates and the prevalence of the symptoms in the same populations, the attempt can be made to estimate the burden of asthma and allergic rhinitis in a study population, as there was generally a good agreement with many previously reported results. In addition, this research identified population groups that were affected the most, and thus may assist in further investigations and in developing more effective strategies for disease management.

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APPENDIXES

APPENDIX 1 :
Summary of the results from ISAAC studies in children

Appendix 2. Prevalence (%) of symptoms by centre and age group

Country	Centre	6–7-year-olds						13–14-year-olds					
		Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever	Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever
			ever	past year					ever	past year			
Albania	Tiranë	2981	16.4	13.1	4.1	10.5	2.9	2957	18.6	12.7	4.0	10.8	2.3
Algeria	Algiers	0	–	–	–	–	–	1173	45.5	37.9	18.2	28.1	24.3
Argentina	Buenos Aires	3005	47.8	38.3	8.7	16.3	15.9	2996	69.2	59.6	21.0	21.0	12.5
	Rosario	3007	50.4	41.8	10.5	20.4	15.7	3008	75.1	65.2	24.6	25.8	14.2
Australia	Adelaide	3063	32.5	29.9	14.5	18.6	23.5	3030	45.0	39.5	22.6	27.2	54.4
	Melbourne	2840	25.7	23.0	9.8	14.1	14.9	2759	41.4	35.9	16.6	24.1	40.5
	Perth	2192	32.1	28.6	14.9	17.2	20.6	3650	48.5	41.5	22.6	26.4	49.2
	Sydney	2804	27.4	24.1	9.4	13.7	12.2	2839	40.2	33.0	15.4	22.1	24.2
Austria	Salzburg	3658	15.0	13.0	6.4	9.0	8.8	3371	28.5	22.1	11.5	8.7	20.0
	Urfahr-Umgebung	2129	11.4	10.3	6.0	6.9	4.0	1515	25.3	21.0	9.2	14.1	14.1
Belgium	Antwerp	6533	19.0	14.7	4.9	9.6	5.0	1515	44.8	36.4	14.5	22.8	17.0
Brazil	Curitiba	0	–	–	–	–	–	3004	40.8	29.8	14.1	17.6	7.9
	Porto Alegre	2846	34.0	28.1	10.6	16.6	26.0	3195	53.4	40.8	17.6	24.2	24.4
	Recife	1410	33.0	22.8	10.3	17.5	11.3	3086	35.0	24.1	11.3	16.5	18.3
	Salvador	0	–	–	–	–	–	3162	68.2	55.0	25.0	15.1	24.7
	Sao Paulo	3005	40.0	33.8	12.5	19.2	28.8	3007	45.3	34.0	12.6	20.5	31.7
Canada	Hamilton	3337	30.5	28.6	14.3	16.2	10.7	3051	51.5	45.8	25.0	30.9	27.7
	Saskatoon	2418	25.6	22.6	8.2	12.7	7.2	1901	39.5	33.8	12.0	19.7	12.1
Chile	Central Santiago	1458	29.7	27.0	11.2	16.9	8.8	2944	35.1	27.9	15.7	20.7	10.8
	Punta Arenas	3060	28.3	23.3	8.8	17.1	11.3	3482	20.0	15.5	8.4	10.8	10.5
	South Santiago	3182	21.6	17.6	7.7	16.1	9.2	3051	34.5	23.3	12.7	19.0	10.6
	Valdivia	3138	20.3	17.4	8.0	11.3	10.9	3231	20.6	17.1	9.8	9.7	10.2
China	Beijing	0	–	–	–	–	–	4167	41.5	33.7	7.9	23.6	6.0
	Chongqing	0	–	–	–	–	–	4296	23.7	20.5	4.9	17.2	2.9
	Guangzhou	0	–	–	–	–	–	3855	46.3	39.5	8.4	26.0	2.9
	Shanghai	0	–	–	–	–	–	3483	26.8	21.9	5.0	17.0	3.2
	Wulumuqi	0	–	–	–	–	–	3207	43.2	36.7	10.1	28.7	8.1
Costa Rica	Nationwide	2942	32.7	26.6	11.6	15.4	5.4	3200	39.2	30.9	14.3	12.8	4.8
Estonia	Narva	0	–	–	–	–	–	1424	28.7	20.8	5.3	24.0	2.3
	Tallinn	3070	15.0	11.6	3.5	8.1	2.7	3560	33.1	22.9	4.7	14.2	14.7
Ethiopia	Addis Ababa	0	–	–	–	–	–	2951	50.0	29.5	10.6	21.6	7.5
	Jima	0	–	–	–	–	–	3027	4.2	3.2	1.8	2.2	4.0
Finland	Helsinki	0	–	–	–	–	–	2855	55.1	45.5	22.9	32.7	30.9
	Kuopio county	0	–	–	–	–	–	2878	46.6	36.2	15.3	26.9	29.0
	Lappland area	0	–	–	–	–	–	3077	43.9	33.3	14.9	24.2	23.2
	Turku & Pori county	0	–	–	–	–	–	3085	43.6	33.3	13.8	24.2	27.0
France	Marseille	0	–	–	–	–	–	3494	54.1	45.4	14.4	20.7	11.0
	Montpellier	0	–	–	–	–	–	3384	63.3	58.0	25.5	57.4	27.1
	Pessac	3202	25.8	22.2	5.9	9.9	9.1	3302	53.6	44.1	14.8	20.3	15.4
	Strasbourg	0	–	–	–	–	–	5403	54.7	44.5	13.6	18.5	14.8
	West Mame	0	–	–	–	–	–	2961	47.9	40.5	12.4	17.7	16.8

Appendix 2 (continued)

Country	Centre	6–7-year-olds						13–14-year-olds					
		Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever	Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever
			ever	past year					ever	past year			
Georgia (Republic)	Kutaisi	3356	10.8	8.0	3.9	5.9	5.7	3297	18.9	12.3	4.5	8.1	4.7
	Tbilisi	3414	8.8	6.6	2.3	4.4	4.3	3449	18.4	13.3	4.3	9.1	6.1
Germany	Greifswald	2853	11.8	10.4	4.5	7.0	2.9	3169	38.0	29.3	12.3	17.5	11.7
	Münster	3739	14.9	12.5	5.4	8.5	6.0	4003	36.5	28.7	14.4	15.0	21.1
Greece	Athens	1654	13.1	11.1	3.5	4.8	9.3	2561	17.2	14.4	6.3	5.9	12.7
Hong Kong	Hong Kong	3618	36.5	32.9	13.7	23.5	1.1	4666	52.1	44.5	24.0	35.3	4.7
India	Akola	2030	2.0	1.5	0.8	1.9	1.5	2138	4.4	3.4	1.4	2.2	2.0
	Bombay (16)	3967	10.0	8.1	2.6	8.2	5.1	4225	8.8	6.7	2.3	6.4	4.0
	Bombay (17)	1148	13.2	11.6	3.2	12.6	6.3	2226	17.3	14.2	7.1	14.9	14.7
	Bombay (18)	3568	7.4	5.9	1.5	5.6	2.9	3178	14.9	11.5	3.4	9.1	7.1
	Borivali	1672	11.4	9.4	3.2	8.7	13.3	3878	11.8	8.7	3.2	7.8	8.2
	Chandigarh	2891	11.1	10.2	4.6	9.9	7.2	3139	10.1	8.1	5.4	6.7	7.0
	Jodhpur	1104	10.5	8.9	2.4	11.5	6.6	1094	22.4	18.0	9.0	17.6	11.9
	Kottayam	2156	28.1	23.8	9.6	24.8	6.0	2047	47.9	37.7	21.4	36.0	15.8
	Madras (2)	1466	9.9	8.3	1.8	9.0	5.8	1903	14.0	11.4	4.5	10.6	7.0
	Madras (3)	2491	16.0	13.5	3.5	11.0	7.3	3086	23.8	11.7	3.2	16.4	7.3
	New Delhi	2938	15.2	13.2	3.4	13.3	5.9	3026	34.6	28.2	10.4	25.8	13.8
	Neyveli	1498	28.6	14.0	4.8	0.5	1.8	3281	35.1	16.3	8.2	9.5	9.0
	Orissa	1520	7.5	5.7	2.8	4.7	7.2	1248	7.8	6.3	3.4	4.9	0.6
	Pune	3248	7.3	6.0	1.6	5.0	2.9	2702	10.8	7.6	1.6	5.5	4.4
Indonesia	Bandung	1390	21.2	20.1	3.8	11.2	0.0	2249	61.7	32.6	5.3	24.3	0.0
Iran	Rasht	3013	7.8	5.2	1.2	3.4	2.3	3182	20.7	13.9	5.9	8.5	4.6
	Tehran	2456	9.8	7.6	1.9	4.3	0.5	2691	28.2	21.2	9.3	10.9	1.7
Irish Republic	Dublin	0	–	–	–	–	–	3147	48.6	41.8	19.3	24.4	24.8
Italy	Ascoli Piceno	0	–	–	–	–	–	1130	24.9	17.8	7.7	7.1	17.1
	Cosenza	0	–	–	–	–	–	1068	34.4	24.3	12.7	9.9	19.4
	Cremona	1392	15.8	11.6	4.4	3.7	4.2	1201	36.6	23.6	10.7	8.6	15.7
	Emilia-Romagna	4472	18.8	12.9	5.4	4.5	5.9	3961	42.4	31.2	15.7	11.3	16.7
	Empoli	1434	20.4	12.9	4.4	5.2	7.6	1046	46.7	33.8	15.8	14.2	17.7
	Firenze	1138	21.2	15.9	6.3	6.2	6.7	1171	45.9	34.4	18.4	12.6	18.6
	Frosinone	0	–	–	–	–	–	1147	38.7	27.0	13.4	9.9	16.6
	Milano	3616	20.5	14.2	5.8	5.3	6.6	3373	45.2	32.4	16.4	11.7	21.0
	Roma	4027	19.3	13.4	5.1	4.8	6.6	3323	39.5	30.2	14.7	9.9	16.4
	Siena	0	–	–	–	–	–	1181	46.6	33.6	17.6	13.1	16.6
	Torino	1429	19.3	12.8	5.1	4.2	5.6	1242	42.1	29.1	15.1	10.1	18.6
	Trento	0	–	–	–	–	–	4426	28.8	18.2	9.0	6.3	12.6
	Verona	2076	16.4	13.6	4.3	5.3	0.9	2208	25.1	19.7	9.9	7.9	4.4
	Viterbo	1231	16.1	11.5	5.0	4.1	4.7	0	–	–	–	–	–
Japan	Fukuoka	2900	30.8	25.6	7.8	17.0	9.8	2831	52.6	41.0	14.8	27.3	22.6
Kenya	Eldoret	0	–	–	–	–	–	3024	32.4	20.5	12.1	13.2	15.9
	Nairobi	0	–	–	–	–	–	3243	44.0	31.0	16.1	26.7	25.3

Appendix 2 (continued)

Country	Centre	6–7-year-olds						13–14-year-olds					
		Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever	Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever
			ever	past year					ever	past year			
Korea (South)	Provincial Korea	5527	34.6	29.3	9.3	20.4	14.9	6990	35.3	28.8	10.0	16.7	7.2
	Seoul	2582	37.7	33.5	10.9	22.0	15.5	2993	38.8	32.2	10.7	18.1	8.4
Kuwait	Kuwait	0	–	–	–	–	–	1056	42.1	31.0	12.5	39.4	17.5
Latvia	Riga	3003	16.7	13.4	3.1	14.5	0.9	3004	29.0	21.4	5.3	20.1	3.5
	Rural Latvia	0	–	–	–	–	–	3145	32.9	23.2	4.7	21.4	4.3
Lebanon	Beirut	0	–	–	–	–	–	2993	33.4	25.4	15.4	14.6	19.6
Malaysia	Alor Setar	2978	16.8	13.0	3.6	19.0	8.8	3298	48.6	37.4	16.7	39.2	33.7
	Ipoh	2506	14.4	11.3	4.6	9.5	7.7	3313	50.3	40.0	18.0	30.9	13.5
	Klang Valley	3109	16.3	13.8	5.0	19.0	11.7	6079	46.5	35.4	14.6	36.5	19.8
	Kota Bharu	3819	18.8	15.1	3.8	20.4	15.9	3113	38.2	29.3	9.6	33.7	20.0
	Muar	2873	12.7	10.0	2.8	14.0	7.3	2833	39.4	25.4	8.0	27.9	15.8
Malta	Malta	3493	23.5	20.8	7.2	12.9	14.8	4184	52.7	47.4	28.9	29.0	32.3
Mexico	Cuernavaca	3097	64.8	23.2	8.6	12.8	3.7	3102#	59.0	22.2	9.4	12.3	5.4
Morocco	Casablanca	0	–	–	–	–	–	3183	36.1	26.6	15.5	25.4	27.4
	Marrakech	0	–	–	–	–	–	2900	29.7	19.4	10.4	23.8	20.9
	Rabat	0	–	–	–	–	–	3276	33.6	25.0	10.2	13.3	18.3
New Zealand	Auckland	3526	27.8	24.8	9.8	17.7	12.4	3206	47.4	39.7	18.9	27.8	33.7
	Bay of Plenty	2681	29.2	25.7	8.7	17.5	11.6	2813	49.3	41.2	18.7	31.1	32.6
	Christchurch	3318	27.4	24.4	11.2	14.6	14.6	3191	42.5	36.9	19.4	24.7	40.4
	Hawke's Bay	3338	27.5	24.8	9.4	15.9	12.9	3550	45.4	38.3	18.1	26.7	38.2
	Nelson	1868	18.4	16.5	7.5	11.1	10.2	1839	43.2	36.0	17.4	24.7	36.1
	Wellington	3838	29.3	25.4	10.4	15.2	12.7	4424	47.7	40.6	19.8	27.2	37.3
Nigeria	Ibadan	0	–	–	–	–	–	3057	55.2	45.3	39.7	38.2	16.1
Oman (Sultanate)	Al-Khod	3891	22.0	15.0	6.2	13.3	7.5	3174	34.6	23.8	11.4	22.1	10.5
Pakistan	Karachi	0	–	–	–	–	–	1829	34.8	29.9	18.1	24.7	21.2
Panamá	David/Panamá	3043	28.1	20.5	7.1	18.2	3.8	2885	33.8	24.1	9.4	16.9	3.2
Paraguay	Asunción	0	–	–	–	–	–	2966	80.5	66.6	34.5	39.0	38.3
Peru	Lima	0	–	–	–	–	–	3158	41.9	34.5	19.3	32.4	32.5
Philippines	Metro Manilla	3558	21.6	18.4	9.2	15.2	26.2	3207	35.9	27.0	15.3	24.0	32.5
Poland	Krakow (1993)	0	–	–	–	–	–	3750	28.8	20.1	10.3	16.1	17.9
	Krakow (1995)	2264	29.0	25.0	10.2	22.7	15.6	2786	26.2	21.2	11.8	15.4	19.8
	Poznan	2710	13.0	11.3	4.6	13.8	4.9	3631	19.0	13.7	6.4	11.6	12.0
Portugal	Funchal	1797	23.9	20.6	11.2	14.1	15.9	3532	29.8	21.1	7.7	11.0	8.9
	Lisboa	2143	26.9	23.4	8.6	13.7	2.9	3030	31.4	20.7	6.5	8.5	5.1
	Portimao	1189	18.0	14.7	5.0	9.1	2.5	1058	28.5	19.7	8.8	9.0	3.1
	Porto	0	–	–	–	–	–	3131	29.8	22.7	6.2	11.6	4.2
Romania	Cluj	0	–	–	–	–	–	3396	15.0	11.5	5.2	8.4	2.2
Russia	Moscow	0	–	–	–	–	–	3411	12.6	9.8	6.2	7.9	3.8
Singapore	Singapore	2353	29.3	26.3	8.5	18.9	6.5	4206	50.0	41.2	15.1	29.9	3.7
South Africa	Cape Town	0	–	–	–	–	–	5173	37.7	30.3	15.1	26.0	29.1

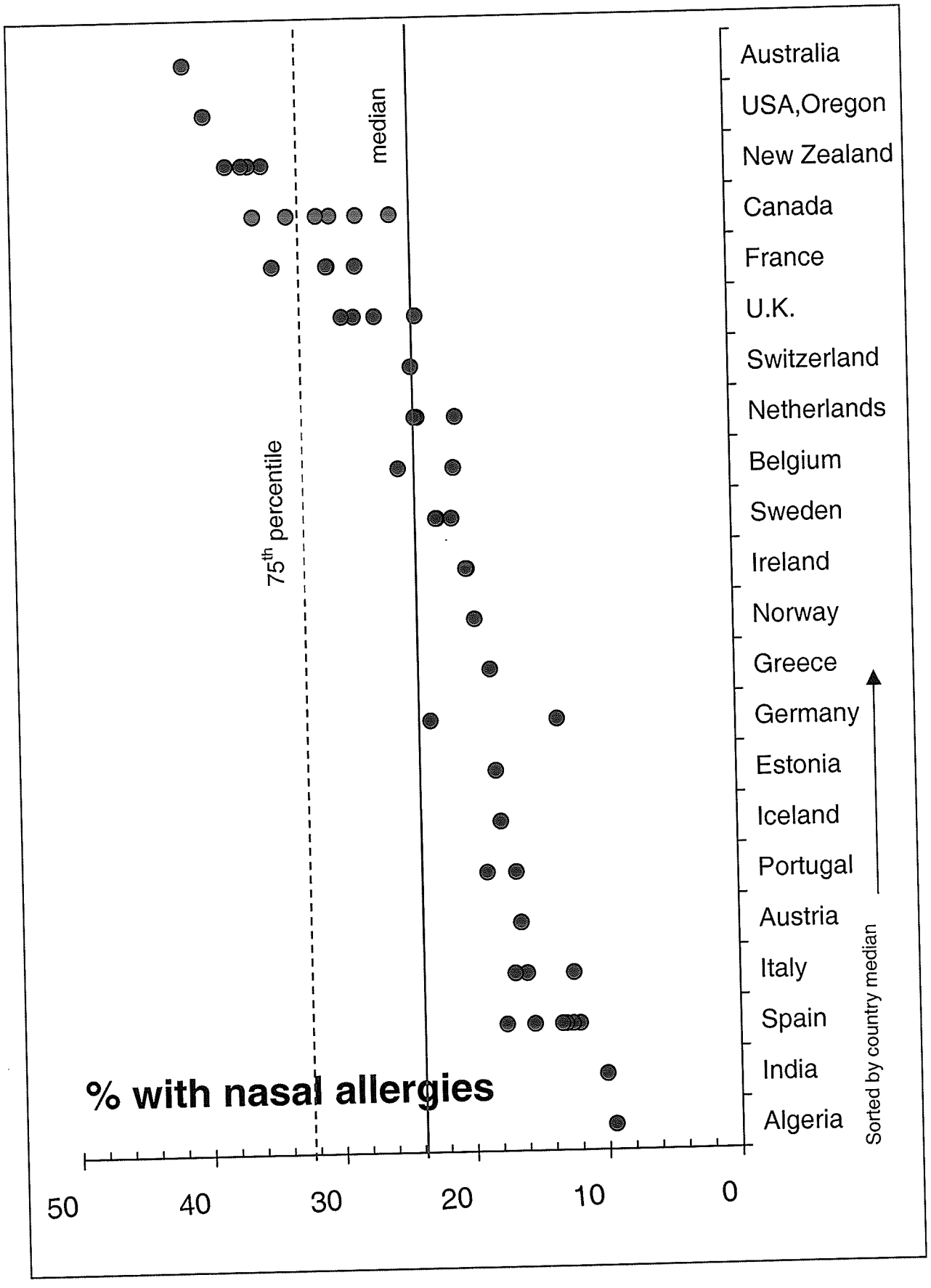
Appendix 2 (continued)

Country	Centre	6–7-year-olds						13–14-year-olds					
		Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever	Sample size	Rhinitis		Itchy eyes*	Activities limited	Hay fever
			ever	past year					ever	past year			
Spain	Barcelona	0	–	–	–	–	–	3031	35.4	26.1	11.7	9.7	8.5
	Bilbao	3019	26.9	18.8	6.5	4.8	6.6	3212	48.5	35.3	17.2	12.5	11.0
	Cartagena	3335	22.7	16.3	6.7	5.6	6.5	3017	43.8	32.7	16.8	12.3	7.2
	Castellón	3594	14.5	9.9	3.8	3.6	3.6	3094	42.4	29.8	13.4	11.6	6.7
	Cádiz	0	–	–	–	–	–	3270	47.9	37.6	21.8	16.0	13.0
	Pamplona	2996	15.6	10.6	3.6	2.5	4.8	3040	49.7	35.5	14.6	9.6	6.1
	Valencia	3940	17.4	11.8	4.4	3.3	5.1	3179	41.2	27.7	12.0	9.6	14.4
	Valladolid	0	–	–	–	–	–	3178	45.2	31.7	12.7	11.1	7.7
Sweden	Linköping	0	–	–	–	–	–	3377	25.4	19.2	11.3	12.5	23.4
	Stockholm & Uppsala	3029	17.1	14.1	5.9	8.5	7.5	3075	35.1	26.7	12.0	15.1	24.8
Taiwan	Taipei	4806	36.5	30.8	14.6	24.3	34.9	11400	35.1	28.8	11.3	21.5	33.2
Thailand	Bangkok	3629	36.3	32.6	10.0	28.1	29.0	3713	50.4	43.2	15.4	39.0	30.7
	Chiang Mai	3828	20.8	18.5	4.8	25.8	17.9	3927	47.0	38.3	15.6	37.1	24.8
United Kingdom	Anglia & Oxford	0	–	–	–	–	–	2324	46.0	37.1	18.2	27.5	38.6
	Guernsey	0	–	–	–	–	–	1170	43.8	33.9	17.7	25.1	35.2
	Isle of Man	0	–	–	–	–	–	1467	50.2	39.4	20.1	29.2	36.4
	Jersey	0	–	–	–	–	–	1135	45.8	36.9	16.9	22.8	36.3
	North Thames	0	–	–	–	–	–	2220	43.8	33.9	15.9	26.4	36.0
	North West	0	–	–	–	–	–	3029	49.8	40.8	18.5	29.2	33.2
	Northeast & Yorks	0	–	–	–	–	–	3709	49.1	39.6	19.4	29.1	33.1
	Scotland	0	–	–	–	–	–	4444	48.5	40.1	20.3	26.8	33.2
	South Thames	0	–	–	–	–	–	2297	46.9	37.2	16.6	27.2	38.4
	South & West	0	–	–	–	–	–	2707	44.9	36.2	16.8	24.2	36.0
	Sunderland	1864	23.7	21.2	9.8	13.3	10.6	2092	34.4	30.0	18.5	19.1	25.9
	Surrey & Sussex	0	–	–	–	–	–	2114	45.5	37.5	22.5	26.6	39.9
	Trent	0	–	–	–	–	–	2207	44.7	35.7	16.4	24.9	35.5
	Wales	0	–	–	–	–	–	2351	45.7	36.8	18.5	27.2	32.6
	West Midlands	0	–	–	–	–	–	2219	48.1	38.2	19.0	30.0	35.9
United States	Chicago (3)	0	–	–	–	–	–	1422	39.2	33.8	17.8	20.7	19.6
	Chicago (4)	0	–	–	–	–	–	3756	47.2	40.6	22.4	37.5	21.5
	Seattle	0	–	–	–	–	–	2330	38.9	29.5	13.4	18.3	33.6
Uruguay	Montevideo	3071	33.8	25.1	6.6	10.4	22.3	3072	51.5	34.5	16.0	13.2	25.1
Uzbekistan	Samarkand	0	–	–	–	–	–	1758	24.1	17.3	10.4	14.1	4.6
	Tashkent	0	–	–	–	–	–	2904	14.8	8.8	3.8	4.9	5.3

* Rhinitis and itchy eyes in the past year (referred to in the text as "rhinoconjunctivitis")

Age range 11–14 years

APPENDIX 2:
Summary of the results from ECRHS studies in adults


median
75th percentile
Australia
USA,Oregon
New Zealand
Canada
France
U.K.
Switzerland
Netherlands
Belgium
Sweden
Ireland
Norway
Greece
Germany
Estonia
Iceland
Portugal
Austria
Italy
Spain
India
Algeria
Sorted by country median
% with nasal allergies
50
40
30
20
10
0

APPENDIX 3:

Summary of publications reporting the prevalence of AR in general populations Medline, 1970–2001

Study	Country (residence)	Year[1]	Method[2]	Number	Age/sex	Prevalence (%) AR	SAR	PAR
Noth & South America								
Lefcoe [1]	Canada	70	Q:H	310	25-74 Male	19.4		
Broder [2]	US	74	E	9,226	All	10.2		
Burrows [3]	US	76	Q:H	3,101	3-54	55.0		
Turkeltaub [4]	US	87	NHANES		12-74	20.4		
Barbee [5]	US	91	Q	1,109	15-54	44.1		
Wright [6]	US	94	Q:H(PD)	747	6	42.0		
Lombardi [7]	US	96	Q	835	8	10.1		
Malone [8]	US	97	Q	36,259	All	16.0		
Nathan [9]/ Meltzer [10]	US	97	Q	22,285	All	14.2	8.8	5.4
Greisner [11]	US	98	E:H	738	40	45.8	41.5	14
Caraballo [12]	Colombia	92	Q	4,000	All	16.4		
Australia & New Zealand								
Turner [13]	Australia	74	Q:C	1,598	6-16	9.1		
Hopper [14]	Australia	68	Q	16,273	Adults	19.2		
		91-93		14,94	29-32	41.3		
Peat [15]	Australia	81	E:H	553	18-55	21.9		
		90	E:H	1,028	18-55	46.7		
		90	E:C		18-55	36.6		
Peat [16]	Australia	90	Q	380	8-10		12/25[3]	
Duffy [17]	Australia	90	Q	7,616	twins	32.0		
Volkmer [18]	Australia	95	Q	14,124	3-4	29.7		
Ponsonby [19]	Australia	98	Q	6,378	7	19.0		

[1] Year of publication, or study (when more than one year reported).
[2] Q – Questionnaire; E – Examination ; PD – Physician Diagnosed AR; H – History (ever); C – Current disease;
[3] First number – percent consistently reporting AR in 3 questionnaires; second – reporting AR at least in one.

Study	Country (residence)	Year	Method	Number	Age/sex	Prevalence (%)		
						AR	SAR	PAR
Sears [20]	New Zealand	93	Q:C	662	13	27.3		
Kimbell-Dunn [21]	New Zealand (farm)	99	Q:C	1,706	All	28.0		
Europe								
Riedler [22]	Austria (farm)	00	Q	2,283	8-10	3.0		
	Austria (rural)				8-10	10.0		
Linneberg [23]	Denmark	89	Q	3,603	15-41		22.0	19.0
		97	Q	817	15-41		32.0	24.0
Haahtela [24]	Finland	79	E	218	14-16	13.0		
Haahtela [25]	Finland	79	E	295	18-19 Male	20.0		
Malmberg [26]	Finland	79	Q	694	Univer	28.0		
					School	13.0		
Haahtela [27]	Finland	80	E:	708	15-17 M	14.0		
			E:		15-17 F	8.0		
Heinonen [28]	Finland (urban)	87	Q:	1,056	Adults	28.8		
	Finland (rural)		Q:	1,100	Adults	26.7		
Huovinen [29]	Finland	75	Q	11,450	18-45 twins		8.5	
		90			18-45 twins		13.5	
Rimpela [30]	Finland	77	Q	7,394	12-18	5.0		
		91			12-18	14.9		
Poysa [31]	Finland	91	Q	3,649	Children	6.0		
Varjonen [32]	Finland	92	Q	1,712	15-16	14		
Pirhonen [33]	Finland	96	Q	1,460	25-64	21.5		
Rasanen [34]	Finland	98	Q	3,530	16(twins)-M	14.1		
					16(twins)-F	10		
Xu [35]	Finland	99	Q:H	8,088	7	3.3		
Hedman [36]	Finland	99	Q	3,102	18-65	37.3		
Kilpelainen [37]	Finland	00	Q:H	10,667	18-24	21.5		
Charpin [38]	France	93		4,008	18-65	35-14		
				1,419		14-6		

Study	Country (residence)	Year	Method	Number	Age/sex	Prevalence (%)		
						AR	SAR	PAR
von-Mutius [39] [40]	Germany-East	91	Q:PD	1,454	9-11		5.1	
	Germany-East	95		2,252	9-11		2.3	
	Germany -West	91		2,623	9-11		8.8	
	Germany-East	91		5,030	9-11		2.7	
Schafer (92)[41]	Germany(W/E)	92	Q	287/987	5-7		2.0	
Kuehr [42]	Germany	92	E	1,376	8	6.9		
Weiland [43]	Germany-West	94	Q	2,050	12-15	23.0		
Weiland [44]	Germany-West	99	Q:PD	2,165	5-7	4.6		
	Germany-East			3,300	5-7	4.3		
	Germany-West	99	Q:PD	2,612	9-11	9.3		
	Germany-East			3,017	9-11	9.8		
Ciprandi [45]	Italy	83	E	4,310	18 Male	1.5		
		95			18 Male	2.2		
Siracusa [46]	Italy	97	Q	824	0-69	15.2		
Skjonsberg [47]	Norway	81	Q:PD	1,772	6-16	4.0		
		93		4,521	6-16	3.8		
Nystad [48]	Norway	81	Q	1,373	6-16	6.6		
		94		2,187	6-16	7.8		
Bakke [49]	Norway	90	Q	4,992	15-70	10.0		
Dotterud [50]	Norway	94	Q	551	7-12	20.6		
Steen-Johnsen [51]	Norway	95	Q:H	4,386	7-13	17.8		
Garcia-Ramos [52]	Spain	92	Q:H	501	High school	40.0		
Azpiri [53]	Spain	99	Q	2,216	10-40		10.6	
Aberg [54]	Sweden	71	E	55,000	17-20 Male	4.4		
		81		57,000	17-20 Male	8.4		
Kjellman [55]	Sweden	77	Q	1,325	7	3.8		
Aberg [56]	Sweden	79	Q	4,682	7-9	5.5		
		91		2,481	7-9	8.1		
Jessen [57]	Sweden	89	Q	1,469	16-82		5.0	
Norrman [58]	Sweden	94	E	1,112	13-16	17.0		
Borres [59]	Sweden	97	Q	1,458	University	24.0		

Study	Country (residence)	Year	Method	Number	Age/sex	Prevalence (%)		
						AR	SAR	PAR
Norrman [60]	Sweden	98	Q	990	17-20	14.3		
Braback [61]	Sweden	98	E	149,398	17-20 M	15.0		
Varonier [62]	Switzerland	70	Q	4,781	5		0.5	0.6
				2,451	15		4.4	1.0
Wuthrich [63]	Switzerland	95	E	8,357	18-60	13.5	11.0	
Braun-Fahrlander [64]	Switzerland (rural)	99	Q	1,620	6-15	12.2		
Ninan [65]	U.K.	64	Q:H	2,510	8-13	3.2		
		89		3,403		11.9		
Butland [66]	U.K.	74	Q	11,195	16	12.0		
		86		9,387	16	23.3		
Leff [67]	U.K.	86	E	395	6		0.1	0.2
					11		9.0	2.0
					14		14.0	2.0
Burr [68]	U.K.	73	Q	965	12	9.0		
		88			12	15.0		
Strachan [69]	U.K.	89	Q:H	12,355	23	16.5		
Sibbald [70,71]	U.K.	91	Q:C	2,969	16-65	24.0	11.0	21.0
			Q:H		16-65	44.0		
Richards [72]	U.K.	92	Q	813	15-59	29.0		
Enright [73]	U.K.	94	Q	5,201	60+	12.0		
Upton [74]	U.K.	72-76	Q	1,708	45-54	5.5		
		96		1,124	45-54	17.5		
Strachan [75]	U.K.	96	Q:H(PD)	11,765	11-16	16.4		
Austin [76]	U.K.	97	Q	1,537	12 & 14	21.0		
Christie [77]	U.K.	98	Q:H	416	5-15	20.0		
Jones [78]	U.K.	98	Q	2,114	> 14	19.8	19.6	
Taylor [79]	U.K.	99	Q	2,813	4-19	12.3		
Brown [80]	U.K.	99	Q	5,609		10.0		

Study	Country (residence)	Year	Method	Number	Age/sex	Prevalence (%) AR	SAR	PAR
Asia								
Miyao-M [81]	Japan	81-90	Insurance		All		0.3-0.7[4]	
Shibasaki [82]	Japan	90	E	419	School		8.4	
Ogino [83]	Japan	90	E	471	School	32.7		
Okano [84]	Japan	92	Q	1,044	School	22.5		
		95		431		26.5		
Bener [85]	S. Arabia	93	Q	3,300	7-12	17.9		
Bener [86]	S. Arabia	94	Q	850	6-14	22.9		
Sakurai [87]	Japan	98	Q	2,307	Male adults	35.5	28.8	
Kucukoduk [88]	Turkey	96	Q	3,118	6-14	11.0		
Kalyoncu [89]	Turkey	96	Q	4,331	University		6.4	1.6
Kalyoncu [90]	Turkey	92	Q:H		6-13	28.0		
		97	Q:H		6-13	18.7		
Selcuk [91]	Turkey	97	Q:H	5,412	7-12	12.3		
			Q:C		7-12	4.5		
Saraclar [92]	Turkey	97	E	3,024	7-12	11.7		
Keles [93]	Turkey (urban)	99	E	386	School	22.8		
	Turkey (rural)				School	6.0		
Ozdemir [94]	Turkey	00	Q	1,603	17-20	10.0		
Kay (83) [95]	Sudan – village 1	83	Q	5,262	All			6.7
	Sudan – village 2			2,634	All			1.5
Leung (94) [96], [97]	China	94	Q	714	12-20	2.1	1.6	
	Hong Kong	94	Q	1,062	12-20	15.7		
	Malaysia	94	Q	409	12-20	11.2		
Ng & Tan (94) [98]	Singapore	94	Q	2,868	20-74	4.5		
Min (97) [99]	Korea	97	Q		All			1.14
Yang (97) [100]	Taiwan	97	Q	4,164	6-12	14.2		

[4] Only seasonal pollinosis as a primary illness

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