THE EPIDEMIOLOGY OF ASTHMA AND WHEEZE IN PRIMARY SCHOOL CHILDREN IN MITCHELL'S PLAIN, CAPE TOWN, WITH SPECIAL REFERENCE TO THE ROLE OF ENVIRONMENTAL TOBACCO SMOKE

Rodney Ehrlich

BBusSc, MBChB,

DOH, MFOM (UK), FFCH (SA)

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I dedicate this thesis to Sally, Mia and Cleo, who make the world worth trying to understand.

CONTENTS

DECLARATION

This thesis is presented in fulfillment of the requirements of the degree of Doctor of Philosophy (PhD) in the Department of Community Health, Faculty of Health Sciences, University of Cape Town, June 1999. The work on which this thesis is based is original research and has not, in whole or in part, been submitted towards another degree, at this university or elsewhere. The university is empowered to reproduce either the whole or any portion of the contents for purposes of research.

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Epidemiologic research is of necessity a collaborative activity and a number of people have contributed to this study. The author's role included the conception and design of the study, development of the questionnaires and supervision of bronchial hyperresponsiveness testing. The literature reviewing and writing were undertaken by the author, who also directed the choice of hypotheses, analytic strategy and data interpretation.

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PRIOR PUBLICATION

Some of the material used in this thesis has previously been published as indicated below.

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CHAPTERS AND SUBHEADINGS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

This study was undertaken in the light of the increasing importance of childhood asthma worldwide, an apparently large burden of asthma morbidity disease in Cape Town, high local smoking rates and a lack of epidemiologic information on childhood asthma in South Africa.

Two detailed literature reviews were undertaken. The first covered epidemiologic aspects of asthma and allergy in South Africa, as inferred from allergen and atopy studies, clinical series, and studies of prevalence and mortality. The second addressed the international literature on whether environmental tobacco smoke is associated with asthma, wheeze or bronchial hyperresponsiveness in general and asthmatic populations of children.

This thesis is based on a self-administered questionnaire survey of the parents of 1 955 sub-B pupils (90% response rate), aged 7 to 9 years, in Mitchell's Plain, a large, working class area of Cape Town

Five empirical questions were asked: 1) is the prevalence of asthma and wheezing in primary school children ? (2) What is the reliability (across two questionnaires) of questions about wheezing and asthma? 3) What are the household risk factors for wheezing and asthma; in particular, to what extent is household environmental tobacco smoke (ETS) a risk factor for asthma/wheeze? 4) Among children with asthma/wheeze, is there an association between ETS exposure and bronchial hyper- responsiveness (BHR), and 5) To what extent is asthma underrecognised and undertreated?

To answer questions 2) to 5), a prevalent case group (defined on asthma symptoms on a standard questionnaire) and a control group were identified from the initial survey. The parents of cases and controls were interviewed at home. All of the symptom questions were repeated, and in addition information elicited on a variety of covariates, including household smoking and damp, medical and family history, and medical care. Urinary cotinine

concentrations were measured in these children by radioimmunoassay. A case-control analysis was conducted of risk factors for asthma/wheeze. In two separate analyses, the case group alone was analysed for the association between ETS and BHR (i.e. for aggravation of asthma), and for the extent of underdiagnosis and undertreatment of asthma.

Prevalence and reliability. The prevalence of wheeze in the previous 12 months (26.8%) was high by international comparison, but not that of asthma ever (10.8%). Symptom prevalences varied with the respondent's familial relationship to the child, while on some questions the interview produced higher wheeze prevalences than the self-administered questionnaire. Reliability of symptom questions varied: asthma ever (kappa = 0.69), recent wheeze (kappa = 0.59), and recent sleep disturbance by wheeze (kappa = 0.56) were the most reliable, while those covering exercise wheeze, speech disturbance and night cough proved less reliable.

Household risk factors for wheezing and asthma. An exposure-response relationship between the urinary cotinine creatinine ratio and asthma/wheeze was observed. In multivariate analysis, predictors of asthma/wheeze were hayfever (odds ratio [OR] = 5.30), eczema (OR = 2.19), parental asthma (OR = 1.77), absence of paternal contribution to income (OR = 1.72), maternal smoking in pregnancy (OR = 1.87), and each additional household smoker (OR = 1.15). Findings were similar, with higher odds ratios for most variables except number of household smokers, when the group was restricted to children with parent reported asthma. Household smoking is thus an important modifiable risk factor in asthma/wheeze among young schoolchildren, with maternal smoking in pregnancy and current household exposure independent contributors to this effect.

ETS and BHR among children with asthma and wheeze. There was no association between BHR and moderate levels of ETS exposure, but children with asthma/wheeze whose mother smoked $\geq$ 15 cigarettes daily showed less BHR than those who smoked less or none. BHR was also less frequent among children sharing a house with 4 or more

smokers, and among those in the highest quartile of cotinine. BHR was unrelated to paternal smoking. In contrast, Forced Expiratory Volume in one Second (FEV1) was lower among children whose mothers smoked currently. These results are consistent with a long-term adverse effect of maternal smoking on lung function but not with a mechanism whereby ETS exposure aggravates existing asthma by increasing BHR. This association may be masked, however, by the degree to which mothers of asthmatic children adjust their smoking.

Underrecognition and undertreatment of asthma. Overall, any past or current asthma was acknowledged by respondents in only 53% of the case group, and current asthma in only 37.1%. While most children had received treatment in the previous 12 months, 66.1% of the recognised group were on current treatment (23.2% on daily treatment), compared to 37% of the unrecognised group (3% daily). Salbutamol and theophylline syrups were the most common types of medication, while inhalers and anti-inflammatory medications were underused. Only a minority reported the child ever having used a peak flow meter, or volunteered knowledge of preventive measures. Current treatment, and to a lesser degree asthma recognition, was greater among children on medical aid and of higher socioeconomic status.

In conclusion, asthma has been neglected in the public health arena in South Africa, in contrast to initiatives emanating from the private medical and pharmaceutical sectors. Given our limited understanding of the forces underlying childhood asthma at the population level, the prospects of primary prevention of asthma are limited, especially in poor communities. Control of exposure of children to tobacco smoke remains, however, the single most practicable public health measure for both primary prevention of asthma, and as an important part of secondary prevention.

Although secondary prevention appropriately emphasises patient and practitioner education, further research is required into management regimens practicable in poorer communities and public sector facilities. A plan for asthma management needs to be given

concrete form within the official national policy of primary health care. The importance of population level research in surveillance of the asthma epidemic, in assessing the effectiveness of various treatment approaches, and in the search for the causes of asthma also needs to be recognised.

CHAPTER 1

INTRODUCTION

1.1. Background

The apparent increase in childhood asthma in its various manifestations over the past three decades in different parts of the world poses a challenge to epidemiologists (Burney 1988). This increase has been variously attributed to greater awareness of the disease and a shift from other diagnoses on the one hand, and to secular changes in environmental influences, diet and behaviour, as well as improved public health measures, on the other (Hendrick 1989, Buist 1990, Gergen 1992, Seaton 1994, Strachan 1995, Magnus 1997, Butland 1997, Hopkin 1997, Platts Mills 1997, Kemp 1997).

Whatever the explanation for its increase, asthma is now recognised as the most common chronic disease of childhood in developed societies, responsible for considerable morbidity, health service and medication use, school absence and family stress. Premature death is fortunately uncommon but remains a feared complication of asthma.

While country wide estimates of the burden of asthma in South Africa are not available, estimates from developed countries suggest a large burden. For example in the United

States, the cumulative incidence of asthma or wheeze among children aged 3-11 years was estimated at around 10 percent in the 1980s (Evans 1987). The substantial morbidity of the disease was reflected in the approximately 163,000 children under seventeen years of age with a hospital discharge diagnosis of asthma in 1987, a rate of 257 per 100,000 population at risk (Gergen 1990). Hospitalisation increased during the 1980s at a rate of about 4.5 percent per annum, with the greatest rate of increase in the 0-4 year age group (Weiss 1990). Asthma in children was estimated to result in an additional 10.1 million days missed from school, and 12.9 million contacts with medical doctors (Taylor 1992). Mortality from asthma among children aged 5 to 14 years increased in the United States by ten percent per annum between 1979 and 1987 (Gergen 1990).

The costs of asthma to society include the direct medical costs of doctors' services, medication and hospital care, the indirect costs attributable to school days lost, work lost and premature mortality, and the intangible cost of the psychosocial effects of the disease (Weiss 1993). The direct medical costs (children and adults) in the USA in 1990 were estimated at $3.6 billion, with a further $ 2.6 billion incurred in indirect costs (Clark 1995). The combined figure of $ 6.2 billion is equivalent to one percent of the total health care expenditure in the USA. The corresponding direct and indirect cost estimates for Australia (1991) were $250 million and $ 207 million, and for the United Kingdom (1988) $722 million and $1.07 billion (ibid.).

Research into asthma has burgeoned over the past two decades. There are many questions needing answers. The first concerns the frequency of asthma. Although asthma defies a gold standard definition, a reasonable picture of prevalence of wheezing illness is emerging, particularly as the studies comprising the International Study of Asthma and Allergies in Childhood (ISAAC) are starting to be published (ISAAC Steering Committee 1998). Research remains skewed towards the developed world, however. For example, of the 110 centres cited as participating in ISAAC, only 10 are from Africa (ibid.)

Secular shifts in asthma prevalence are more difficult to measure, because of the problems of comparability, and time trend information has been slower in emerging. In almost all cases where information is available on time trends, an increase in some measure of asthma or wheezing has been noted (Gergen 1992, Anderson 1994, Strachan 1995, Nystad 1997, Goren 1997). The likelihood is that the increase in real, although it has been argued that the lack of comparable objective measures between study points renders this interpretation still inconclusive (Magnus 1997).

A number of risk factors for asthma have received attention, although the distinction between factors inducing the disease and those triggering acute asthmatic episodes or maintaining chronicity remains a source of confusion. It is likely that while genetic inheritance lays down a predisposition to asthma in individuals, the early childhood environment, including *in utero* experience, determines the rate of expression of the disease. Its severity and chronicity may in turn be subject to a wider variety of household and community influences, including medical care, beyond the inducing ones.

There appears to be a close association between childhood asthma and allergy. The interaction between immune predisposition and immune activation as a result of early challenges to the immune system by infection and antigens, has thus suggested a theory that may explain a rising prevalence of the disease (Shaheen 1995, Strachan 1995, Hopkin 1997, Cookson 1997). Current speculation, supported by some empirical evidence (Shaheen 1996, Shirakawa 1997, Matricardi 1997), is that certain viral and bacterial infections in early life, including measles and tuberculosis, may protect against asthma through preferential activation of the T-Helper Type 1 (TH1) cell mediated immune response pathway. A decline in the incidence (or severity) of these diseases [including the protective effect of immunisation (Kemp 1997)] allows activation of the TH2 cell mediated pathway, which in turn regulates the production of IgE antibodies that underlie the immediate hypersensitivity response. The effect at the population level is an increase in the incidence of asthma.

Of other potential risk factors for childhood asthma, exposure of the child to environmental tobacco smoke or its products, particularly from maternal sources, is of great interest. In many developed countries, smoking rates among women increased steadily after world war II, with declines only in recent years among better educated women (Gergen 1992). In the developing world, the smoking habit among women in still relatively uncommon but is predicted to increase with urbanisation and aggressive marketing by the tobacco industry (Mackay 1994). Control of tobacco is already a public health policy goal, and although gains have been limited in many countries, reduction of exposure of children to environmental tobacco smoke may be one way of achieving some degree of both primary and secondary prevention of asthma.

Although asthma cannot be cured, the quality of life of asthma sufferers can be greatly improved by appropriate management. There has been a refinement of drug treatment over the past three decades, including a shift from regimens which may have caused harm (Sears 1990). An understanding of trigger factors has created the potential for prescribing avoidance activities. Unfortunately, the quality of case management has not kept up with recommendations from the academic centres. Variations in quality of care typically follow lines of privilege and poverty in society.

Epidemiologic research into allergy in South Africa received a promising start in the work of Ordman (Ordman 1947, 1955) who described patterns of allergic illness which anticipated discovery of the house dust mite by Voorhorst and Spieksma in 1964. A comparative study of childhood asthma in the rural Transkei and urban Cape Town published in 1979 has become a classic migrant study contributing to the theory of asthma as a disease of urbanisation (Van Niekerk 1979). Since then very little population based research has been published from South Africa, so that much of what is believed about childhood asthma in South Africa is based on clinical experience.

Cape Town is a highly suitable site for asthma research. Cape Town was one of the high prevalence allergy areas identified by Ordman. Current clinical and popular belief

is that Cape Town's environment is conducive to allergy and asthma. These views are based on utilisation patterns in public health services, and a few relatively small population studies. Larger scale population based data are lacking. Cape Town has the further advantage of sufficient infrastructure both to carry out population based research and to be able, at least potentially, to use the results to influence health promotion and health care interventions.

This thesis is an attempt to answer some of the important questions about childhood asthma in Cape Town using the tools of epidemiology.

1.2. Thesis Objectives and structure

This thesis is based on a population study of asthma in primary school children carried out in Mitchell's Plain, a large suburban area of Cape Town. The area was chosen because it is held to be a high asthma prevalence area, with a large relatively stable population and network of primary schools accessible to ongoing research, an important consideration given the recent history of school turbulence in South Africa. The area's relatively poor socioeconomic profile raises questions of access to health services and quality of care, questions of public health importance in the current moves towards achieving greater equity in health in South Africa. Previous studies have measured high levels of smoking in the areas of which this community is a part (Steyn 1987). The area also has a relatively secure mix of private and public medical care services, potentially able to support future intervention research.

The research project consisted of studies addressing five related questions:

1. *What is the prevalence of asthma and wheezing in primary school children in Mitchells Plain?*

2. *What is the reliability of responses to questions about wheezing and asthma in this*

population?

3. *What are the household risk factors for wheezing and asthma in this population? In particular, to what extent is household environmental tobacco smoke a risk factor for asthma/wheeze?*

4. *Among children identified with asthma and wheeze, is exposure to environmental tobacco smoke associated with increased bronchial hyperresponsiveness?*

5. *To what extent is asthma underrecognised and undertreated in this population and what are the predictors of underrecognition and undertreatment?*

Chapter 2 is a comprehensive review of what is known epidemiologically about asthma and allergy in South Africa. The aim is to provide a context for this study and for the questions asked. Because of the importance of categorisation by "race" in South African epidemiologic research and the problems in trying to interpret and report epidemiologic data by "race" (or conversely without reference to "race"), a brief discussion of the subject is included.

Chapter 3 is a literature review of epidemiologic studies of the association between environmental tobacco smoke and asthma and wheezing in childhood. The aim is to determine the current weight of epidemiologic evidence on whether, to what extent and how environmental tobacco smoke causes the various manifestations of asthma and wheezing.

Chapter 4 describes the geography, climate and social characteristics of Mitchell's Plain and its population. The aim is to provide readers with a basis for comparison with studies of other populations. The chapter follows with a description of the sampling procedures for the various phases of the study. Sample size calculations are provided to enable an evaluation of the statistical power to answer the questions posed. Ethical

considerations are discussed.

The next four chapters present the methods, results and discussion of each of the study phases, namely: prevalence and reliability of asthma symptoms (Chapter 5), association of environmental tobacco smoke and other household risk factors with asthma/wheeze in the population (Chapter 6), association of environmental tobacco smoke with bronchial hyperresponsiveness in children with asthma/wheeze (Chapter 7), and underrecognition and undertreatment of asthma (Chapter 8).

Chapter 9 concludes with a consideration of the implications of the main findings and their limitations, a discussion of prospects for public health use of the results in primary and secondary prevention of asthma, and recommendations for future research.

The appendices contain the questionnaires used in the study.

1.3. A note on nomenclature and style

1.3.1. Asthma and wheeze

There is no single definition of asthma for epidemiologic purposes, nor any definitive test or gold standard. As a result, identification of a group of children in epidemiologic studies using questionnaires (with or without bronchial hyperresponsiveness testing) will result in some heterogeneity within such a group. For example, while most childhood asthmatics wheeze at some stage, not all wheezing in childhood is asthma (**Fig. 1.1**). Conversely, cough rather than wheeze may characterise asthma in a minority of children. Although the asthma/wheeze distinction is less problematic in primary school children than in infants and toddlers, in anticipation of objections to the lack specificity of the term asthma, the term *asthma/wheeze* or the phrase *asthma and wheezing* is used in Chapters 6 and 7, in which a "case" group is defined. These chapters address

questions of aetiology rather than clinical specificity and define the case group on the basis of a symptom questionnaire.

In Chapter 8, in which inferences are drawn about diagnosis and treatment, the stronger assumption is made that the study group is asthmatic for practical clinical purposes. The children are thus referred to simply as *asthmatic*. In that chapter, the case group is defined on the basis of a stronger definition (based on two consecutive symptom questionnaires) and is likely to be somewhat more specific than the group studied in Chapters 6 and 7. In contrast, the term *asthma recognition* refers to a parental response to the question "has the child ever had asthma".

1.3.2 Environmental tobacco smoke (ETS)

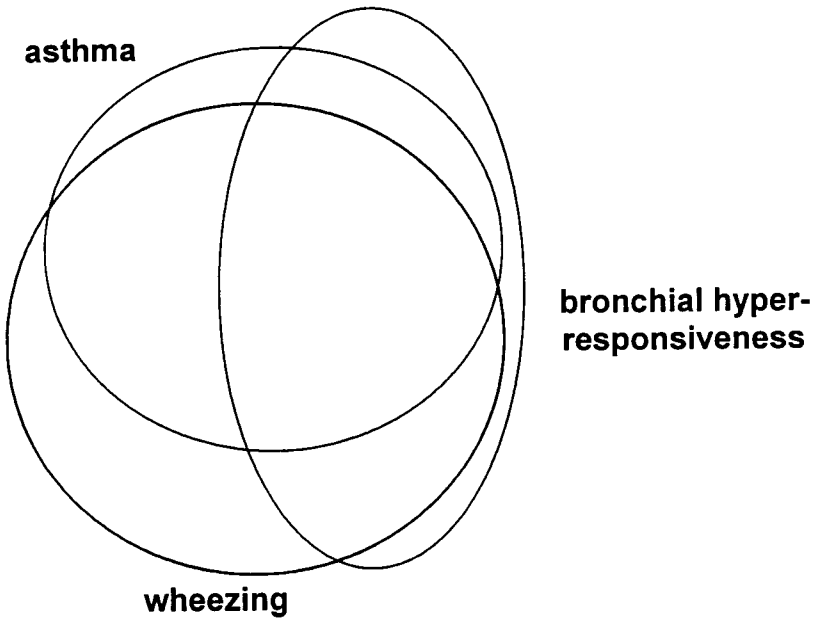
The term ETS exposure is used in the main, rather than passive smoking, and includes in some contexts *in utero* absorption of tobacco constituents by the foetus. The focus in this study is on parental and other household smoking, which can be assumed to the major sources of ETS exposure of young schoolchildren.

1.3.3. Bronchial hyperresponsiveness (BHR)

Non-specific bronchial hyperresponsiveness refers to an abnormal tendency for the airways to constrict in response to certain pharmacologic and physiologic stimuli at a dose or level at which most people would not react.

The interrelationship between BHR, asthma and wheezing is itself the subject of contention, and our understanding of this relationship has changed as population based data have become available. A schematic representation of the interrelationship is displayed as a Venn diagram in **Fig. 1.1**. While many children with recognised asthma have BHR, this trait may vary over time between "normal" and "abnormal" in individual asthmatic children. Conversely, BHR may be demonstrable in otherwise asymptomatic children and in children with other causes of respiratory tract disease such as bronchitis.

Figure 1.1 Relationship between asthma, wheezing and bronchial hyperresponsiveness in epidemiologic studies



1.3.4. Referencing

Referencing is by first author and year of publication in parentheses in the text. When a study is mentioned in the narrative, only the first author is cited, without the rather cumbersome *et al.* An alphabetic bibliography, in the Vancouver style, is appended to each chapter. Although this entails overlap of chapter lists, it provides a more focused bibliography for each chapter.

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CHAPTER 2

LITERATURE REVIEW: THE EPIDEMIOLOGY OF ASTHMA IN SOUTH AFRICA

2.1 Introduction

Early publications on asthma in Africa and other parts of the developing world reflected the belief that childhood asthma in Africa and the tropics was uncommon, and/or that the age of onset of asthma was later than in the Western world (Godfrey 1979, Cooksen 1987, Weinberg 1989). This was based, *inter alia*, on the relative scarcity of asthmatics in hospital and clinic populations (Van Niekerk 1977, Abdurrahman 1982, Cooksen 1987).

Prior to the early 1990s, relatively few prevalence studies from Africa had been reported. These suggested an effect of urbanisation on increasing the prevalence of a condition that was rare in rural populations. Godfrey (1975) could find virtually no asthmatics in rural Gambian villages (1975), while a number were identified in urban areas. In a 1980 report from semi-urban Zimbabwe, Cooksen reported a (cumulative) prevalence of

asthma symptoms of 1.2 percent in children and adolescents and 1.57 percent in adults. A later study of Zimbabwean schoolchildren (Keeley 1991), found an urban prevalence of reversible airways obstruction of approximately 3 to 6 percent compared to 0.1 percent in a rural population. Similar findings in the Transkei area of South Africa were reported by Van Niekerk (1979), discussed further in section 2.4. In contrast to the above studies, Carswell (1976) reported a prevalence of asthma in 3.3 percent of rural Tanzanian schoolchildren.

Even allowing for the variation in the definition of asthma or of bronchial hyperresponsiveness (BHR), it is clear from recent studies that one cannot treat Africa as a homogeneous entity. In a study by Ng'ang'a (1998), asthma symptoms were reported by 26.0 percent of Nairobi schoolchildren compared to 10.9 percent of rural schoolchildren. The urban rural difference in exercise induced bronchospasm (fall in FEV1 of 15 percent or more) was in 9.8 vs 6.1 percent. In contrast, Yemaneberhan (1997) reported a prevalence of recent childhood wheeze of only 2.4 percent in children under 9 years in a provincial Ethiopian town, and 1.1 percent in subsistence rural children.

South Africa appears to offer fertile ground for the study of chronic diseases, including asthma (Mann 1982). Differences between rural populations with persistent traditional features and their "urbanised" counterparts have offered the opportunity for studying risk factors for asthma associated with urbanisation and migration. Differences in asthma or allergy between groups defined by race or ethnicity have also attracted attention as providing possible clues to aetiology. Asthma has also become a common enough clinical disease in the community and in medical practice to be regarded by practitioners, teachers and parents as needing study.

To date there has, however, been relatively little in the way of epidemiologic study of asthma in South Africa. Most of the published literature has taken the form of clinical series derived from specialised clinics in teaching hospitals or paediatric practices, or small comparative samples derived from a single facility.

Reasons for the paucity of published population based studies are speculative. The shortage of epidemiologic expertise in South Africa has possibly meant a concentration on clinical series. There also seems to be a lack of imperative to publish studies that have been carried out.[1] Violence and uncertainty in many communities during the late apartheid era (Hoffman 1986) are another possible reason.

2.2. Ordman and the distribution of allergens in South Africa

David Ordman pioneered the ecological study of allergy in South Africa in the 1940's, 50's and 60's and his work merits specific description on both scientific and historical grounds (Potter 1996).

In a series of studies Ordman established the basic pattern of environmental allergens in South Africa (Ordman 1947, 1955, 1970, 1971). Although he was concerned with all atopic phenomena, i.e. allergies of the upper respiratory tract, bronchial tree and skin, his observations are of obvious relevance to asthma. He contributed two sets of fundamental observations to the study of allergy in South Africa.

The first were those pertaining to seasonal allergy, which he related to seasonal patterns of aeroallergens, i.e. pollen grains and fungal spores (Ordman 1947, 1970). These patterns were based on regional distributions of these aeroallergens and corresponding patterns of skin prick allergies seen in clinical and laboratory practice. He identified grass pollens as the most important of the aeroallergens, at least in relation to nasal allergy, with their flowering period occurring between October and March. Of lesser importance in inducing allergic symptoms were tree, *compositae* and weed allergens, depending on the degree of contact with the plant.

[1]Two large studies, one of Transkeian schoolchildren conducted in the mid 1980s, and another in the 1990s of Cape Town schoolchildren with a Transkeian comparison, remain unpublished.

Ordman's other major epidemiologic observation was that allergy was often worse at the coast and improved when the sufferer moved inland (Ordman 1955, 1971). He hypothesised initially that there were specific climatic features that were responsible for this phenomenon, acting either directly on the bronchi or by promoting some allergenic agent. He showed that coastal towns had in common narrow ranges of both temperature and humidity at the high end of the scale, in other words, warm, moist climates. Following the identification in 1964 of the housedust mite by Verhoor *et al.*, Ordman was able to show that the distribution of house dust mites correlated well with the distribution of relative humidity in South African towns (Ordman 1971). Coastal towns and some inland towns with high relative humidities (Louis Trichardt, Vryheid) all showed high mite counts.

Ordman's environmental observations in the Transvaal have been updated by Cadman, who studied aeroallergens in the Pretoria-Witwatersrand-Verneeniging area between 1986 and 1987 (Cadman 1991). She confirmed that grass pollens were the single most important component of airborne pollen, comprising 52 percent of the total. Of the total airborne pollen, almost 60 percent was perennial, auguring badly for grass sensitive individuals in this region.

Porter (1991) examined distributions of aeroallergens in the Cape. In apparent contrast to the Reef, he found that mould spore concentrations exceeded those of pollens throughout the year except October and November. However, as on the reef, grass and *compositae* pollens in concentrations of >50 spores/m^3 were found perennially, with a seasonal peak from October to December.

However, the studies of aeroallergens, like any environmental agent, must be accompanied by laboratory, clinical and epidemiologic studies on human populations in order to decide their importance. For example, Potter (1991) has pointed out that of 8 000 flowering species in the Cape Peninsula only a few are of known clinical importance, while the allergenicity of a number of other local grasses is unknown.

There has been little attempt to correlate aeroallergen patterns with the population distribution of atopy or asthma in South Africa. Even where atopy is measured in the community, however, its distribution does not necessarily explain the distribution of asthma, and atopy and asthma are best conceptualised as distinct phenomena for epidemiologic purposes (Burney 1992).

2.3. Hospital case series of asthmatics

Case series contribute to the epidemiologic study of asthma by identifying features of the disease among people reaching teaching hospitals and specialist practices and by suggesting hypotheses for further study.

The selected nature of these samples entails a number of limitations which should counsel caution in attempting to generalise to larger source populations. In South Africa, income and race based patterns of health care use determine the population seen at a given hospital. There may be further selection effects determining who gets referred to a teaching hospital, and within the hospital, who are seen at specialised clinics. Problematically, the very features that may be of interest as outcomes, (eg. severe allergy, atypical features) may be among the factors determining referral to a particular clinic.

It is the exception for hospital cases in South Africa to be related to a population denominator and expressed as population rates. The main reason is that the base population using the hospital is unknown. Teaching hospitals, in particular, may have wide catchment areas. A steady and in recent years rapid process of urbanisation among a large section of the population makes assumptions about base populations hazardous. The absence of rates makes it difficult to use these data for comparative purposes, either spatially or temporally.

Comparability among studies is compromised by a number of differences between them. Secular changes may distinguish samples drawn in different years. There is no standard

way of taking histories, which, in the clinical context, are never blind of the diagnosis, introducing spurious correlations. While standardisation is possible in skin-prick testing, the antigenic preparation, the definition of a positive test and the range of allergens tested may all vary.

Nevertheless some attributes of the populations using a given hospital, as well as broad regional differences may be inferred from the various studies. Two sets of observations, in particular, are of interest. The first is the distribution of specific allergic reactivities by region or population, and the second concerns the relative scarcity or otherwise of black[2] asthmatic cases.

2.3.1. Distribution of specific reactivity to allergens

Van Niekerk (1977) noted that house dust and house dust mite elicited by far the most frequent positive reactions in skin testing of 103 asthmatic Cape Town children aged one to 13 years. While about a quarter reacted to house-dust mite, only 10 percent responded to cat dander, 7 percent to grasses and 6 percent to parasites (*Ascaris lumbricoides*). Potter (1991) confirmed the relative importance of house dust reactivity in allergic children in Cape Town, with much lower rates of skin prick reactivity to grasses and cat allergen and feathers.

Similar findings regarding the importance of reactivity to house dust mite among adult asthmatics in the Cape were made by Walls (1983) and by Joubert (1988) at Tygerberg hospital. In the former study, of adults, over 90 percent of asthmatics with clinical allergic features showed skin reactivity to housedust mite *D. Pteronyssimus*, although over 80 percent also reacted to danders and about 60 percent to grass pollens.

[2] See section 2.7 for a general discussion on the use of race categories in epidemiologic research. In what follows, race categories are reported in the way they are used by the authors. In most cases, differences in clinical features between race groups seem to be attributed to differences in urbanisation and environmental conditions.

Joubert (1988) compared coloured and white asthmatics aged 12 to 40 years with respect to skin reactivity. While the two groups showed no difference in mite reactivity (about 70 percent), the white sample had a much greater proportion with sensitivity to animal danders and grasses than the coloured asthmatics. The reverse held for fungal antigen (*Aspergillus fumigatus*) and parasite (*Ascaris*).

Evidence from Durban, another coastal city, was provided by Fraser (1979) who reported on a small group of mainly teenage asthmatics from the Allergy Clinic at Addington Hospital. Over 80 percent reacted to house dust and dust mite, but only 30 percent to "dust and animal hair" and 7 percent to grasses. Besides the high dust mite: grass ratio (even higher than at the Cape), of further interest was that 30 percent reacted to cockroach. Very similar findings were reported two decades later by Manjra (1995).

Inland, Mercer (1991) reported on allergic features of a group of children seen in the paediatric allergy clinic in Bloemfontein in the Free State province. In contrast to the Cape findings, only 32 percent of these children reacted to "house-dust" and only 26 percent to *D. pteronyssimus* The most common response was to Bermuda grass allergen (56 percent of children) and to cat hair (55 percent of children).

On the Transvaal highveld, Luyt (1994) and Green (1997) described two case series of children and adolescents (ages 1 month to 18 years), one (black) from the Baragwanath teaching hospital in Soweto, the other (white) presenting to private paediatricians in Johannesburg. Between 40 and 50 percent of all asthmatics responded positively to grass and maize (corn) pollens and to house dust mite. The main difference was that the white asthmatics showed much higher positive response proportions to mould antigens (53% of subjects), and cat and dog antigens than the black subjects. Surprisingly, in a similar study of young asthmatics in Durban, where average humidity is much higher than around Johannesburg, only 4 percent of subjects had skin prick reactivity to mould (Manra 1995). However, the mould antigen preparations used varied in these studies from indoor species (Luyt 1995) to unspecified mixtures (Green 1997, Manjra 1995), thus

limiting comparison.

Potter (1998) investigating specific IgE to cockroach antigen among atopic patients in two coastal cities (Cape Town and Durban) and two Highveld cities (Pretoria and Johannesburg), found the rate of sensitisation to be about the same in all four centres (of the order of 30 to 40 percent).

These findings confirm Ordman's observations that house dust mite is more likely to be a cause of allergic asthma at the coast where the climate is conducive. Grass and grain aeroallergens take on a larger relative role inland. Reactivity to cat and dog dander would seem to be related to higher degrees of indoor pet ownership which is a feature of better off homes. Study of the distribution of mould allergy requires the standardisation of method and materials before any firm conclusions can be drawn.

2.3.2. Relative underrepresentation of black asthmatics

Interest in the relative scarcity of asthma in rural African populations is reflected in studies of clinic populations. Wesley (1969) reported that paediatric admissions for asthma to a Durban hospital between 1963 and 1967 were uncommon. Asthma made up 0.8 percent of white paediatric admissions and only 0.02 percent of black admissions, a relative proportion of 40:1.

In contrast, a more recent study of admissions in 1992 and 1993 to the predominantly black Baragwanath hospital in Johannesburg found that asthma constituted 3.8 percent of all paediatric admissions. Although from different regions, these data suggest that asthma has become more commonplace among black children in South Africa.

Early underrepresentation of black children with asthma in Cape Town was similarly reported made by Van Niekerk (1977). While black children accounted for 17 percent of all outpatient attendances at the Red Cross Children's hospital in Cape Town, they represented only 0.36 percent of the allergy (asthma) clinic attenders. Ehrlich (1994b)

examined admissions to the same hospital between 1984 and 1990: black children contributed 37% of bronchiolitis and 48% of pneumonia admissions, but only 12% of asthma admissions.

Two accounts from Groote Schuur Hospital in Cape Town point to possible biases in specialist clinic populations, however. Walls (1982) reported on 304 adult asthmatics seen at the Allergy Clinic between 1973 and 1976, of whom apparently only 8 (2.5 percent) were black. Yet of 1 020 patients admitted with acute asthma to the Groote Schuur Hospital casualty department between August 1975 and July 1976 one sixth (16.6 percent) were black (Westerman 1978), which was probably not far off the relative representation of blacks in the population of Cape Town at that time. One can speculate about the reasons for this anomaly, but it shows that specialist clinic populations may be highly selected and not too much should be inferred from them about the true underlying distribution of the condition.

2.4. Population based prevalence studies

Although descriptive, local prevalence surveys are of interest because they enable the importance of the disease in the community to be weighed. Their results are of value to those arguing for health care resources to be devoted to prevention and care of the disease. Furthermore, differences in prevalence between groups, typically defined by age, sex, geography, race, education or income, are the starting point of observational epidemiology by suggesting aetiologic hypotheses which can be tested in analytic studies.

There is a scarcity of sound prevalence data in South Africa. Until 1994, there had been only five published studies, and one published in non peer reviewed form, which contributed population prevalence data. These vary in the populations studied, their age range and the measures of asthma used, and are summarised in **Table 2.1.**

In 1979 Van Niekerk *et al.* published their much cited comparative study of rural and urban Xhosa-speaking children. The rural children were drawn from the Tsolo area, a hilly

grassland area 1100 m above sea-level with a summer rainfall climate. The urban sample was recruited in Guguletu, a township of Cape Town 22 km inland. Bronchial hyperresponsiveness was measured, and defined as a fall in Forced expiratory volume in one second (FEV1) or Peak expiratory flow (PEF) of 15 percent or more following running for six minutes at maximum effort. The results showed a 3.17 percent prevalence among the urban children compared to 0.14 percent among the rural children (A prevalence odds ratio of 22; 95 percent confidence interval 3.5 to 906, can be calculated from their data).

Some caution is in order regarding the point estimate prevalences Van Niekerk obtained, and to some extent the size of the urban rural difference. Exercise testing is a relatively insensitive measure of asthma, or at least reflects different airway characteristics from that of other tests of BHR (Clough 1991). Also, if rural children were fitter than urban children, a given exertion might imply a different cardiorespiratory load in the two groups and therefore differential sensitivity of the test.

Vermeulen, in a study whose results have thus far appeared only as a brief summary, (Vermeulen 1990) took another research team to the rural Transkei in 1988. Unlike the previous study, he used histamine challenge as a measure of BHR, requiring a greater than 20 percent fall in FEV1 for a positive test. Among 1014 children aged 8 to 16 years, he found 14.2 percent with BHR. Among the children with BHR thus identified, 62 (43 percent) were considered to be asthmatic on clinical evaluation, giving an overall asthma prevalence of 62/1014 or 6.1 percent.

There are a number of possible explanations for the difference between the two Transkeian studies. The first is that they used different tests. While exercise testing may be relatively insensitive to asthma, histamine challenge may lack specificity, identifying, for example, children with infective bronchitis, which may be more common in rural populations.

The second explanation is that there was a large secular increase in BHR among Transkeian children over the decade. This might be explained by the penetration of "western" habits and specifically, beds, mattresses and associated soft furnishings into remote Transkeian villages. Alternatively, if the TH1/TH2 hypothesis is true, the increase may be related to increased access to immunisation services and/or decline in family size.

A third possible explanation is that as Vermeulen studied teenagers as well as pre-teens he might have picked up the later-onset asthmatics missed by the Van Niekerk study. These are, however, speculations and their development must await the publication of Vermeulen's study.

Stewart (1990) also used exercise challenge to study BHR among white and coloured school children in Cape Town. He used a less stringent criterion level: a 10 percent fall in FEV1. Overall, BHR was more common among white than coloured adolescents (5.8 percent vs. 4.1 percent). However, in their age stratified data, coloured pre-teens (6 to 9 years) had a higher prevalence of BHR than whites. The authors speculate that these differences may be due to a higher school drop-out rate among coloured asthmatic children. However, there is no evidence for this thesis.

Table 2.1 Previous South African studies of the prevalence of asthma and bronchial hyperresponsiveness

Study	n (population, ages)	Measure of outcome	Prevalence (%)	
		CHILDREN		
Van Niekerk (1979)	671 Transkei (rural) 694 Gugulethu* (urban) (6 – 9 years)	Exercise challenge: ≥ 15% fall in FEV1 or PEF	Rural Urban	0.14 3.17
Vermeulen (1990)	1041 Transkei (8 – 16 years)	(a) Histamine challenge: ≥20% fall in FEV1 (b) Clinical asthma		14.2 6.1
Terblanche (1990)*	494 coloured 698 white (8 – 17 years)	Exercise challenge: > 10% fall in FEV1	Coloured White	4.1 5.8
Nagel (1995)*	1180 white (12 years)	Exercise challenge: ≥ 15% fall in FEV1		5
		ADULTS		
Wicht (1979)*	507 white (20 – 80 years)	Self-reported asthma	Male Female	7.8 11.9

FEV1: Forced expiratory volume in one second.

PEF: Peak expiratory flow

* Cape Town

A similar study of 12 year old white schoolchildren in Cape Town (Nagel 1992, Burr 1994) found a prevalence of BHR on exercise testing of 4.1 percent, using a 15 percent fall in PEF as the criterion. A parent reported prevalence of "current asthma" of 8.7 percent was also recorded in this study.

These studies of children and teenagers tell us that the prevalence of exercise-induced bronchoconstriction in Cape Town, using different definitions, is of the same order of magnitude, varying between about 3 and 6 percent. It is difficult to make any confident inferences about race differences, because of the differences in era, BHR criteria or age groups in these studies.

Regarding asthma, Vermeulen's Transkei study provided an estimate of the prevalence of clinical asthma (6.1 percent). Nagel's study of white schoolchildren was part of a cross-national comparison with New Zealand, Wales and Sweden (Burr 1994). Wheeze in the past year was reported as commonly in his group (17.8%) as in New Zealand and Wales, and asthma ever (11.5%) on a par with that of Wales but somewhat less than in New Zealand. Swedish prevalences were the lowest.

There has been only one adult prevalence study. As part of a large study of obstructive airways disease in white adults in the Bellville area of Cape Town, Wicht (1990) used a modified version of the Medical Research Council (UK) questionnaire. Asthma was defined in different ways, but one set of figures was based on a positive response to the question: "Is there any history of bronchial asthma?" The prevalences derived are the highest among any of the studies they cite from a number of countries. This should be seen against the background of the very high prevalence of 45 percent for the "diffuse obstructive pulmonary syndrome" (including a range of syndromes and symptoms) found in the same study. Their asthma measure is a cumulative prevalence which depends on quality of recall, access to medical care and physician practices in the area. Besides these sources of differences between this and other studies, there is the conceptual problem of distinguishing asthma from other forms of chronic obstructive airways disease

in adults, particularly that due to smoking. Nevertheless, in the absence of comparative South African data, the Wicht study remains the only population based estimate of adult asthma available.

2.5. Studies of mortality

There have been two studies of asthma mortality, each of a limited nature. The first, by Benatar (1986) was restricted to deaths in Cape Town. He noted that whites had a considerably lower risk of asthma deaths than blacks and coloureds.

Ehrlich (1994a) examined national death certification in the white and coloured populations to determine whether South Africa had experienced the same rise in asthma mortality observed in other countries, and whether mortality rates differed by socioeconomic status using race as a proxy. (Black death certification was considered too inaccurate for longitudinal analysis [Botha 1985]). Caution must be exercised about inferences from death certification, and from examination of time series. However, there does appear to have been an increase in death rates during the 1960s in both groups. Among whites, the trend since then has been downwards, with a possible small peak among older ages in the late 1970s. Among coloureds, the high rates of the early 1970s have persisted.

A striking finding was the high relative risk of death from asthma among coloureds compared to whites (in 1988: 4 to 5 fold for all ages; 2.5 fold among those aged 5 to 34 years). Over the period 1970 to 1987, white rates in the younger age group were comparable to those reported for the United Kingdom, while rates in the coloured population were comparable to (even higher in some years) than those reported from New Zealand. The authors speculate that the difference in mortality between the two groups is likely to be due to greater severity of asthma and differential quality of asthma management associated with socioeconomic disparities.

2.6. Aetiologic studies

Eloff (1990) conducted an ecologic correlational study which aimed to relate the prevalence of asthma serious enough to warrant restricted training among white military conscripts, with air pollution indices by region. (The study is available as a report in a conference Proceedings only). Of interest was the geographic distribution of these rates. The study has the advantage of large numbers, a relatively homogeneous population and the ability to generate geographical rates. A possible bias is that conscripts may exaggerate their afflictions, and that such exaggeration may be unequally distributed among men from different towns. Further, but unpredictable biases may arise from different criteria for medical restriction used in different training centres.

Nevertheless the data are interesting and essentially confirm Ordman's observation of 40 years ago that asthma is more common at the coast. The major exception is the Central Rand (now Gauteng) with a rate second only to that of Durban. This is unexplained as areas with higher pollution levels such as the far east Rand has just over one third of the asthma prevalence. There was no correlation between asthma prevalence and measures of ambient air pollution by city or area. The study raises a number of interesting questions, and is a creative use of routinely collected data.

Potter (1990) used a case control design to examine the precipitants of acute asthma among children admitted to the Red Cross Children's Hospital in Cape Town over a one month period. He found no association between meteorological variables, recent exposure to allergen, skin prick sensitivity and likelihood of admission. The only difference between cases and controls was the higher rate of acute respiratory infection in the cases. However, the study was small with low statistical power. In addition, the use of well asthmatic controls from a specialist clinic creates potential biases. For example, respiratory infections not precipitating an asthmatic episode may have kept controls away from the clinic on any given day. As the clinical examinations were unblinded as to acute/well status there is likely to be relative overreading of signs in the acute cases. Signs such as "coryza" and "bronchitis" in the acute cases do not necessarily indicate

infection, and may merely be manifestations of the allergic asthmatic response.

Richards (1996) examined the association between passive smoking and a variety of outcomes, including reported respiratory disease and lung function, among 726 high school children aged 16 years in the Vanderbijlpark area of the Transvaal. He found associations between exposure to parental smoking and reports of respiratory illnesses, symptoms such as cough and earache, low birth weight and learning difficulties. No significant association between parental smoking and reported asthma or allergy, lung function (n=395) nor serum IgE concentrations (n=363) was found.

2.7. Conclusions

Allowing for the variability in quality and method of the epidemiologic evidence that is available, certain tentative conclusions can be drawn about asthma in South Africa.

1. The nature of the allergic response underlying asthma in South Africa varies geographically, with house dust mite a major contributor at the coast, and grasses more common inland. Although there is one study (other than Ordman's clinically based observations) suggesting that asthma is more prevalent at the coast (Eloff 1990), there are also anomalous data and the difference remains to be confirmed.

2. Although the evidence is indirect, the hospital studies and serial Transkei studies are compatible with the widely held view that childhood asthma is much more common now than two to three decades ago. This accords with the trends noted in a number of other countries.

3. Urbanisation, or at least the changes associated with "westernisation", underlie an increased prevalence of asthma over time in the black South African children. The nature of these changes is speculative.

4. Race as used in these studies is a proxy (to some extent implicit) for access to health

services, socioeconomic status, environmental conditions and urban status. Apart from the effect of urbanisation mentioned above, the evidence for consistent interpretable differences between race groups in prevalence of asthma symptoms, BHR or immune markers is scanty.

5. Asthma mortality shows a pattern most suggestive of relative socioeconomic advantage in the population, with a recent decline among whites and a high level among coloureds.

2.8. Postscript: A note on the use of race categories in epidemiology

In seeking to describe the distribution of disease in South Africa, epidemiologists have frequently used a categorisation which seemed obvious on biological and sociological grounds, namely that of "race". (Quotation marks will be used in this section to signal that the meaning and use of terms are under discussion).

Much of the descriptive epidemiology (of a number of diseases) undertaken over the past four decades in South Africa has thus sought to describe, and less commonly to explain, the distribution of disease among the four "races" that formed the legal basis of apartheid regulation. These four "races" (alternatively termed "population groups" and more recently "ethnic groups") are: black (alternatively African), white (Caucasian), coloured (mixed race) and Asian (Indian).

The uncritical use of race categories in health research in South Africa (Ellison 1996, 1997a, 1997b, 1997c) and elsewhere (Muntaner 1996, National Institutes of Health 1998) has recently been the subject of a persuasive critique, with some qualification (Walker 1997a, 1997b).

A number of arguments have been adduced against the use of race categories in epidemiologic research. First, it needs to be recognised that the division of the human species into "races" is a social construction, varying historically with political and

geographic circumstances (National Institutes of Health 1998). This is well illustrated by the South African four group classification. (It is notable that no biologistic definition of race was ever attempted in apartheid law).

A major problem with the use of race categories in epidemiology is the explicit or implicit inference that phenotypic differences between "races" are coterminous with genetic differences which determine predisposition to disease (Ellison 1997c). As distinct from the ways in which groups defined as "races" are treated differently in a given society, the biologic basis for the division of humankind into 3 or 4 "races" has been shown to be arbitrary (Diamond 1994). Humans are remarkably alike. Within the relatively small amount of human genetic variability, interindividual rather than intergroup variation accounts for 85% of the variation observed. Only about 6 percent of the variability represents differences between "races" as conventionally classified. (Hoffman 1994, National Institutes of Health 1998). Because of the importance of mean appearance phenotype (skin colour, eye shape, hair type, height) in the social construction of groups, it is a short but fallacious step to infer a genetic basis to any measurable disease difference between these groups.

An example of this type of biologistic inference is the study of serum IgE levels in 52 "white", 58 "coloured" and 53 "black" mother-newborn pairs drawn from public sector maternity units attached to a teaching hospital in Cape Town (Haus 1988). No further individual level data are given, other than that the black mothers had to have lived in the urban area for at least a year to enter the study. The main finding of the baseline study was that, contrary to expectation, "black" neonates had a mean and median cord blood serum IgE that was higher than that of the other two groups, particularly among those with no atopic family history. The authors go on to conclude that ".... newborn infant(s) in black Third World populations.... appear to represent a pool of genetic high IgE-responder phenotypes". While the authors emphasise that recent urbanisation may be an important environmental influence on the mothers of black infants, the results are also taken to reflect genetic differences between the groups, with wide generalisability.

While "race" categories have been used in a variety of ways in the South African medical and epidemiologic literature (Ellison 1997b), the most defensible usage is to reflect environmental and social stratification. The reality of apartheid as it evolved in South Africa over 350 years has been the reinforcement or creation of sharp social, economic and geographic divisions between "races". This has been overlaid with historical differences in cultural and religious practice, which correspond to varying degrees to the political categorisation. There are thus real *mean* differences between the "races" in income, education, occupation, geography, urbanisation, early nutritional and infective experience, diet, housing quality and quality of medical and public health services. Differences between "races" can thus be taken to signify the workings of these environmental influences, and hence an important subject of aetiological inquiry.

The problem with this approach is that the more differences there are between groups, the more difficult it is to identify which one is responsible for the observed differences in disease - a problem of collinearity and confounding. Given that comparisons are often ecological (as in speculating about causes of mortality rate difference between the "races"), the unpredictable influence of confounding and effect modification (Greenland 1989) (the ecologic fallacy) further reduces the likelihood of reaching aetiologic conclusions. One is thus left more or less permanently at the level of hypothesis generation.

There is a more overtly political argument in favour of studying "race" differences in disease, which has wide acceptance. In order to monitor progress towards greater social equity, it is necessary to retain the classification which was originally the basis of that inequity (Walker 1997a, Ellison 1997c). This is the (unpublished) but apparent position of most official and non-governmental agencies concerned with collection of health data. A counterargument, however, is that the reliance on "race" inhibits (the admittedly more difficult) measurement of health relevant individual level characteristics such as diet and housing, as well as social descriptors related to wealth, power, and discrimination (Ellison 1996).

This author is broadly in sympathy with the current critique of the use of racial categories in epidemiology, while recognising some limitations. There is very little that can be done about historical data sets where "race" is one of the few variables by which death and disease outcomes can be stratified. Such stratification has and can still tell us something about our society and the role of the environment. However, the tendency to make unsupported inferences about genetic differences between "races" should be challenged. Further, this author believes that the research programme comparing disease outcomes by "race" is approaching intellectual exhaustion, especially as social and economic change is producing increasing heterogeneity within "races". The time has come for speculation about the nature of environmental or cultural differences between "races" to be replaced by research which tests specific hypotheses, either by collecting individual level data or by using more sociologically informed ecologic variables.

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CHAPTER 3

ENVIRONMENTAL TOBACCO SMOKE AND CHILDHOOD ASTHMA: AN EPIDEMIOLOGIC REVIEW

3.1. Importance of the question

The rising tide of childhood asthma has encouraged the search for preventable causes of this condition. The apparent increase in both childhood asthma and tobacco smoking in adults in many populations has focused attention on a possible association between the two phenomena, which if causal, would be of inordinate public health importance (Weiss 1992).

As discussed in Chapter 2, asthma is probably more common among South African schoolchildren than three decades ago. Tobacco usage in South Africa, while common and recognised as a major cause of ill health in adults (Yach 1988, 1992), is unevenly distributed in the population. Smoking surveys in recent years have tabulated smoking prevalences by age, sex and race (a surrogate for social class, cultural acceptance of smoking, and probably differential marketing by the tobacco industry) (Steyn 1987, 1997, Yach 1988, Reddy 1996). In the latest national survey (Reddy 1996), overall smoking rates among South African men and women respectively were: Asian: 48%, 7%; black: 53%, 10%; coloured: 58%, 59%, and white: 43%, 27%. These differences were confirmed by a study of volunteer population of women attending antenatal services in four South African cities. Among the sample attending public sector clinics, 46 percent of coloured women reported smoking during their pregnancies, compared to 3.6 percent of black women and 2.6 percent of Asian women. Among women attending private practices (i.e. of higher socioeconomic class), 27.6 percent reported smoking in pregnancy.

Smoking trends over time in South Africa have not been published, but were obtained by the author from a market survey company which polls an annual national random sample of South Africans. Between 1975 and 1992, prevalence of tobacco usage (defined by use of at least one packet of 20 cigarettes per week) declined only among white men and women, while remaining constant or rising among the rest of the population. (South African Advertising Research Foundation - personal communication).

In the light of the above, even a modest association between ETS and childhood asthma could have a substantial public health impact in some South African communities.

3.2. Strategy of this chapter

The great interest in the subject of ETS and its influence on childhood respiratory illness has resulted in a large number of studies and literature reviews over the past 15 years or so. This literature was reviewed by the author in 1992 (Ehrlich 1992). Since then, a sizeable number of further studies on the subject have appeared.

A series of systematic reviews of the association between ETS and asthma, wheezing, BHR and allergic sensitisation has recently been published by Strachan and Cook in a five article series in Thorax (Strachan 1997, Cook 1997, Strachan 1998a, 1998b, Cook 1998). The authors reviewed approximately 170 relevant studies, including some unpublished work. Where possible, they summarised results quantitatively in the form of pooled estimates of effect. (The used odds ratios for comparability across all study designs). Heterogeneity of individual study findings were tested statistically, and pooling was done according to random effects or fixed effects model assumptions. Covariates adjusted for in the various studies were reported in summary form. Publication bias was assessed by examining results from some large unpublished studies, and by noting whether smaller studies tended to show mainly positive findings.

Meta-analysis of observational studies is a way of reducing a large amount of data to interpretable form for comparison purposes and for examining patterns of divergence (Greenland 1987, 1994). However, this type of meta-analysis has been criticised for conferring spurious precision on biased estimates (Shapiro 1994). Pooled measures of effect do not in fact reduce the need for critical qualitative appraisal of sources of bias and confounding.

The problem of this chapter is to reduce a large amount of heterogeneous material to digestable form. It was decided that this would not be served by either a *de novo* review or a reproduction of tables summarising every study. The objectives of this chapter are instead twofold. First, to re-examine the findings of the author's 1992 review (Ehrlich 1992) in the light of Strachan and Cook's recent meta-analyses and other relevant publications. This will also provide a temporal view of the evolution of evidence on the subject. The second aim is to examine the evidence qualitatively within an epidemiologic framework of confounding, effect modification and misclassification, i.e. threats to validity.

Earlier reviews of the evidence linking ETS to childhood respiratory illness concluded that parental, and particularly maternal, smoking is associated with both an elevated risk of lower respiratory illness in children under two years of age, and with a small decrement in lung function or rate of lung growth in childhood (Weiss 1983, Guyatt 1985, Fielding 1988, National Research Council 1986, US Department of Health and Human Services 1986, Samet 1987a, Spitzer 1990). This conclusion regarding lower respiratory illness in infancy and early childhood was supported by Strachan and Cook's meta-analysis (Cook 1997).

There was less confidence in the earlier reviews about imputing a role to ETS in the development of paediatric asthma. To focus this review on the questions set in Chapter 1, the emphasis is on the occurrence and exacerbation of asthma and persistent or recurrent wheezing in primary school children. This review thus covers aetiologic studies in which asthma, wheezing or BHR in children were examined as outcomes. The different outcomes of interest reflect the view of asthma as a heterogeneous condition encompassing most recurrent or chronic wheezing in children, at least in those over two years of age (Lee 1983, Konig 1987). Studies of non-specific BHR are included as this attribute is an important physiologic characteristic of asthma.

Studies which reported on cough, which may be the only symptom of asthma in a minority of children (Konig 1987), on non-specific respiratory symptoms such as breathlessness or "chestiness" , or on a composite index of respiratory outcomes, have not been included in the primary review. There is also a substantial literature on ETS and reduction of lung function or lung growth in children. While lung function deficits are a manifestation and complication of asthma, this literature is also not reviewed in any detail.

In what follows, biologic plausibility is considered briefly as background to the epidemiologic review. The epidemiologic reports are grouped and their findings summarised by study design. The Discussion section deals with methodological considerations which might be invoked to explain differences between study findings. The Conclusions section attempts to tie the foregoing together including a brief discussion of causal pathways. The chapter concludes with estimates of the burden of disease attributable to ETS in the USA.

3.3. Plausibility

An association between ETS exposure and paediatric asthma has biologic plausibility. Environmental tobacco smoke is a complex mixture of particulates and gases (Schmeltz 1975) which could function as irritants or as antigens (Lehrer 1978), initiating or worsening inflammatory or immunologic responses in airway walls of exposed children. Either by altering resistance to infection or by increasing permeability of the epithelial barrier to allergens and irritants (Hulbert 1981), ETS may enhance BHR, stimulate an IgE response, or cause airways narrowing directly through mucus hypersecretion or stimulation of irritant receptors (Holt 1984).

Maternal smoking during pregnancy provides an alternative route of absorption of tobacco smoke ingredients by the child. Smoking by the mother in pregnancy is associated with lower birth weight (Sexton 1984, Nilsen 1984) and increased foetal and infant mortality (Kleinman 1988, Cnattingius 1988). Effects of nicotine on foetal

airway structure (Wang 1894) and on foetal lung growth (Collins 1985) have been shown in rodents. While maternal smoking in pregnancy appears to accelerate human foetal lung maturity and decrease the risk of neonatal respiratory distress syndrome, the mechanics of this process may entail other abnormalities of growth in the respiratory system (Lieberman 1992). An association with elevated serum IgE levels in newborns has also been suggested (Magnusson 1986).

In adults, active smoking does not appear to be a consistent predictor of asthma (Welty 1984, McWhorter 1989, Vesterinen 1988, Strachan 1996). This may be due in part to the methodological difficulties of disentangling asthma from other forms of obstructive airways disease. Strong selection factors may be present as well, as asthmatics may be less given to start smoking or be more likely to quit. The association of active smoking with total serum IgE level and specific IgE responses in adults is also inconsistent (Gerrard 1980a, Burrows 1981, Zetterstrom 1981, Jarvis 1995), with an apparent protective influence in the case of certain antigens (Jarvis 1995). Active smoking seems to be associated with elevated BHR (Gerrard 1980b, Welty 1984), although age (Burney 1987) and atopy (O'Connor 1989) may be important effect modifiers of this relationship.

The relation between ETS exposure and asthma in adults is also unclear. This association was recently reviewed by Coultas (1988), who concluded that limited evidence from a relatively small number of studies pointed to small increase in risk of asthma among passively exposed adults, and to exacerbation of asthma among those already diagnosed.

Nonetheless, there are a number of reasons why an effect of ETS exposure on asthma may be observable in children and not in adults. *In utero* or early exposure of the growing and maturing respiratory system to products of tobacco smoke may occur during critical periods of susceptibility to such agents. Further, as younger children spend a high proportion of their time indoors at home and have little control

over their exposure, they are likely to have significant continuous exposure to household smoking. Finally, an association in children may be easier to discern before occupational exposures, active smoking, and self-selection effects exert their impact.

3.4. Epidemiologic studies of parental smoking and asthma, wheeze and bronchial hyperresponsiveness in children

The majority of studies have used a general population study base, with either prospective or cross-sectional (prevalence or "prevalent case control") analysis. This approach has been complemented by a relatively small number of incident case control studies, in which newly diagnosed asthmatics are compared to non-asthmatic controls. The hypothesis examined is whether ETS exposure is associated with the occurrence of asthma or wheezing, rather than with their exacerbation or severity (although a few studies have attempted both). Studies of asthmatic populations alone, which are more clearly able to answer questions of exacerbation, are fewer in number.

The studies are summarized under four headings, according to study design or outcome. **Table 3.1** summarises, in anticipation, the main conclusions under each heading.

3.4.1. Cohort studies of asthma and wheeze

Cohort studies should be less subject to bias than cross-sectional or case-control studies, as they are able to record parental smoking status in advance of the diagnosis or symptoms (including during the important periods of pregnancy and infancy), and to make more than one measurement of exposure. Loss to follow-up remains a problem, while retrospective reporting by parents of earlier exposures may still suffer from recall bias. Cohort studies are also able to measure directly incidence and measures of risk or burden of disease derived from incidence.

3.4.1.1. Cohort studies: 1992 review

Two large prospective birth cohort studies, one from Britain (Leeder 1974) and one from New Zealand (Horwood 1985) showed little or no association between parental smoking and asthma or wheezing after adjustment for covariates. Two smaller cohort studies, one following children to 12 months of age (Arshad 1992a), the other to five years of age (Cogswell 1987), found a significant excess of wheezing among children of smoking parents. Only the former (Arshad 1992a) adjusted for potential confounders; a significant effect remained only among infants whose parents both smoked.

Among prospective studies that separated maternal smoking from other sources of smoking, all found some association between maternal smoking and *wheezing*. Those that examined children one to two years of age have found a consistent relationship (Fergusson 1985, Anderson 1987, Wright 1991, Arshad 1992b). The effect was not detectable among older children in two of the longer-term studies (Fergusson 1985, Anderson 1987) although in the latter study smoking in pregnancy was the only exposure variable available. McConnochie (1989) did, however, find an effect of maternal smoking on the incidence of new wheezing in older children.

TABLE 3.1 Effect of environmental tobacco smoke (mainly parental smoking) on asthma and related features: summary of epidemiologic evidence

Outcome / study design	Findings
Asthma and wheezing	
Cohort studies	Consistent positive association parental smoking with wheezing in early childhood. In older children, maternal smoking associated with wheezing; less so for diagnosed asthma.
Case control and prevalence studies	Large body of evidence: smoking by mother and by both parents associated with asthma and wheezing. Less so for father's smoking.
BHR	Evidence suggests that parental smoking increases BHR, but publication bias a possibility.
Allergic sensitisation	Evidence inconsistent; overall suggests no association with parental smoking.
Aggravation of existing asthma	Suggestive association parental smoking with various indices of severity. Few studies of any one outcome, e.g. BHR among asthmatics.

The evidence with regard to maternal smoking and *diagnosed or reported asthma* in these studies was equivocal, however. Fergusson (1985) and Sherman (1990) found no association, while Neuspiel (1988) found an effect of maternal smoking on wheezy bronchitis (based on maternal reporting) but none on asthma. By stratifying by years of maternal education, Martinez (1992) was able to demonstrate an association between maternal smoking and diagnosed asthma that was restricted to children of less educated mothers.

3.4.1.2. Cohort studies: 1998 update

Strachan and Cook (Strachan 1998b) reviewed 10 papers reporting on six cohort studies, including four of the cohorts included above. An association of maternal smoking with incidence of wheezing has persisted, while the findings regarding diagnosed asthma have remained contradictory. In their meta-analysis, a stronger association with "asthma or wheezing" was found in cohorts covering the ages from birth to early school years (pooled odds ratio 1.31, 95% C.I. 1.22-1.41), than in those covering the school years or the whole of childhood excluding infancy (pooled odds ratio 1.13, 95% C.I. 1.04 - 1.22).

3.4.2 Cross-sectional and case-control studies of asthma and wheeze

Survey based cross-sectional studies and clinic based case-control studies are easier to do than cohort studies and therefore more numerous. They suffer the disadvantage of collecting symptom and diagnosis information contemporaneously with smoking data. Parents of symptomatic or diagnosed children may alter their smoking habits or report such habits differently from parents of asymptomatic or undiagnosed children. Also, smoking during later childhood may not reflect the child's exposure at critical earlier periods.

3.4.2.1. Cross-sectional/case control studies: 1992 review

Among reports which did not separate out maternal smoking, considerable variability of findings was apparent. A number showed a significant positive effect, particularly if both parents were smokers, (Weiss 1980, Dodge 1982, Burchfiel 1986, Somerville 1988, Dekker 1991, Chinn 1991). However, there were important studies in this group showing little or no positive effect even with large samples (Schilling 1977, Schenker 1983, Strachan 1988, Strachan 1990, Dijkstra 1990). In others, the effect appeared only in one sex (Burchfiel 1986, Somerville 1988) or in some large geographic subsamples but not others (Chinn 1991), was observable only if a cofactor such as dampness at home was present (Andrae 1988), or became insignificant after adjusting for parental symptoms (Lebowitz 1976).

Studies which were able to separate maternal smoking from smoking from other sources were notably consistent in their findings. Almost all found an association of maternal smoking and childhood asthma (Gortmaker 1982, Kershaw 1987, Weitzman 1990, Goren 1991, Willers 1991, Ehrlich 1992), some form of wheezing (Ekwo 1983, Ware 1984, McConnochie 1987), or a combination of asthma and wheeze (Forastiere 1992). Exceptions were Schenker (1983) who reported no significant relationship between maternal smoking and diagnosed asthma or persistent wheeze, and Goren (1992) who found an association with asthma but not with wheeze.

3.4.2.2. Cross-sectional/case control studies: 1998 update

There are now a large number of studies in this category. Strachan and Cook (Cook 1997, Strachan 1998b) have divided them into "case-control" studies (asthma defined either in a health service setting or by some measure of greater severity if survey based), and prevalence studies (typically survey based with a variety of questionnaire derived wheeze or asthma outcomes).

Of the 19 case-control studies reviewed by Strachan and Cook, three were included in the earlier review. Strachan and Cook refer to these case-control studies as prevalence based. In theory, case control studies based on incident cases are clearer to interpret for purposes of aetiologic inference than studies based on prevalent cases, since in the latter type incidence may be entangled with duration of the disease. There is in fact limited evidence from a number of small studies that ETS increases the risk of wheeze persistence (duration of disease) from early to mid-childhood, although this effect is not seen in large cohorts followed into adolescence (Strachan 1998b). However, since asthma follows a chronic or recurrent course with variable delays to presentation and diagnosis, the distinction between incident and prevalent cases studied in health service settings is not necessarily a clear one.

Strachan and Cook's conclusion from case control studies is similar to that of the author's 1992 review. Smoking by either parent (or presumably by both, although this is not explicit) is associated with asthma (pooled odds ratio 1.37, 95% C.I. 1.15-1.64), with a fair bit of heterogeneity. When maternal smoking is examined separately the association is slighty stronger (pooled odds ratio 1.59, 95% C.I. 1.27-1.99) with less heterogeneity. Paternal asthma shows no association with asthma.

The prevalence studies reviewed by Cook and Strachan (Cook 1997) are mainly population surveys based on self-administered questionnaires to parents, and include 25 papers with asthma as the outcome, and 41 with some form of wheeze as the outcome. Of these, 14 were included in the 1992 review (which included some not in the later review). In the studies reviewed, the reported asthma definition varied between asthma that was parent reported, doctor diagnosed, current, recent or "ever", while the wheeze description varied broadly among current, ever or persistent wheezing.

In these cross-sectional studies, smoking by the mother only (versus neither parent) was consistently associated with an odds ratio greater than one, with few exceptions [pooled odds ratios: asthma = 1.36 (95% C.I. 1.20-1.55); wheeze = 1.28 (95% C.I. 1.19-1.38]. These odds ratios increased to approximately 1.50 when both parents smoked. Again, there was greater variation among the findings for smoking by the father only (versus neither parent), with only the pooled odds ratio for wheeze (1.14, 95% C.I. 1.06 -1.23) being significant.

3.4.3. Studies of bronchial hyperresponsiveness (general population)

3.4.3.1. BHR studies: 1992 review

Five studies of the relation between BHR and parental smoking or ETS exposure in general populations of children were included. The children in these studies were necessarily older (6 years and up) than in the studies reviewed in the previous

sections because of the need to be able to complete a BHR test. Three of these studies, which related bronchoconstrictor challenges to maternal smoking (O'Connor 1987, Martinez 1988, Frischer 1992) found strong associations between maternal smoking and BHR among asthmatics. Among non-asthmatics, however, the association was absent (O'Connor 1987) or weaker (Frischer 1992), while Martinez (1988) demonstrated it only among boys. No association between ETS exposure smoking and exercise-induced bronchospasm was found by Strachan (1990), using salivary cotinine as a marker of ETS exposure. One study measured BHR among infants aged two to ten weeks (Young 1992): an association with parental smoking was demonstrable, but only in the absence of a family history of asthma.

3.4.3.2. BHR studies: 1998 update

Apart from the neonatal study (Young 1992), Strachan and Cook (Cook 1998) were able to find 10 studies from which odds ratios for the association between ETS and BHR in schoolchildren could be calculated. Of these, five were included in the author's 1992 review. The later review is more suggestive than the earlier one of an association between parental smoking (in most cases maternal smoking) and BHR (pooled odds ratio 1.29, 95% C.I. 1.10-1.50). However, Strachan and Cook point out that in a further five studies from which only p values could be derived, the associations were all non-significant while in another four studies in which BHR and ETS were measured *inter alia*, no findings were given in the published reports. They conclude that publication bias may well explain the small positive association found overall.

3.4.4. Studies of asthmatic populations

Studies of asthmatic children address the relationship between ETS exposure and exacerbation or severity of asthma rather than occurrence of asthma.

In the 1992 review, direct evidence of aggravation was more limited than for occurrence, as relatively few asthmatic populations had been carefully studied in this

regard. The available data suggested that asthmatic children whose mothers smoked had more severe asthma, were more likely to be on medication and to have more frequent visits to the Casualty department (Emergency Room) than those whose mothers did not (Murray 1988, Evans 1987, Murray 1986, Murray 1989, Weitzman 1990a).

Further, a consistent finding in four separate populations including two small sub-populations described in the previous section, is that parental smoking was associated with a greater frequency of BHR among asthmatics (Murray 1986, 1988, 1989, O'Connor 1987, Martinez 1988), and with lower lung function indices among wheezing or asthmatic children (Sherrill 1992).

In contrast, frequency of symptomatic days (Evans 1987) and hospital admissions (Evans 1987, Weitzman 1990b) among asthmatic children were not related to either household or maternal smoking. Similarly, ETS exposure could not be shown to provoke acute airflow limitation or increased BHR in a chamber study of a small group of asthmatic children (Oldigs 1991).

In their 1998 review, Strachan and Cook (Strachan 1998b) have extended the evidence but have noted the same inconsistencies. In general, clinic based studies of asthmatic children are more likely to show an association between ETS exposure and severity or exacerbation indices than subpopulations with asthma or wheeze identified in surveys (e.g. Henderson 1995). This may reflect the greater heterogeneity and inclusion of milder forms of wheezing in survey based compared to clinic based studies.

3.4.5. Allergic sensitisation

Because of the importance of atopy in childhood asthma, studies addressing the association between ETS exposure and markers of allergic sensitisation could throw light on a possible mechanism. Allergic sensitisation may thus be an intervening

variable in the association between ETS and asthma.

3.4.5.1. Allergy: 1992 review

The evidence that ETS exposure in children is positively associated with immune markers was mixed. Atopy as manifested by skin test reactivity was found to be related to maternal smoking by Martinez (1988) and by Weiss (1985). The former group also reported increased IgE levels and eosinophil counts and percentages in male children of smokers. Elevated IgE levels were also found in the cord blood of newborns of smoking mothers (Magnusson 1986), and in infants of smoking parents (Kjellman 1980). In contrast to these findings, Oryszczyn (1991) found no association between maternal smoking in pregnancy and cord blood IgE. Similarly no association between parental smoking and total IgE was found in a small cohort of children followed from birth to five years of age (Cogswell 1987), or between such smoking and either total IgE or specific IgE to common allergens in a study of older children (Ownby 1988).

3.4.5.2. Allergy: 1998 update

Strachan and Cook (Strachan 1998a) reviewed 28 papers in which associations between parental smoking and cord blood IgE, postnatal serum IgE (almost all total rather than specific), or skin prick tests were examined. Summary of the evidence is made difficult by small sample sizes, lack of adjustment for confounders in a number of studies, and inconsistency and heterogeneity among studies. However, the reviewers conclude that the evidence is against any positive association between maternal smoking and total IgE, whether in the perinatal period or in later childhood. Similarly, there is unlikely to be an association between perinatal ETS exposure and specific skin prick test reactivity in older children - if anything such exposure appears protective. No conclusion could be reached regarding concurrent ETS exposure and skin prick test results in older children.

3.5. Discussion

The large number of studies to date point to an association between maternal smoking and asthma or wheezing in children. The effect size is relatively small. There is greater inconsistency with regard to the influence of sources of ETS other than maternal, the timing of effect and a possible differential impact on "wheezing" compared to that on "asthma".

Considered below are methodological factors which might produce bias in studying this association, either generating negative findings in the presence of a real association, or contributing to a spurious positive association. These factors are discussed under the following headings: (1) exposure variation and misclassification (2) outcome variation and misclassification (3) confounding, and (4) effect modification.

3.5.1. Variation in and misclassification of ETS exposure

Validation studies have suggested that parental reporting of their smoking status is reasonably accurate (Emerson 1995). However, some misclassification of the child's actual dose of tobacco smoke ingredients is inevitable. Important factors other than parental smoking status affecting the child's dose include the number of cigarettes smoked in actual proximity to the child by each parent, the number, size and ventilation of rooms in the home, and the child's age and possibly sex. Smokers other than parents (at home or elsewhere) could be the source of important exposure.

Season or climate may substantially affect the degree of exposure. In a study of asthmatic children in Vancouver, an association between maternal smoking and asthmatic severity was demonstrable only in the cold, wet season but not in the warm, dry season (Murray 1988). This seasonal effect could be explained by a greater exposure to tobacco smoke in cold wet weather, when ventilation is reduced to conserve energy and when children spend more time indoors. Among children in Edinburgh, salivary cotinine concentrations measured in spring were about 70%

lower than in winter (Jarvis 1992). This source of variation in true exposure may explain differences between studies from different climatic regions.

To the extent that misclassification of exposure in a given study is unrelated to the occurrence of asthma, i.e. non-differential; it would usually weaken the observed relation between ETS exposure and asthma. Differential misclassification would arise if misclassification of ETS exposure status or dose were related to asthma or wheezing. This might occur, for example, if parents of symptomatic children denied or understated their smoking; this too would bias the association towards the null.

It is in distinguishing between maternal and paternal smoking that critical differences in effect are observed. Almost all of the studies examined in the earlier review that separated the two sources of ETS exposure found a maternal effect that exceeded the paternal effect (Murray 1988, Murray 1989, Burchfiel 1986, Neuspiel 1989, McConnochie 1986, McConnochie 1989, Gortmaker 1982, Ekwo 1983, Ware 1984, O'Connor 1984, Forastiere 1992). The importance of maternal smoking is supported by studies which were able to quantitate maternal smoking. Among the five studies (Murray 1988, Fergusson 1985, Neuspiel 1989, Ware 1984, Weitzmann 1990) in which cigarettes smoked daily by the mother was used as the exposure variable, exposure-response relationships were observed in four (Murray 1988, Neuspiel 1989, Ware 1984, Weitzmann 1990).

This predominance of the maternal effect may also explain why smoking by "one parent alone" is frequently observed to have little or no significant effect on wheezing or asthma whereas an effect appears if both parents smoke (Leeder 1974, Dodge 1982, Burchfiel 1986, Arshad 1992, Forastiere 1992). Given that the smoking habit is still more common among men than among women in most social strata (Marcus 1987, Covey 1992) and that the single smoker is thus more likely to be the father, the "one parent smoking" category will more often reflect the weaker impact of parental smoking. Studies that fail to separate out maternal smoking will thus dilute or

understate the true association.

3.5.1.1. Cotinine as a biomarker of ETS exposure

Some biochemical evidence of the relative contribution of maternal and paternal (or nonmaternal) smoking to tobacco smoke absorption by children has been obtained by measuring cotinine, a metabolite of nicotine, in the serum, urine or saliva of the child. Chilmonczyk (1990) found that median urinary cotinine level among non-breast fed infants was much higher if the mother alone smoked (25 ug/L) than if only other household members smoked (8.9 ug/L). Greenberg (1989) and Patishall (1985) were also able to show a greater contribution of maternal than nonmaternal smoking to cotinine levels in infants. Jarvis (1985) measuring salivary cotinine in 11-16 year-olds found that the median salivary cotinine was also higher if the mother was the only smoker (1.35 ng/ml) than if the father was the only smoker (1.00 ng/ml). The ratio of "maternal" to "paternal-derived" cotinine (1.35) in this study was less than that found in infants by Chilmonzcyk (2.8) and suggests that the difference in cotinine contribution from the two parental sources probably declines with age.

Cotinine has been used also as a means of refining measurement of exposure in studies of ETS exposure and asthma, with inconsistent results. Strachan (1990) found no relationship between wheeze in the past year or exercise-induced reduction in FEV1 and salivary cotinine in seven year old Scottish children. Similarly, Reese (1992) found no difference in urine cotinine levels between Australian asthmatic children admitted to hospital and nonrespiratory controls. In contrast, Ehrlich (1992) found elevated urinary cotinine levels in asthmatic children compared to controls in a hospital based study in New York city, as did Willers (1991) in comparing asthmatic children from a Swedish hospital with school based controls.

The use of cotinine as a biomarker of ETS exposure in children is not without interpretational problems, however. A single cotinine concentration provides a measure of recent exposure. The reliability of cotinine as a marker of usual or

chronic exposure has been the subject of conflicting evidence (Jarvis 1987, Henderson 1989, Coultas 1990, Emerson 1995), as has its relationship to

environmental measures of nicotine concentration (Henderson 1989, Coultas 1990). Furthermore, while correlation of cotinine with reported exposure has been confirmed in a number of studies in children (Greenberg 1984, Chilmonczyk 1990, Rylander 1989, Patishall 1985, Jarvis 1985, Coultas 1987), there is a considerable interindividual variation for any given smoking status.

Urinary cotinine may reflect a number of influences other than reported parental smoking status, including the child's age (Reese 1992) and sex (Strachan 1990), which need to be controlled for. It has been argued that dietary contribution to nicotine and cotinine levels, mainly from vegetables and tea, may confuse inferences about ETS exposure (Idle 1990). However, it appears that improbably large intakes of vegetables (or tea) by children would be needed to have a measurable effect on cotinine (Davis 1991).

3.5.2. Variation in definition and misclassification of asthma and wheezing

There is no single definition of asthma for epidemiologic purposes (Samet 1987b). A wide variety of outcomes have thus been examined, including parent reported asthma (with or without a doctor's diagnosis), health service use for acute asthma, past wheezing over various periods, persistent wheezing, wheezing only with colds, etc. Of these, wheezing has been shown to be associated with ETS exposure more frequently or more strongly than has "asthma". These include studies showing an association with wheezing where there was clearly no association between ETS exposure and asthma (Somerville 1988, Neuspiel 1989, McConnochie 1989), and others in which the odds ratio for asthma was elevated but lacked statistical significance (Dodge 1982, Burchfiel 1986, McConnochie 1986).

The heterogeneity of outcomes and effects in these studies has two implications.

First, outcomes may differ in their degree of misclassification, arising from faulty parental recall and varying diagnostic practices in that population. Misclassification of outcome, if non-differential with respect to ETS exposure, will usually reduce the effects observed (Rothman 1986). Second, given the diversity of risk factors underlying asthma or wheezing in children, ETS exposure may affect certain forms of wheezing but not others. Each of these possibilities will be considered in turn.

3.5.2.1. Misclassification of outcome

With respect to recall of wheezing, a wide range of prevalences has been reported in different questionnaire studies using differently worded questions. Responses regarding recent or persistent wheezing are likely to be subject to less error than recall of any past episode of the condition. A number of the studies reviewed inquired about "persistent" wheeze using questions from (or similar to) the American Thoracic Society, Division of Lung Disease questionnaire (Ferris 1978) (Weiss 1980, Schenker 1983, Somerville 1988, McConnochie 1986, Ekwo 1983, Ware 1984, Rona 1991). Of these, most found a positive association with parental smoking (Weiss 1980, McConnochie 1986, Ware 1984, Somerville 1988, Rona 1991), one a negative relation (Schenker 1983), while one was equivocal (Ekwo 1983).

Wheezing reports are also likely to be less accurate the longer the period of recall required. For example, in a cohort study with interviews when the child was 7, 11 and 16 years of age, the lifetime incidence of "asthma or wheezing" recalled by parents at the third interview (11.6 percent) was only half that of the cumulative incidence (24.7 percent) over the three interviews (Anderson 1987).

Recall of diagnosed asthma by parents may be more accurate because it is regarded as a more serious condition by both parents and physicians. Although few ETS exposure studies have directly validated parental reports of asthma, there is some evidence that questionnaire-based reports of physician diagnoses are reasonably

accurate (Gortmaker 1982, Samet 1987b) and reliable (Forastiere 1992, Frischer 1992). The prevalence of reported wheezing or asthma may vary also according to the respondent: in one study prevalences were higher when the respondent was female (Dekker 1991). Mothers may thus report more illness in children than do fathers.

A more serious problem arises from underdiagnosis of asthma. Almost all surveys of asthma and wheezing have found wheezing prevalences twofold or more higher than those of asthma. The relationship between the two in any population presumably reflects factors relating to the distribution of risk factors, as well as local clinical practice and acceptance of the diagnosis of asthma. In general, substantial underdiagnosis of childhood asthma occurs (Speight 1983, Bauman 1992).

Misclassification of asthma will be non-differential if the factors affecting underdiagnosis are unrelated to ETS exposure. In this case, the power of these studies to detect a real association with diagnosed asthma may be lower than those using wheeze as the outcome. Underdiagnosis of asthma is probably not non-differential, however. Children from lower socioeconomic class backgrounds may be less likely to be diagnosed asthmatic or be reported as asthmatic by their parents (Leeder 1976). Since smoking is more common among those of lower socioeconomic status as measured by education (Pierce 1989) and occupation (Covey 1992), this difference in diagnostic labelling will introduce differential misclassification. The effect would also be to bias the association of ETS and asthma towards the null.

3.5.2.2. Differential effect of ETS by type of wheezing

There is some evidence for the view that maternal smoking may affect certain types of wheezing more than others, in particular wheezing related to respiratory infection ("wheezy bronchitis"). Neuspiel found that maternal smoking was related to a diagnosis of post-infancy wheezy bronchitis but not to that of asthma. Similarly, Ekwo (1983) found maternal smoking to be associated with "wheezing with colds"

but not to "wheezing without colds". Despite controversy about the separability of wheezy bronchitis and asthma (Williams 1969, Lee 1983, Wilson 1989), the distinction is still used by medical practitioners and would be reflected in responses in questionnaire studies. If ETS exposure causes wheezing by increasing the likelihood of respiratory infection, the subgroup of wheezers affected by ETS exposure may thus be less likely to be diagnosed as asthmatic. This may partly explain the more frequent (and often stronger) association of ETS exposure with reported wheezing than with asthma in epidemiological studies.

3.5.3 Confounding

Positive confounding has to be considered as an explanation for some or all of the elevation in risk observed. There are a number of possible confounders. This section focuses on some identified as being particular importance (1) active smoking by the child, (2) parental symptoms, (3) socioeconomic status (SES), (4) use of fuels such as gas in the home, or some combination of these. Any of these factors could be associated with increased childhood asthma or wheezing independently of the effect of ETS exposure on such asthma or wheezing. Confounding would arise if the factor were in addition distributed differently between the children of smokers and non-smokers. These will be considered in turn.

3.5.3.1. Active smoking by the child

Children whose parents smoke are more likely to smoke themselves (U.S. Department of Health, Education and Welfare 1979). Active smoking by older children, as a cause of wheezing (Withers 1998), might thus result in confounding of the relation between ETS exposure and asthma. Active smoking cannot conceivably account for the positive association between parental smoking and wheeze found in studies of children under eight years of age. This includes most of the longitudinal studies. In the cross-sectional or case-control studies of older children, four inquired about active smoking by the child (Weiss 1980, Dodge 1982, Ware 1984, Ehrlich 1992). Of these, Weiss (1980) controlled for active smoking, while admitting to

smoking was rare or absent in the children or young adolescents in the the other three studies. Similarly, among the studies of asthmatic populations, Murray (1988) found only 1.6 percent (4 of 247) of asthmatics aged 6 to 17 years who admitted to smoking. However, underreporting by children of their smoking habits is probable and some degree of positive confounding (increasing with age) cannot be excluded.

3.5.3.2. Parental symptoms

A number of the studies reviewed have found that parents with chronic respiratory symptoms such as wheeze report more symptoms in their children than parents without such symptoms (Leeder 1976, Lebowitz 1935, Schilling 1977, Schenker 1983, Ware 1984). Controlling for parental symptoms has attenuated the ETS exposure - wheeze relationship to different degrees. Lebowitz (1976) found that an association between parental smoking and children's wheezing all but disappeared once parental symptoms were taken into account. In the study by Ware (1984), the odds ratio relating maternal smoking to wheeze fell only modestly from 1.31 to 1.23 after adjusting for parental illness. Other studies have found that the effects of ETS exposure were still detectable after controlling for parental symptoms (Weiss 1980, Burchfiel 1986, Martinez 1992).

The link between parental and children's symptoms is a complex one and may be the product of a number of associations (Colley 1974). It may be due to a direct effect of tobacco smoke on both the parents and children. Alternatively, it may be due to cross-infection within the family (Colley 1974). To the extent that parental respiratory infections are due to their smoking habit, cross-infection would an indirect mechanism for the impact of parental smoking on children. Common symptoms may derive also from hereditary tendencies in asthma (Leeder 1976, Hopp 1984). However, parents with asthma would, if anything, be less likely to smoke than non-asthmatics; this would reduce the likelihood of observing an association between parental smoking and childhood asthma. Finally, parents with symptoms may simply overreport symptoms in their children, creating a spurious association between their

smoking and wheezing in their children.

Adjusting for parental symptoms is needed where factors other than ETS exposure underlie the association between symptoms in parent and child. If however, this association is due to a common impact of ETS exposure, either directly, or indirectly through cross-infection, some degree of overadjustment will occur if parental symptoms are controlled for in the analysis (National Research Council 1986). As these effects are difficult to disentangle, analysis with and without parental symptoms is advisable.

3.5.3.3. Socioeconomic status (SES)

In developed countries, smoking prevalences are typically highest among people of lower SES as measured by occupation (Cuvey 1992) and education (Pierce 1989). On the other hand, the relation between SES as conventionally measured and childhood asthma is unclear. Although asthma has been found by some investigators to be more common among children of higher SES (Leeder 1976), other studies have failed to confirm this (Horwood 1985, Gortmaker 1982) or have found the converse (Schwartz 1990). Wheezing, in contrast, appears to be consistently correlated with lower SES (Leeder 1976, Neuspiel 1989, Schwartz 1990, Arshad 1992b) and with less parental education (Ware 1984, Dekker 1991).

Most studies which have adjusted for confounding have included some measure of SES as a potential confounder without removing the association between ETS exposure and wheezing or asthma. Conventional measures of social class such as parental occupation or educational status may not, however, fully capture important influences on respiratory health (Pullan 1980, Schwartz 1990). These influences include housing quality such as presence of dampness (Strachan 1988, Andrae 1988), family size (Colley 1974), maternal care factors (Pullan 1980) and other risk factors for respiratory infection (Graham 1990). Even after adjustment for parental education or occupation, ETS exposed and unexposed children may differ in other

potentially important respects. Residual confounding by SES may thus remain.

3.5.3.4. Home fuel (gas) use

Gas stove or heater use as a cause of respiratory illness in children in developed countries has been included as a potential confounder in a number of studies. It has not been found to be related to asthma nor wheezing (Weiss 1980, Schenker 1983, Dodge 1982, Ekwo 1983, Ware 1984), and is thus unlikely to confound an observed relationship with ETS exposure.

Finally, even if individual confounders are controlled, combinations of potential confounders may have unpredictable effects. A number of studies have adjusted the risk due to maternal smoking for multiple covariates such as demographic factors, home characteristics and family history of allergy. In these studies there was in most cases little or no reduction in the odds ratio relating ETS exposure to wheeze or asthma (Neuspeil 1989, Gortmaker 1982, Ware 1984, Weitzman 1990), a result confirmed by Strachan and Cook in their review (Cook 1997. Strachan 1998b). In their meta-analysis of prevalence studies, those authors found a marked reduction in heterogeneity if studies which had not adjusted for any confounders were excluded. In addition, the pooled odds ratio for asthma, although not for wheeze, was somewhat reduced by exclusion of such studies.

3.5.4. Effect modification

Variables that have been identified as potential effect modifiers of the relation between ETS exposure and asthma include age, sex, maternal education and use of day care. Differences in these factors between study populations may explain some of the conflicting findings. Alternatively, failure to stratify within a study by the effect modifier may result in masking of a real association in the relevant stratum.

Discussion of effect modification is complicated by the probable association of all of the above variables with *exposure*. Variation in effect with a given factor may be due

to a correlation of that factor with the child's dose of tobacco smoke undetectable by questionnaire. This is probable in the case of age. maternal education and day care use, and somewhat less probable in the case of sex.

In their examination of the age-dependence of the assocation between ETS and asthma/wheeze, Strachan and Cook concluded that the evidence supports an age-related effect of ETS on wheezing, with stronger associations seen in younger children under about 7 years of age than in older schoolgoing children (Cook 1998, Strachan 1998b). The evidence is not entirely consistent, however. Some longitudinal studies have found associations with maternal smoking in older children and not in younger children (Strachan 1996), while Murray (1989) found that older asthmatic children were more severely affected by parental smoking than were younger children.

Some of the decline in risk with age is probably due to lower ETS exposure with age (Irvine 1997). If there is real effect modification, it suggests that ETS exposure may have a greater impact in producing the early wheezers rather than the persistent or late onset wheezers as defined by Martinez (Godfrey 1985, Martinez 1995).

With respect to sex, a number of studies have suggested that boys may be more susceptible to the effects of ETS exposure (Burchfiel 1986, McConnochie 1986, McConnochie 1989, Martinez 1988, Murray 1989). Others have failed to confirm this (Ware 1984) or found girls to be at greater risk (Somerville 1988). Although some studies have found greater ETS exposure of boys than girls, the increased susceptibility among boys is unlikely to be fully explained by greater exposure. Rather, sensitivity to ETS exposure may be conditioned or mediated by the same factors that make boys more susceptible to childhood asthma in general (Evans 1987). For example, in the population studied by Martinez (1988) and Ronchetti (1990), parental smoking was related to increased skin test reactivity, serum IgE and eosinophilia only among boys. McConnochie (1989) reported a strong interaction between

maternal smoking, male sex and a family history of asthma in their effect on wheezing. A child with all three factors was 21 times more likely to wheeze at age thirteen years than a child with none.

Martinez (1992) found an effect of maternal smoking on the cumulative incidence of asthma only among children of mothers with twelve or fewer years of education (while maternal education had no independent association with asthma). Lower maternal educational levels may entail a number of modifying factors (other than ETS exposure) affecting the child, including poorer nutrition, less health consciousness and greater exposure to other antigens, all of which may potentiate the impact of ETS exposure.

Effect modification by use of day care was reported Wright (1991), with an effect of heavy maternal smoking (more than 20 cigarettes daily) demonstrable only among children who did *not* use day care. The simplest explanation is that children who more spend more time at home with smoking mothers have greater exposure to tobacco smoke. However, among children in day care, a strong positive interaction between maternal smoking and smoking by the caregiver on lower respiratory illness has been found (Holberg 1993).

3.6 Conclusions

The question of causality can be approached through the time honoured Bradford Hill criteria (Hill 1965). In particular, does the evidence meets the criteria of consistency, temporality, dose-response, strength of association and biological plausibility (Rothman 1986)?

There is strong *consistency* across many studies using different study designs, in the association between maternal smoking and wheezing in childhood. Where such studies have sought to quantitate maternal smoking, an *exposure-response association* has generally been found.

There are a number of possible explanations for the maternal predominance. Children spend more time in closer proximity to their mothers than to their fathers and correspondingly inhale more smoke from this source. Mothers are also likely to smoke more cigarettes in the house than smoking fathers. Maternal smoking in pregnancy may also play an important aetiologic role, although the close correlation of postnatal smoking with smoking in pregnancy makes it difficult to separate the effects of the two periods of exposure. This is discussed further below.

While there is strong evidence of the importance of exposure to ETS in early life, the evidence suggests at least some ongoing or contemporaneous effect of maternal smoking on wheezing occurrence and asthma severity. This is suggested by those studies (section 2.5.4. above) demonstrating equal or increased susceptibility of older children to ETS, including those showing an association of ETS with new wheezing in older cohorts of children (McConnochie (1989) or variation in the severity of the ETS-asthma association by season (Murray 1988, 1989).

Also, while an association with paternal smoking alone is generally less evident, an exposure response association with cumulative number of household smokers is apparent. While number of smokers might be confounded with intensity of maternal smoking, it is plausible that the effect of number of smokers is due to an increase in the total dose of ETS received by the child.

The relationship of maternal smoking to diagnosed asthma is weaker. This discrepancy may reflect the limitations of epidemiologic measurement of asthma rather than absence of an effect. Widespread underdiagnosis of asthma mayl reduce the power of questionnaire studies to detect a relationship with parental smoking. Two other explanations suggest themselves, however. ETS exposure may exert its effect mainly by increasing the frequency of respiratory infections. In such cases, physicians may be less inclined to diagnose the wheezing associated with these episodes of infection as asthma. Alternatively, parents of children diagnosed as

asthmatic may quit (or reduce) their smoking. Meinert (1994) has shown that parents of children with BHR are more likely to quit smoking during the child's early childhood - a "healthy passive smoker" effect.

For demonstration of *temporality*, i.e. that ETS exposure clearly precedes (and is not influenced by) the onset of asthma, one looks to cohort studies. Although the evidence here is supportive of an association between maternal smoking and wheezing in childhood, certain negative studies remain to be explained, in particular the cohort studies of Horwood (1985) and Strachan (1996). The Horwood study is of New Zealand children whose environment may be different from those in the UK or USA. It is noteworthy that only eight percent of the children in that study had received the diagnosis of wheezy bronchitis, the rest being diagnosed with asthma. In contrast, in the 1970 birth cohort study of British children by Neuspiel (1989) more than twice as many wheezing children had been diagnosed with wheezy bronchitis as with asthma (as recalled by the mother). This reflects local diagnostic practice and perhaps maternal recall, but may also reflect different distributions of risk factors, such as allergens and infection, in different populations.

Strachan's (1996) study of the 1958 national British cohort found a consistent effect of maternal smoking (including reported smoking in pregnancy) on asthma or wheezing bronchitis only after age 16 years. This is in apparent contrast to the findings of the 1970 British Cohort Study (Neuspiel 1989, Lewis 1995), which showed an effect of maternal smoking on any wheezing by 5 years of age. An intriguing speculation is that the 1970 cohort had an greater susceptibility to ETS at young ages than the 1958 cohort.

The *strength of the association* may be assessed from the pooled odds ratios as calculated by Strachan and Cook. These vary somewhat by study design and age but are of the order of 1.3, which indicates a weak association. It has been argued that measures of effect of this order are below the resolving power of epidemiology

to exclude confounding (Shapiro 1994, Taubes 1995, Witorsch 1991). Although many studies have attempted to adjust for potential confounders, this is likely to be imperfect (Witorsch 1991). In addition, unknown confounding is always a possibility. However, the consistency of the findings in different populations across a large number of studies which have adjusted for a variety of confounders, shifts the onus to demonstrate such confounding onto the sceptics.

Biological plausibility was considered in section 3.2. above. However, the mechanism of the effect of maternal smoking in producing wheezing in children remains elusive. It may induce the asthmatic state, it may maintain or aggravate the asthmatic state once established, it may trigger acute attacks, or act at all these levels. Pre- and postnatal influences may be involved.

Population studies of BHR in older children have failed to establish a consistent association with ETS exposure. Respiratory infection may play an important mechanistic role. There is strong evidence that ETS exposure increases the risk of acute respiratory infection among children under two years of age, including infection with respiratory syncytial virus (Pullan 1980). To the extent that such illness, particularly bronchiolitis, is a risk factor for later asthma, wheezing and increased BHR (Pullan 1982, McConnochie 1984, Weiss 1985, Peat 1987), it may provide one (indirect) pathway for the effect of early ETS exposure on subsequent wheezing among a subgroup of children. In older children, on the other hand, there are few if any data on the association between ETS exposure and viral respiratory infections.

Distinguishing the contribution to later wheezing of smoking in pregnancy from that of postnatal smoking requires populations in which maternal smoking habits can be separated according to the periods of interest. Taylor (1987) was able to show that prenatal rather than postnatal smoking by the mother was a risk factor for respiratory infection among British children. However, when data from the same cohort were analysed for an effect on wheezy bronchitis up to age ten years, no difference was

apparent between children of mothers who smoked only in pregnancy and those who smoked only after the child's birth (Neuspiel 1989).

Recent studies have examined the role of prenatal smoking on lung function in infants. Hanrahan (1992) was able to demonstrate that children born of smoking mothers had reduced forced expiratory flow rates compared to children of nonsmoking mothers, an effect independent of postnatal smoking. This finding was confirmed by Stick (1996) who showed reduced respiratory function in neonates a few days old associated with *in utero* smoke exposure. Young (1991) were unable to show such an effect, although their measurement of smoking was cruder than in the study by Hanrahan, and pre- and postnatal influences were not separable in their study. They did, however, find elevated levels of BHR among infants whose parents smoked, apparent only among those with no family history of asthma.

The significance of the above finding by Hanrahan (1992) and Stick (1996) is considerable if taken with the reports of Martinez (1988a, 1992, 1995), linking decrement in early airway function to increased risk of wheezing lower respiratory illnesses in early childhood. Maternal smoking during pregnancy may thus influence the development of airways (Wang 1984) or lung parenchyma (Collins 1985, Lieberman 1992) to produce irreversible structural changes at birth which predispose to future wheezing illness. The exact mechanism and anatomic location of the lesion and its relationship to airflow limitation and BHR remain to be elucidated.

Separating prenatal from postnatal smoking epidemiologically may become easier in the future as women quit smoking for the duration of pregnancy in response to publicity about adverse effects. A problem is that mothers who quit in pregnancy may diff on a number of factors from those that persist. For example, mothers who smoke in pregnancy may smoke more intensely pre- and postnatally than mothers who quit in pregnancy and resume after the child is born. Without quantitation of smoking, therefore, merely comparing the effects of maternal smoking status by

period of interest would be misleading. One strategy would be to randomise mothers to anti-smoking interventions in pregnancy and follow the children after birth. This would control for some of the confounding associated with quitting and allow more careful quantitation of maternal smoking. This design has been used in studies of pre-term smoking mothers in which positive effects of quitting on birthweight have been shown (Sexton 1984, Haddow 1991).

It is this author's opinion that the results of the studies described, coupled with the methodological considerations discussed, support the hypothesis that maternal smoking causes wheezing episodes in children of all ages. This conclusion is based on the strong consistency among a number of large studies of different designs which have examined maternal smoking specifically, reasonable evidence of temporality, some demonstration of exposure-response relationships, exclusion of the influence of known confounders, and reasonable biological plausibility. The pooled effect size is relatively weak, but in the absence of empirical demonstration of confounding, one can accept the evidence as sufficient for public health purposes, even in the face of residual uncertainty.

There are relatively few studies among children already indentified as asthmatic. In this regard, the evidence is suggestive (and coherent with our conception of the triggering of asthma by respiratory irritants) that maternal smoking is associated with aggravated clinical expression of the disease.

Further epidemiological research is likely to refine measures of exposure and contribute towards understanding mechanisms of effect, including during intrauterine and early neonatal life. Clarification is needed also of the association of maternal smoking with atopy and BHR and the relationship of such smoking to viral respiratory infection in older children.

Most of the research comes from developed countries. Studies are also needed in

developing countries where living conditions associated with poverty, the burden of other disease, and in certain populations very high smoking rates, may modify or aggravate an association between ETS and asthma. Local studies are also invaluable as a means of influencing indigenous public health action by providing an estimate of the burden of disease attributable to ETS.

3.6.1. Burden of disease in the USA

Although the measure of effect is relatively weak, the public health implications of the association between ETS and wheezing and asthma are impressive. Various authors have estimated the burden of illness attributable to ETS for the United States by calculating the excess prevalence or number of cases or episodes and the associated cost. Stoddard (1995) using age specific odds ratios declining with age (overall 1.36) estimated that 380 000 excess cases of childhood wheezing or asthma (7.5 percent of all such cases) were attributable to maternal smoking for 1987. Of these, 136 000 were under 2 years of age. Aligne (1997) using a relative risk of 1.4, estimated 1.8 million annual excess outpatient visits and 28 000 excess hospitalisations attributable to parental smoking, implying $180 million in additional direct expenditures.

3.7 References

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CHAPTER 4

POPULATION, SAMPLING AND ETHICAL CONSIDERATIONS

4.1. Study area

Cape Town lies on the southwestern tip of the African continent at 34 degrees latitude south of the equator and 17 degrees longitude east of Greenwich (**Fig. 4.1**). The climate is Mediterranean, with hot dry summers and cool wet winters. Mean monthly relative humidity was 75.3 percent in 1993, ranging from 66 percent in November to 87 percent in May. Temperature ranges are moderated by the coastal situation and warm Mozambique oceanic current (1993: daily minimum 12.0^{0}C., daily mean 16.6^{0}C., daily maximum 23.6^{0}C.) Strong south easterly winds are a feature of the spring and summer months. Autumn is associated with still warm days and temperature inversions.

Mitchell's Plain is situated at the southeast rim of the Cape Peninsula on the high water table sandy plain known as the Cape Flats, bounded by the coastal dunes of False Bay to

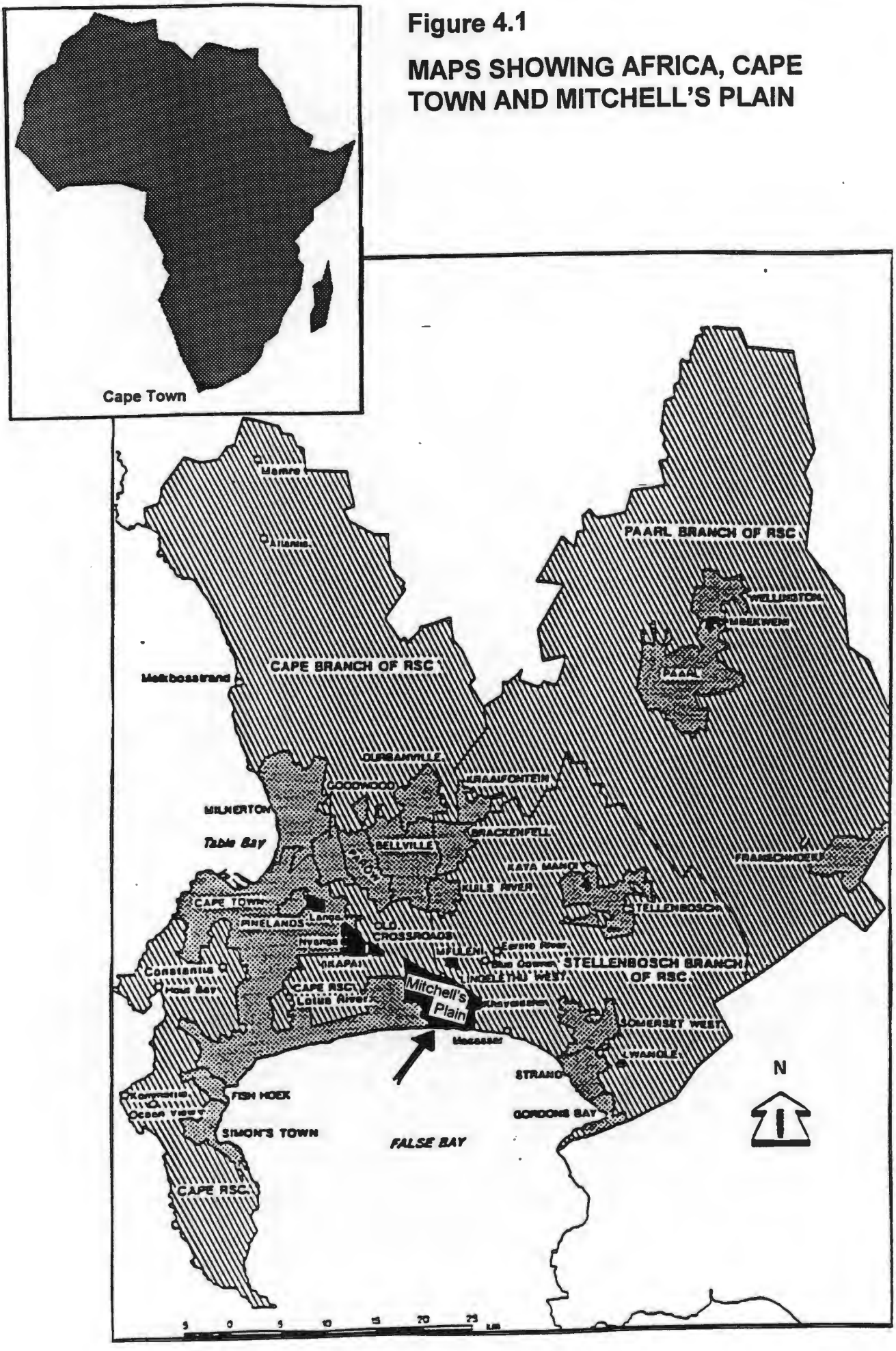


Figure 4.1

MAPS SHOWING AFRICA, CAPE TOWN AND MITCHELL'S PLAIN

the southwest (**Fig. 4.1**). Vegetation is sparse shrub, with Acacia being prominent. The area is dusty owing to coastal dune sandblasting by the southeasterly winds, and damp owing to the coastal location and high water table of the Cape Flats.

Although there is a small industrial area to the west, Mitchell's Plain is at some distance from heavier smokestack industry. Ambient air pollution in Cape Town in recent years has tended to be of the photochemical smog variety (Bailie 1994), concentrated in the central metropolitan business area and along traffic routes into the city, which lies approximately 50 km from Mitchell's Plain. Relatively high levels of secondary pollutants such as ozone have, however, been measured at some distance from traffic sources (Loewenheim 1988), and may be contribute to ambient air pollution in Mitchell's Plain. No local monitoring is done in the area.

4.2. Study population

Mitchell's Plain consists of a number of municipally defined suburbs. For purposes of this study, the area covered included Beacon Valley, Eastridge, Lentegeur, Parklands, Rocklands, Tafelsig, Westridge and Woodlands.

Mitchell's Plain was initiated by the municipal housing authority as a large scale development in the 1970s to house people classified as coloured by apartheid legislation, including many who had been moved from other parts of the Cape Peninsula by apartheid segregation policy. In the two decades since, the area has grown rapidly, with its population increasing from approximately 8 000 in 1976 to over 200 000 by 1990. Housing ranges from mainly single storey free standing homes with gardens to poorer terraces of two storey flats.

In the 1990 census the population of Mitchell's Plain was approximately 210 000 people, of whom 30 000 were aged 5 to 9 years (RSA 1991). About two thirds were Afrikaans speaking, almost all of the remainder speaking English. There were approximately 40 000 homes. The average family size was 5.2 (City of Cape Town Municipality, Urban Policy Unit - personal communication).

Mean annual household income was R19 600[1] at the 1990 census (range across suburbs R15 012 to R25 537), compared to R31 340 for the City of Cape Town municipal area as a whole (RSA 1991). Only 40 percent of the population were classified as economically active, of whom 6.9 percent were categorised as "unemployed (not looking for work)". The true proportion of chronically unemployed is likely to be much higher, however.

The relative socioeconomic status of Mitchell's Plain can by gauged by the position of its suburbs on a scale ranking the 73 suburbs within the municipal boundaries of the City of Cape Town according to a "levels of living index" (comprising indicators of income, education, overcrowding, welfare and unemployment) (City of Cape Town Municipality - *ibid.*). None of the Mitchell's Plain suburbs fall into the upper third of this ranking (middle to high income areas: index range 1 to 7.7). Only one suburb, Westridge, falls into the middle third (middle to low income areas: index range 8 to 17.5). All of the remaining suburbs fall into lower third (public housing estates/township category: index range 17 to 51), although none are in the poorest end of this category (7 areas: index range 39 to 51).

Medical services are provided in the area by a number of private general practitioners and by public health services in the form of one community health centre (general outpatients) and 5 polyclinics (providing antenatal services, immunisation, and treatment of sexually transmitted diseases and tuberculosis). There is good road access to private and public hospital facilities between 10 and 15 km away. Immunisation coverage in 1991/92 was 94.2 percent for Diphtheria/Whooping cough/Pertussis, 95.3 percent for Polio and 87.7 percent for Measles (City of Cape Town Municipality, Health Department - personal communication). A coverage figure is not available for BCG immunisation, which is carried out by perinatal services, but is assumed to be very high.

Mitchell's Plain is believed by residents and clinicians to be a high allergy and high asthma area. There is only indirect evidence for its status in this regard compared to other areas. First, using race as a socioeconomic and geographic marker, between

[1] Approximately R3.50 = $US1.00 in 1990.

1984 and 1990 coloured children in general contributed 83 percent of asthma admissions to the Red Cross War Memorial Children's hospital (Ehrlich 1994) compared to only 51 percent of pneumonia and 61 percent of bronchiolitis admissions, suggesting overrepresentation in asthma admissions. Underrepresentation of black children in admissions for asthma could produce the same effect, however (see section 2.4.2.).

Second, a large number of asthma admissions to the Red Cross War Memorial Children's hospital come from the Mitchell's Plain area (Lachman 1990). However, it is not possible to determine whether the proportion of asthma admissions exceeds the proportion of all cause admissions represented by children from Mitchell's Plain.

4.3 Sample size considerations

4.3.1 Prevalence study

The precision goal in the part of the study directed at establishing prevalence of asthma and defining a case group was a confidence interval of no more than 3 percent on either side of the sample proportion. Previous studies in the United Kingdom, Australia and New Zealand of similarly aged children had recorded a prevalence of one year wheezing of between approximately 10 and 25 percent (Strachan 1988, Clifford 1989, Robertson 1991). Assuming a prevalence of asthma in this population on the case definition used (four or more different asthma symptoms within the past 12 months, or reported asthma plus one symptom - see section 6.2.1.) of 15 percent, a population of a little under 2000 Sub-B children would give a confidence interval of 13 to 17 percent. The target sample size was thus 2000 primary schoolchildren. From this group, it was expected that 300 cases would be identified.

4.3.2. Risk factor study

The calculation for this purpose was based on the hypothesis that maternal smoking is associated with the occurrence of asthma/wheeze, and further that maternal smoking occurs in 40% of the population (Steyn 1987). Given 300 cases, and an equal number of

controls assumed to reflect the population or background rate of maternal smoking of 40%, the study would have an 80% power to detect an odds ratio of 1.60 at the 95% level of significance. This odds ratio estimate was within the range of reported elsewhere (see Chapter 3).

4.3.3. Bronchial hyperresponsiveness (BHR) and underrecognition studies

These hypotheses were subsidiary to the above, and accordingly no independent sample size calculations were performed. Power considerations are raised in the relevant chapters (7 and 8).

4.4. Sampling and response rates

Children in the second year of primary school (sub-B or grade 2), typically aged 7 or 8 years, were the target population. This age group was chosen for a number of reasons. First, although asthma may begin at a young age (arguably in infancy), the diagnosis is difficult in young children, many of whom have transient wheezing (Martinez 1995). By schoolgoing age, the diagnosis of asthma becomes more specific.

Second, schoolchildren are an accessible population for study and cooperation is generally high. Seven years was considered the youngest age at which children are able to carry out the forced expiratory manoeuvre required for the histamine challenge test. Analysis of age distributions of asthma admissions to the regional children's hospital between 1979 and 1990 revealed a second peak at approximately school going age, the first being at three years of age (author - unpublished data). Finally, compared to older ages where school dropout becomes a factor, schoolgoing at this age is likely to be reasonably complete.

The cluster sampling frame consisted of all 35 primary schools in Mitchell's Plain. Given approximately three sub-B classes per school and 35 children per class, this provided a sampling frame of 3 675 children. A simple random sample of 18 schools was selected from the 35 primary schools. Two of these schools were chosen for an initial pilot study, and a third for a subsequent pilot study, leaving 15 schools for participation in the first

phase of the study.

What follows is an overall description of the sampling procedure. Each phase is described in more detail in the relevant chapter. The sampling is illustrated in **Fig. 4.2.**

4.4.1 Prevalence study (Chapter 5)

Self-administered questionnaires were distributed to the parents of all 2 172 sub-B children on the class lists of the sample schools. Questionnaires were returned by 1 955 parents, a response rate of 90%.

4.4.2 Risk factor study (Chapter 6)

Of the 1 955 who responded to the self-administered questionnaire, 83 subsequently participated in a second pilot study, 114 did not give consent to be interviewed further, and 22 failed to provide enough questionnaire information. From the remaining sample of 1 736 children, a "current asthma/wheeze" case group of 368 was defined (see section 6.2.1.), and a control group of 294 selected from the remainder of the sampling frame. Of these 662 cases plus controls, the parents of 620 (348 cases, 272 controls) were successfully interviewed in the second phase of the study, a response rate of 97.9%.

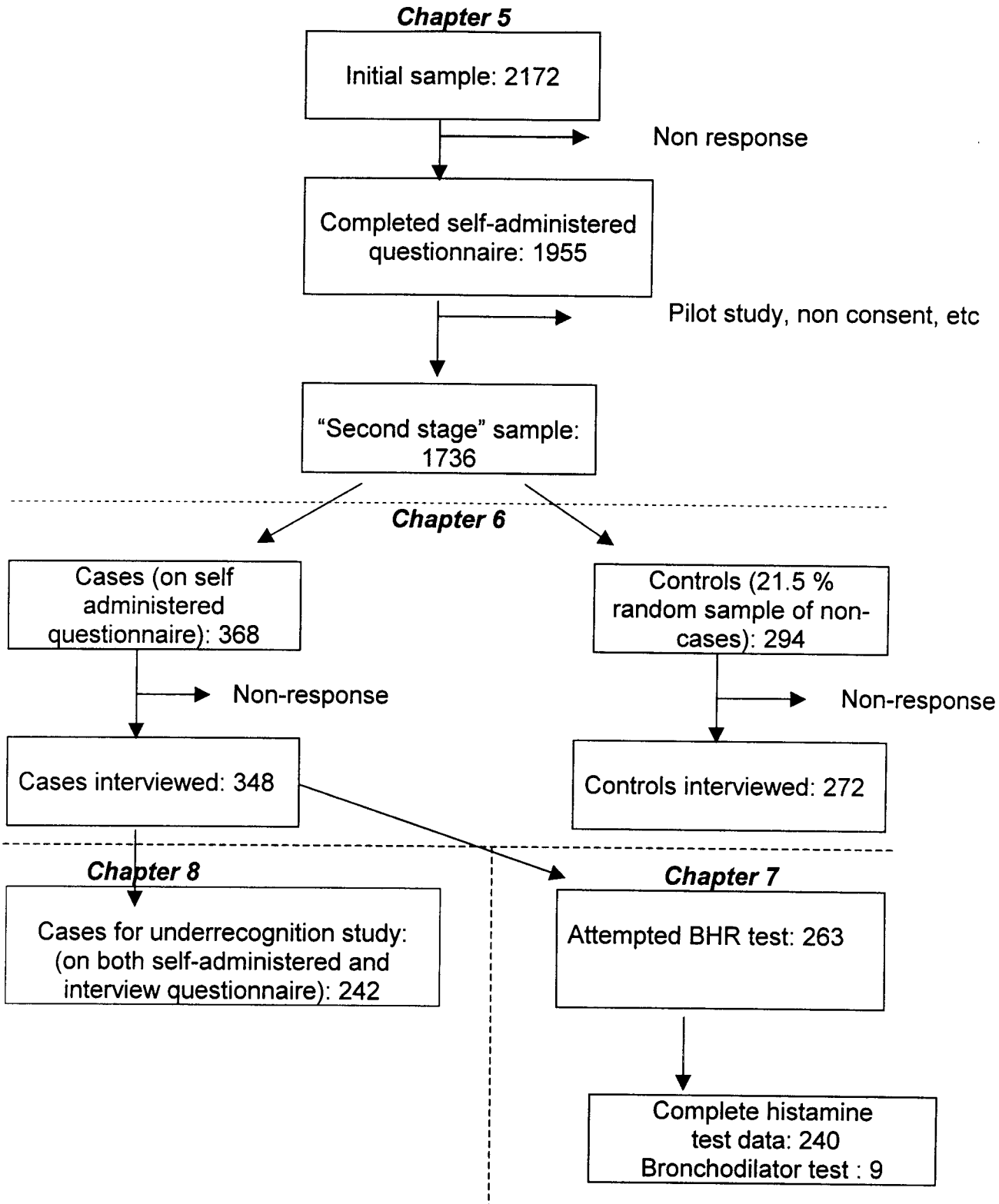
4.4.3. Bronchial hyperresponsiveness study (Chapter 7)

For BHR testing, the group of 368 case children were randomly ordered in lists by school, and a sample chosen with the aim of achieving a minimum of a 70% sample per school. It was necessary to sample because of resource constraints. A total of 263 cases attempted the BHR test (a 72.5% sample from the total case group of 368). Of those, 249 subjects had usable BHR test results, a response rate among those tested of 93.2%.

4.4.4. Underrecognition study (Chapter 8)

For purposes of evaluating recognition and treatment of asthma, those children who met the criteria for case status on *both* the self-administered and home interview questionnaire were defined as having asthma. A total of 242 had full information.

Fig. 4.2 Overall sampling pathways



4.5. Pilot studies

Two pilot studies were undertaken. The first, carried out at two schools, was designed to train the study team, test the self-administered and interview questionnaires and procedures, the procedure for collecting urine specimens and the assay for urine cotinine. Non-specific BHR was tested initially by means of a standard exercise running test (Van Niekerk 1979).

As a result of the pilot, the questionnaires were modified to improve comprehensibility and ease of response. The exercise test was abandoned in favour of a histamine challenge test. Of concern was that of the 40 children identified in the pilot questionnaire with asthma/wheeze, only 2 had positive exercise tests (5%, 95% C.I. 0.16 - 16.9). This insensitivity may be have been due to the difficulty in standardising the running effort made by the participants. Histamine challenge may be more sensitive for asthma than exercise testing, although less specific. However, the relationship between either test and asthma is complex and probably reflects different physiological responses (Clough 1991). The possible impact on the study of the unpredictable Cape Town spring with regard to rain was a further factor in the decision to switch from exercise to histamine.

Histamine was chosen for the bronchoconstrictor challenge rather than methacholine because experience in its use existed in Cape Town (Vermeulen 1991) and because histamine phosphate was readily available. The histamine challenge test was itself piloted in a third school, and a satisfactory procedure established.

4.6. Timing

The self-administered questionnaires were completed in July 1993, winter months. Home interviews, urine collection for cotinine assays and BHR testing were conducted between September and November 1993, spring months.

4.7. Ethical considerations

4.7.1 Approval and consent

The study was approved by the Ethics and Research Committee of the Medical Faculty of the University of Cape Town.

Permission to conduct the study was obtained from the Department of Education. At each school the permission of the school principal and sub-B teachers was sought in face-to-face discussion.

As part of the self-administered questionnaire sent to parents, the study was described, the voluntary nature of participation indicated and confidentiality assured. Returned signed consent was requested. The sample of children for the home interview, histamine challenge test and urine test was drawn from those whose parents gave signed consent.

The home interviews were conducted by trained interviewers after contacting the parents in advance by telephone, or by leaving a note or via neighbours if there was no telephone. Confidentiality and voluntary participation were again explained.

The parents of the children to be histamine tested were re-informed by letter the week before the test, including a request to withhold medication on the morning of the test if the child was otherwise well. The parents of each child undergoing histamine challenge received another letter after the test containing the test result and appropriate advice concerning their child's symptoms and treatment.

The histamine challenge test was performed by trained pulmonary technologists under supervision of a medical practitioner according to an internationally accepted protocol. Further detail about the test is given in Chapter 7.

4.7.2. Interested parties

Parties with a potential interest in the results were identified as academic Departments of

Paediatrics and Child Health in the Western Cape and elsewhere in South Africa, researchers internationally, public sector clinical facilities, private and public sector medical practitioners and other clinical professionals, community agencies and personnel such as schools and school nurses, and parents and residents of Mitchell's Plain and similar areas to which the results could be generalised. Associations and agencies such as the National Asthma Education Programme and the Council for Tobacco and Health have a natural interest in the results.

4.7.3. Dissemination of results

Publication of the results has been sought in peer reviewed journals. Results have also been presented at annual meetings of the Allergy Society of South Africa and the Epidemiologic Society of Southern Africa. The Medical Research Council of South Africa has publicised some of the results in press releases, in radio interviews and in its Annual Report. The National Asthma Education Programme has made use of some of the results in campaign activities.

A pamphlet, mainly for use by teachers, was developed based on the findings and sent to every primary school in the Western Cape. The author has also addressed the Mitchell' s Plain Community Health Forum , a joint network of residents and health care providers, on the study findings.

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CHAPTER 5

PREVALENCE AND RELIABILITY OF ASTHMA SYMPTOMS

5.1 Background and objectives

Measurement of the prevalence of childhood asthma in different populations has become an important international research programme. There are a number of reasons of this. Prevalence surveys measure the size of a problem in a population, which, if substantial, attracts public health interest, effort and resources. Serial prevalence surveys are also needed to test the hypothesis that asthma is becoming more common.

Since asthma is a common chronic condition, prevalence surveys offer possibilities for examining associations between asthma and putative risk factors at the individual level. At the ecologic level, differences in prevalence between populations may also suggest aetiologic factors (Lewis 1998).

Finally, prevalence surveys provide a means to examine the usage of health care and the quality of care at the population level rather than in selected clinic populations. Identification of barriers to and determinants of good asthma care in turn enable the design of interventions which may reach all sectors of a population.

This prevalence research programme has stimulated the search for a standard method to study differences in childhood asthma occurence between populations and, in the longer term, to examine secular trends in the disease. Although an objective test of bronchial hyperresponsiveness may be desirable in a survey of asthma prevalence (Toell 1992), questionnaire studies remain the mainstay of population based asthma epidemiology (Burr 1992). Recent efforts have thus been devoted to the development of standard questions to measure the prevalence and severity of childhood asthma (ISAAC Coordinating Committee 1992, Pearce 1993, Burr 1994) and to the measurement of the reliability and validity of these survey instruments (Shaw 1992a, 1992b, 1995).

The primary objective of the study reported in this chapter was to determine the prevalence of asthma and asthma-like symptoms in a population of Cape Town primary school children. The study design enabled also the examination of the of repeatability ("reliability") of parental reports of asthma symptoms between a self-administered and

interviewer administered questionnaire a few weeks apart. The questionnaire used in this study was based closely on one being developed at the time for use in the International Study of Asthma and Allergy in Childhood (ISAAC) (ISAAC Coordinating Committee 1992). However, the study was not itself part of the ISAAC project.

5.2. Methods

5.2.1. Self administered questionnaire

The overall sampling strategy has been described in section 4.4. The final study group consisted of a random sample of 15 schools chosen from the 35 primary schools in Mitchell's Plain, Cape Town. Questionnaires, in English or Afrikaans depending on the medium of instruction of the child, were distributed in July 1993 (winter) to teachers and sent via the children to the parents of all 2 265 sub-B children (second grade, typically aged 7 to 8 years) on the class lists of the sample schools.

The project was advertised as a survey of breathing problems in children. The Afrikaans translation was refined by discussing the questions with Afrikaans-speaking health care professionals working in this community, and by asking parents of asthmatic children attending an allergy clinic to describe their children's symptoms.

Over 8 schooldays, the children were encouraged to have their parents return the questionnaires. The English version of the questionnaire is presented in **Appendix 1**. Symptom questions referred either to the previous 12 months, or to occurrence ever. Asthma refers to *asthma ever*, with no reference to a doctor's diagnosis.

5.2.2. Home interviews

A subsample of 662 children was chosen whose parents answered the self-administered questionnaire and gave consent for further participation. Selection of the subsample was determined by the design of risk factor phase of the project (see section 6.2.), and included children with multiple symptoms of asthma, or with the diagnosis of asthma (n = 368) and a random 21.5 percent sample of children with few or no symptoms (n = 294).

The parents of children in the subsample who lived within the study area were visited by five bilingual interviewers between six weeks and three months after the self-completed questionnaires were returned. These visits took place in the spring months September to November, 1993.

In the longer questionnaire used in the home interview, all of the asthma and symptom questions in the self-administered questionnaire were repeated in the same order. The English version of the questionnaire is included as **Appendix 2**.

The interviewers were trained by group demonstration, and by conducting interviews in a one week pilot study with report-back sessions. In addition, a sample of six households per interviewer were telephoned by the field manager four to twelve weeks after the interview and six selected questions (from all sections of the interview questionnaire) repeated. There was high concordance (93.8%; 95% confidence interval 90%-97%) between the interview and telephone responses.

5.2.3. Statistical methods

Symptom prevalences on the self-completed questionnaire were analysed by respondent, age, sex and language. Prevalences based on the interview data were calculated taking into account sampling fractions. The effect of cluster sampling by school was found to be minor, and no adjustment was made. The responses to the questions on asthma and asthma treatment were compared to responses to the wheeze questions. Differences were evaluated statistically by chi-squared tests. Agreement between responses to the two questionnaires was expressed as percent concordance or observed agreement (P_0: concordant responses/total responses), and by the kappa statistic (chance corrected agreement)(Landis 1977).

5.3. Results

5.3.1. Self-administered questionnaire

Of 2 265 children on the February class lists, 2 172 were still registered at the school at the start of the study in July. Seven children were absent during the entire week in which

the questionnaire was handed out. A total of 1 955 questionnaires were returned, a response rate of 90.0%.

The sample was equally distributed by sex. Of the 90% of children for whom ages were given, 46.5% were 7 years of age, 33.5% were 8 years, 8% 9 years of age, the remainder being outside this range **(Table 5.1)**. Afrikaans was the medium of instruction for 55% of children, and English for 45%. The mother alone was marked as the respondent in most cases (71%), followed by the father alone (14%), mother and father together (7%), grandmother (5%) and other (3%).

Table 5.1 Characteristics of prevalence study sample (n = 1955)*

		n	%
Age (years)	6	11	0.6
	7	909	46.5
	8	654	33.5
	9	152	7.8
	10	29	1.5
	11-13	4	0.3
	Unknown	196	10.0
Sex	Male	951	48.6
	Female	971	49.7
	Unknown	43	1.7
Language**	Afrikaans	1075	55.0
	English	880	45.0

* Based on self-administered questionnaire
** Based on medium of instruction

Symptom prevalences based on the self-administered questionnaire are listed in **Table 5.2**. Of note was that 26.8% of respondents reported recent wheeze in the child, and 6.4% reported four or more attacks of wheeze in the previous 12 months. Asthma (ever) was reported by 10.8% of the sample.

Table 5.2 Prevalence of asthma symptoms by type of questionnaire

	Self-administered questionnaire			Interviewer-administered questionnaire		
	Total respondents	Prevalence (%)	95 % C.I.	Total respondents	Prevalence (%)	95 % C.I.
Past 12 months						
Wheeze	1899	26.8	(24.8-28.8)	619	34.4	(30.5-38.3)
Wheeze frequency (≥4 episodes)	1825	6.4	(5.3-7.6)	618	10.2	(8.0-12.4)
Sleep disturbance by wheeze (any)	1856	20.4	(19.0-22.8)	614	22.9	(19.8-26.0)
Speech disturbance by wheeze	1881	9.3	(8.0-10.7)	614	10.4	(8.4-12.4)
Wheeze after Exercise	1884	20.0	(18.2-21.9)	620	16.7	(14.2-19.2)
Night cough	1883	25.4	(23.5-27.5)	619	26.9	(23.2-30.6)
Tight chest	1885	23.9	(22.0-25.9)	618	21.9	(18.8-25.0)
Wheeze ever	1896	30.3	(28.2-32.4)	620	41.7	(37.2-46.2)
Asthma ever	1905	10.8	(9.5-7.8)	619	10.6	(8.8-12.4)
On regular asthma Treatment	1895	6.6	(5.5-7.8)	–	–	–

C.I. : Confidence interval

Boys had a slightly higher prevalence than girls of most symptoms, but only the excess in wheeze ever (32.6% vs. 28.2%, p = 0.03) and asthma (12.2% vs. 9.5%, p = 0.06) attained or approached statistical significance.

There was no difference in asthma or recent wheezing by language group. There was a small excess of some recent symptoms in the Afrikaans group compared to the English group: sleep disturbance (22.7% vs. 17.5%, p = 0.04), speech disturbance (10.6% vs. 7.5%, p=0.03) and night cough (27.4% vs. 23.0%, p=0.03).

There were consistent and significant differences in symptom prevalences reported by different respondents (**Table 5.3**). A joint response by mother and father gave the highest prevalences, with mother and grandmother separately reporting somewhat lower prevalences, and father alone the lowest.

Table 5.3 Prevalence of asthma symptoms as reported by different respondents (n=1955)

	Mother and father (n=130)	Mother (n=1363)	Grandmother (n=97)	Father (n=271)
Past 12 months				
Wheeze	28.6	27.3	27.4	24.3
Wheeze frequency (≥4 episodes)	7.1	6.6	5.5	4.7
Sleep disturbance by wheeze (any)	24.4	21.5	18.7	16.9
Speech disturbance by wheeze	17.2	9.4	10.8	3.8
Wheeze after exercise	24.2	20.7	20.2	13.4
Night cough	31.3	26.6	22.8	18.2
Tight chest	26.4	24.9	21.1	20.2
Wheeze ever	28.9	32.4	25.3	24.9
Asthma ever	15.5	10.8	10.3	10.0
On regular asthma treatment	11.8	6.7	4.1	5.9

5.3.2. Relationship of reported asthma to wheeze and treatment

The proportion reporting asthma rose with the number of episodes of wheezing in the previous 12 months **(Table 5.4)**. However, even among children with more than twelve attacks of wheeze in the previous 12 months, only 18 of 30 (60%) were reported as having asthma, and only 16 of 29 (55%) as being on regular treatment. Similarly, among children reported as having recently had all six of the separate symptoms described in the questionnaire, only 47% were reported as asthmatic and 39% as being on regular treatment (data not shown).

Table 5.4 Reported asthma by wheeze frequency (n=1955)

Episodes of wheeze (past 12 months)	n	Reported asthma	(%)
0	1354	53	(3.9)
1 - 3	347	87	(25.0)
4 - 12	86	36	(41.8)
> 12	30	18	(60.0)*

*P< 0.0001 for trend

The likelihood of regular treatment for a given wheeze frequency was strongly influenced by whether asthma was reported by the respondent (**Table 5.5**). Among those children with more than twelve wheezing episodes, the proportion on regular treatment rose to 72% if asthma was also reported, compared to 27% if it was not.

5.3.3. Interviewer administered questionnaire

Of the total of 1 955 returned self-administered questionnaires, 22 lacked usable information, 83 were used in a pilot study of the interviews, and 114 parents did not give consent to be interviewed. Of the remaining total of 1 736, a subsample of 662 was chosen as described above. Of these, 29 lived outside the study area, leaving 633 eligible subjects. Six of these subjects changed their consent, 6 could not be interviewed and one interview was incomplete. A total of 620 interviews (97.9% of eligible) were thus successfully completed.

Table 5.5 Regular asthma treatment by wheeze frequency and reported asthma (n=1955)

	On regular treatment	
Episodes of wheezing in past 12 months	Asthma ever	
	No	Yes
0	1.1 %	26.4 %*
1 – 3	4.2 %	37.2 %*
4 – 12	10.4 %	74.2 %*
> 12	27.2 %	72.2 %*

*$P<0.05$ for difference between yes and no groups

5.3.3. Interviewer administered questionnaire

Of the total of 1 955 returned self-administered questionnaires, 22 lacked usable information, 83 were used in a pilot study of the interviews, and 114 parents did not give consent to be interviewed. Of the remaining total of 1 736, a subsample of 662 was chosen as described above. Of these, 29 lived outside the study area, leaving 633 eligible subjects. Six of these subjects changed their consent, 6 could not be interviewed and one interview was incomplete. A total of 620 interviews (97.9% of eligible) were thus successfully completed.

5.3.4. Reliability

The repeatability of responses between the self-administered and interviewer administered questionnaires is shown in **Table 5.6**. Observed agreement ranged

between about 70 and 80 percent, except for the question on asthma for which observed agreement was closer to 90 percent. Chance corrected repeatability (kappa) showed greater variation, however, ranging from "fair" (Landis 1997) (0.21 to 0.40) to "substantial" (0.61 to 0.80). The questions about asthma, recent wheeze and recent sleep disturbance were the most reliable, while those inquiring about recent wheeze frequency, speech disturbance and night cough, and about wheeze ever, were less reliable.

Table 5.6 Reliability of responses* between of self-administered versus interviewer-administered questionnaire (by all respondents and by mother)

	All (n=620)		Mother respondent on both occasions (n=394)	
	Proportion observed agreement (Po)	kappa	Po	kappa
Asthma ever	0.89 (0.86-0.91)	0.70 (0.64-0.76)	0.90 (0.87-0.93)	0.72 (0.64-0.80)
Wheeze	0.80 (0.77-0.83)	0.59 (0.53-0.65)	0.83 (0.79-0.86)	0.65 (0.57-0.73)
Sleep disturbance by wheeze	0.78 (0.74-0.81)	0.56 (0.50-0.62)	0.81 (0.77-0.85)	0.62 (0.54-0.70)
Tight chest	0.73 (0.69-0.76)	0.46 (0.40-0.50)	0.77 (0.73-0.82)	0.55 (0.47-0.63)
Wheeze after exercise	0.72 (0.80-0.86)	0.44 (0.36-0.52)	0.76 (0.71-0.80)	0.51 (0.43-0.59)
Wheeze frequency (≥4 episodes)	0.83 (0.80-0.86)	0.44 (0.34-0.54)	0.82 (0.78-0.86)	0.44 (0.32-0.56)
Wheeze ever	0.71 (0.68-0.75)	0.42 (0.34-0.50)	0.71 (0.67-0.76)	0.42 (0.32-0.52)
Night cough	0.68 (0.65-0.72)	0.37 (0.29-0.45)	0.70 (0.66-0.75)	0.41 (0.31-0.51)
Speech disturbance by wheeze (any)	0.76 (0.73-0.79)	0.33 (0.25-0.41)	0.76 (0.72-0.80)	0.37 (0.27-0.47)

* Previous 12 months unless otherwise specified

Reliability was only slightly greater when the mother was the respondent on both occasions than for the whole group (**Table 5.6**). Numbers were too small to calculate the kappa statistic separately for classes of respondent other than the mother.

Calculated symptom prevalences (i.e. weighted by sampling fractions) based on the interview responses are shown in **Table 5.2**. For some of the questions, viz. sleep disturbance, speech disturbance, night cough, tight chest, and asthma, the prevalences found by the two questionnaires were close. For recent wheeze, wheeze frequency ($\geq$ 4 episodes) and wheeze ever, the interviewer administered questionnaire produced significantly higher prevalences.

5.3.5 Selection bias

Possible selection effects, in choosing the subsample for home interviews from a smaller group of parents (n = 1 736) than the group who returned the self-administered questionnaire (n = 1 955), were examined (see section 5.3.3.). After correction for the sampling fractions, there was no significant difference in responses to the self-administered questionnaire between the subsample (n = 662) and the original respondent group (n = 1 955).

5.4. Discussion

Information based on parental recall of symptoms or diagnoses in children is subject to inaccuracy or error resulting in misclassification. Ideally, the extent of such misclassification would be measured against a "gold standard" . However, there is no gold standard for asthma in epidemiologic studies, nor any easy way of independently verifying parental reports in such studies.

An alternative way of evaluating measurement error is to assess repeatability or reliability, which was estimated in this study by comparing responses in approximately one third of the self-administered questionnaires to those of an interviewer administered questionnaire. Kelsey (1986) has argued that reliability is easiest to interpret when low - in such

cases it can be inferred that accuracy is poor as well. By contrast, high reliability does not necessarily imply high accuracy if there are similar errors (e.g. underreporting) in both sets of measurements. Nevertheless, it is reasonable to have more confidence in those questions (e.g. asthma or recent wheeze) with relatively good reliability than those (e.g night cough) that showed poor reliability. This is especially so as the two instruments were somewhat different and applied with a time interval between them of a few weeks to months.

The impact of misclassification resulting from measurement error on the estimates of prevalence obtained (i.e. a binary outcome measure) is difficult to predict. Assuming the error is random (i.e. misclassification is as likely in either direction), the prevalence estimate will remain unbiased although the confidence interval may be widened. In this study, the symptom prevalences derived from the two questionnaires were close. Notably, the prevalence of asthma remained the same. Although wheeze prevalences (recent, frequent recent and ever) were significantly higher in the interview, the interpretation for public health purposes is the same on either questionnaire.

Other studies have examined the repeatability of asthma symptom reports by parents. Peat (1992) in a study of children aged 8 to 10 years of age in Sydney, also followed a self-administered questionnaire with a home interview. Findings regarding recent symptoms were similar to those found in this study: "substantial" repeatability for wheeze (kappa 0.65), and "fair" for post-exercise wheeze (kappa 0.41) and night cough (kappa 0.41). Their question about wheeze ever (kappa 0.67) showed somewhat greater repeatability than in this study, as did asthma referring to a doctor or hospital diagnosis (kappa 0.78).

Studies which have compared responses to repeated self-administered questionnaires (Salome 1987, Clifford 1989, Luyt 1993) have found questions concerning wheeze (ever or recent) to be more repeatable than in this study.

There are a number of possible reasons for the incomplete agreement between

responses to the first and second questionnaire, even with the same respondent. First, the mode of administration was different. In particular, a personal interview may elicit different responses from a self-administered questionnaire, perhaps because of more considered answers by the respondent or interviewer pressure. Second, parental recall is likely to fade with the passage of time so that recent experience is more vivid. Where there is seasonality in symptoms, prevalences will vary through the year. In this population, asthma hospital admissions peak in May (autumn) and November (early summer) (Ehrlich 1994). The interviews thus overlapped with a seasonal rise in asthma severity, and this may have contributed to higher wheezing prevalences in the second round of questioning.

A third possibility is that responses to the second questionnaire were influenced by having completed the first questionnaire, which could have increased awareness of these symptoms. Finally, some parents whose home language was different from the language of school instruction of their child may have switched languages between the self-administered questionnaire and the interview. Different connotations of terms such as asthma and wheeze in the two languages might have caused a change in response in some cases.

Reported prevalence was influenced also by the respondent's relationship to the child. Lower rates of reporting of symptoms in children by fathers have been found elsewhere - (Clifford 1989, Schenker 1983). Mothers are likely to spend more time with the children and to be more involved with any ill-health, during the day or night. Theirs may thus be the more accurate perception. The higher rates reported when both parents are marked as respondents confirm a similar finding elsewhere (Clifford 1989) and may represent a pooling of the recall of the two parents.

There are a few comparable South African studies, all from Cape Town. In a 1989 study of higher socioeconomic status (white) school pupils (aged 12 years) in Cape Town, 17.8 percent were reported by parents with recent wheeze, considerably less than in this study (Burr 1994). A similar figure to this (16.1%) was found in the Cape Town ISAAC study of

school pupils aged 13 to 14 years, covering the whole socioeconomic spectrum and reporting on their own symptoms (ISAAC Steering Committee 1998). The children in those studies were older than in the current study; however, studies elsewhere have shown relatively little difference in recent wheeze between children aged 7 and 11 years (Robertson 1991, 1993).

In contrast to the wheeze discrepancy, reported asthma in the above studies, viz. 11.5 percent (Burr 1994) and 13.1 percent (ISAAC Steering Committee 1998) were closer to the prevalence found in the current study. These findings regarding asthma prevalence are higher than those from a 1987/8 Cape Town study of schoolchildren of mean age 13 years (range 6 to 20 years), in which a history of doctor diagnosed asthma was reported in only 4 percent of coloured schoolchildren compared to 9 percent in white schoolchildren (Terblanche 1990). One explanation for the discrepant findings in the latter study might be that reference to a doctor's diagnosis in the question about asthma lowers the reported prevalence, the more so in a lower socioeconomic status population.

For international comparison, recent surveys of similarly aged school children (particularly 6 to 10 years) which used equivalently worded questions were examined (**Table 5.7**). The question regarding wheeze in the past 12 months was common to a number of studies. Asthma was linked to a doctor's diagnosis in some of the studies. Both asthma ever (independently of a doctor's diagnosis) and doctor diagnosed asthma are presented for comparison.

The prevalence of recent wheeze in Cape Town (26.8 percent on the self-administered questionnaire) is at the high end of the range, comparable to that reported in Australia and Chile (Robertson 1991, 1993). The prevalence of reported asthma (doctor diagnosed or not) shows less variation, with this study towards the lower end of the range.

The larger discrepancy in our study between wheeze and asthma than in most other studies (including Burr's Cape Town study [1994]) could be explained by overreporting of wheeze, underreporting of asthma or underdiagnosis of asthma in this study.

Table 5.7 International comparison of prevalence of reported wheeze and asthma in young schoolchildren (aged approx. 6 to 10 years)

Year of study	Reference	Location	Ages (years)	Wheeze (previous 12 months) %	Asthma ever* %
1993	This study	Cape Town, South Africa • Self-administered • Interviewer	7-9	 26.8 34.4	 10.8 10.6
1992	Peat 1994	• Belmont, Australia • Wagga-wagga, Australia	8-10 8-10	27.6 23.1	(37.7) (29.7)
1990	Robertson 1991,1993	Melbourne, Australia La Serena, Chile	7 7	23.1 26.2	24.1 9.4
1992	Strachan 1994	Great Britain	5-7 8-10	16.7 15.9	(12.8) (12.6)
1985	Asher 1988	Auckland, New Zealand	8-10	14.8	(14.2)
?	Nystad 1997	Norway, 4 cities	6-8	11.0-15.3 (range)	
1996	Ronmark 1998	Northern Sweden	7-8	11.7	(5.7)
1995	Ones 1997	Istanbul, Turkey	6-12	8.2	(9.8)
1994	Sekuk 1997	Edirne, Turkey	7	7.7	(18.3)
1994-1995	SIDRIA 1997	Northern, central Italy	6-7	7.7	9.0
1990	Robertson 1993	St Gallen, Switzerland	7	7.3	4.3
?	Veale 1996	Rural Australia (Aboriginal communities)	8-12	1.9	

*Doctor diagnosed asthma in parentheses

Overreporting of wheeze is a possibility. A higher proportion of recent wheezing (75.2 percent) in this study fell into the "infrequent" category (1 to 3 episodes, as opposed to 4 or more episodes) than in recent studies in Melbourne (Robertson 1993) or Great Britain (Strachan 1994). Parents in our population might thus be more inclined to report

occasional wheezing than elsewhere.

Underreporting of diagnosed asthma is unlikely as an important cause of low asthma prevalence. This is confirmed by the close association in this study between the reporting of asthma and regular asthma treatment (**Table 5.4**).

A more likely explanation for the wide wheeze-asthma discrepancy is that access to accurate medical diagnosis is relatively poor in this population. Among children with four or more episodes of recent wheeze, only 46.5% were reported by their parents as having asthma. This is similar to the findings of Bauman (1992) in south-western Sydney, where 61 percent of children with at least three episodes of cough and wheeze in the previous 12 months had been labelled as asthmatic. Another marker of severity in this population was wheeze severe enough to interfere with speech (9.3 percent). Even among these children, asthma was reported in only 38.5 percent.

Underdiagnosis renders accepted treatment regimens and education of parents about allergen reduction and avoidance less likely, and in turn may contribute to high symptom prevalences (Anderson 1983). In this study, children with the combination of the label asthma and frequent wheezing were much more likely to be on regular asthma treatment, than frequent wheezers not reported as having asthma (**Table 5.4**). This theme is examined in more detail in Chapter 8.

There are, however, plausible environmental causes of a high underlying prevalence of wheeze in this group. These factors include close proximity to the coast and climatic conditions conducive to housedust mite proliferation (Ordman 1971, Manjra 1994). Housedust mite has been shown to be the most prevalent type of immediate skin prick reactivity among asthmatic children in Cape Town (Van Niekerk 1977, Potter 1991).

Smoking prevalence among women is as high as 41 percent in the population of which this area is a part, with a quarter of women smoking more than 10 cigarettes daily (Steyn 1987). In view of the association between maternal smoking and childhood wheezing and

asthma (reviewed in Chapter 3 and investigated in Chapter 6), such smoking may be a further cause of the high prevalence of asthma symptoms. The popularity of softdrinks and foodstuffs preserved with sulphites, which may be potent triggers of bronchospasm, may play some role in increasing symptoms in susceptible individuals (Steinman 1993). It has also been suggested that infestation with *Ascaris lumbricoides*, an intestinal parasite common in this population, may contribute to the induction or severity of asthma by enhancing immune reactivity to a range of aeroallergens (Joubert 1980).

In conclusion, the findings of this study support the recent advice (Peat 1992) that some caution is needed in the interpretation of a single prevalence survey of childhood respiratory symptoms. This applies particularly to questions designed to assess wheeze severity, situational wheeze and nocturnal cough. Variation of reported symptoms by mode of administration and the respondent's relationship to child could add to the imprecision of prevalences. However, the high wheeze prevalences reported in both questionnaires in this study, and the relatively low frequency of recognition of asthma, confirm that asthma and underdiagnosis are public health problems in this population of some magnitude.

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CHAPTER 6

RISK FACTORS FOR CHILDHOOD ASTHMA AND WHEEZING: IMPORTANCE OF MATERNAL AND HOUSEHOLD SMOKING

6.1. Background and study objectives

Among the environmental causes of childhood asthma and wheezing, household factors contributing to their occurence or severity merit particular attention, since their identification might allow focused preventive strategies. Such household factors include indoor allergens (Sporik 1990, Jones 1998) and environmental tobacco smoke (ETS) (see Chapter 3) and less consistently, damp and mould (Verhoeff 1995, Brunekreef 1989, Dijkstra 1990, Williamson 1997) and oxides of nitrogen (Dijkstra 1990, Infante-Rivard 1993). An association between salt intake, another potentially modifiable risk factor at the household level, and asthma or bronchial hyperresponsiveness (BHR) has also been suggested (Burney 1986, 1987, 1989, Pistelli 1993).

The findings in Chapter 5 established that sub-B schoolchildren in Mitchell's Plain, Cape Town, have a high prevalence of wheezing with probable underdiagnosis of asthma. Features which may contribute to the risk of asthma or wheezing in this population include a climate conducive to house dust mite proliferation (Van Niekerk 1977), and a high prevalence of cigarette smoking among men and women (Steyn 1987, 1997, Reddy 1996) including a high prevalence of maternal smoking in pregnancy (Steyn 1997). Of these, ETS is the factor more amenable to public health intervention given current knowledge.

The objective of this phase of the study was to measure the association between household risk factors, particularly ETS exposure, and current asthma or wheezing. For this purpose a prevalence case control design embedded in the previously described prevalence survey was used. Because of the problem of underdiagnosis, the case definition included children with wheezing and related symptoms with or without a reported diagnosis of asthma.

To strengthen the study, urinary cotinine, an objective measure of current ETS exposure, was measured in the children.

6.2. Method

6.2.1. Selection of cases and controls on self-administered questionnaire

Cases and controls were selected from the prevalence survey described in chapter 5 (see also section 4.4.2. and **Fig. 4.2**). In summary, two groups were chosen from the 1 736 children available after the pilot study subjects and non-responding subjects had been withdrawn from the sampling frame. The "current asthma/wheeze" case group (n = 368) was defined as those children with (1) parent reported asthma, plus at least one symptom in the past 12 months (n = 162), or, (2) in the absence of reported asthma, affirmative responses to four or more symptom questions referring to the past 12 months (n = 206). This resulted in a score on a scale of 0 to 10 (**Table 6.1**). Case status was based on a score of 4 or more.

The control group consisted of a random sample of children with few or no symptoms drawn from the remaining children (n = 294, 21.5% of potential controls).

6.2.2. Definition of risk factors and covariates on interview administered questionnaire

The parents of cases and controls were interviewed between six weeks and three months after the self-completed questionnaires were returned. In the longer questionnaire used in the home interview, the asthma symptom questions were repeated, and further

information sought on: sociodemographic features; the child's medical history; household smoking; breastfeeding; household factors such as pets, energy/fuel use, visible damp and mould; dietary salt preference; family history of asthma; and the respondent's history of recent chest illness (**Table 6.2**).

Table 6.1 Questions and scores (in parentheses) used in questionnaires as basis of case definition (maximum score = 10)

1. Has your child had wheezing or whistling in the chest in the last 12 months?

   If yes: 1.1. How many attacks of wheezing or whistling has your child had in the last 12 months?

   1-3 (**1**) 4-12 (**2**) more than 12 (**2**)

2. In the last 12 months, how often, on average, has your child woken up due to chest wheezing or whistling?

   never (**0**) not every week (**1**) every week (**1**)

3. In the last 12 months, has wheezing or whistling in the chest ever been so bad that your child couldn't talk properly or had to whisper? (**1**)

4. In the last 12 months, has your child's chest every sounded wheezy or whistly, during or after running or playing hard? (**1**)

5. In the last 12 months, has the child had a troublesome dry cough in the night that was not from a cold or chest infection? (**1**)

6 In the last 12 months, has the child had a tight chest ? (**1**)

7. Has your child ever had asthma? (**3**)

Table 6.2 Variables tested as predictors of asthma/wheeze

Personal
- Sex.
- Birthplace.
- Birth month.

Socioeconomic
- Medical insurance.
- Number of persons/children in child's bedroom.
- Number of rooms in house.
- Mother's education/occupational status.
- Male parent's education/occupational status/presence.
- Male parent contributes to family income.
- School: low, medium or high socioeconomic status.

Child's history
- Eczema ever.
- Hayfever ever.
- Breastfed.
- Tonsils removed.

Family history of asthma
- Mother.
- Father.
- Sibling.

Environmental/dietary exposures
- *Damp and mould
- *Dietary salt preference,
- Cooking/heating energy source.
- Pets (cat or dog).

*Smoking exposures
- Mother's smoking: ever; pregnancy; current; first year of child's life; current daily consumption.
- Male parent's smoking: ever; first year of child's life; current; current daily consumption.
- Number of other people smoking in house.
- Smoking in child's bedroom.
- Urinary cotinine concentration.

Respondent
- Mother as respondent.
- Recent chest illness or symptoms (wheeze, tight chest, coughing up phlegm or chest illness in past 12 months).
- Time spent at home during week.

* Of *a priori* interest.

The questions used to define dietary salt preference and household damp are reproduced in **Table 6.3**. Based on analysis of results from the pilot study, positive "salt preference" was defined as a positive response to the highest category in any of the salt questions, and entered as a single variable into the analysis. Answers to the damp/mould questions (with each room represented in a separate question) were analysed as separate variables.

Table 6.3 Questions on which variables *household damp* and *salt preference* were defined

Damp

1. Within the past year has there ever been wet or damp spots on surfaces inside the child's present home (e.g. walls, ceiling, carpets)? (Yes/no/don't know).

2. Have you ever noticed mould or mildew growing on any surface (walls, ceiling, carpets)? (In the child's bedroom/in the living room/in the kitchen/in the bathroom/in any other inside area of the child's home: Yes/No).

3. Has there been a leak, flooding or water damage in the child's home in the past year? (Yes/no/don't know)

Salt preference

1. When food is cooked for the family, how much salt (Aromat/Fondor) is added? (2 or more teaspoons/1 teaspoon/just a pinch or one shake/none/don't know).

2. Does the child (or anyone else) add extra salt or Aromat/Fondor to the food the child eats? (No, no extra salt or Aromat/Fondor is added/yes, but the child's food is tasted first before adding/yes, even before the food is tasted/don't know).

3. How often did the child eat salty snacks during the last week (i.e. chips, niknaks, salted peanuts, salty biscuits, biltong, dried sausage)? (Never/1-2 times/3 or more times/don't know).

4. How often did the child eat cold meats (polony, viennas) during the last week? (Never/1-2 times/3 or more times/don't know).

6.2.3. Urinary cotinine

Urinary cotinine is a specific metabolite of nicotine with a half life of approximately 20 to 40 hours, and is a validated marker of exposure to environmental tobacco smoke (U.S. Environmental Protection Agency 1992; see also section 3.5.1.1.).

In parallel with the home visits, a specimen of urine was collected from the children at school. These were frozen on the day of collection to minus 20^0C. and later analysed by radioimmunoassay, adapted from a method by Knight (1985). This method uses polyclonal rabbit antiserum, I^{125} labelled cotinine, with cotinine added to horse serum as a standard. The method has a detection sensitivity of 5 ng/ml, and an inter-assay precision of < 10%. Quality control was exercised by measuring known standards from the supplying laboratory. To allow standardisation for varying diuresis, urinary creatinine was measured by the Jaffe reaction on a Beckman CX5 discrete analyser.

6.2.4. Statistical analysis

As the design effect of sampling schools rather than individuals was found to be small, no adjustment for this effect was made. Bivariate analysis was carried out to identify potentially significant risk factors or confounders of asthma/ wheeze. Odds ratios and confidence intervals were estimated for categorical variables using one of the levels of that variable as the reference group. For continuous variables, the odds ratio is used as a "summary" measure of effect referring to a unit increment in that variable.

The use of prevalence odds ratios rather than prevalence ratios to estimate the "relative risk" in aetiologic studies based on prevalent cases has been the subject of debate (Lee 1993, Stromberg 1995, Thompson 1998). Thompson (1998) has recently examined how the relationships between the prevalence odds ratio (POR), prevalence ratio (PR) and incidence rate ratio (IRR) vary for a hypothetical dynamic cohort under varying parametric assumptions.

Examination of the outcomes using values from Thompson's model (Thompson 1998)

closest to those likely in the cohort under study here reveals minimal difference between the various measures of effect. For example, assume an underlying IRR of asthma of 1.5 (incidence rates in exposed and unexposed respectively = 0.03 and 0.02) and "recovery" rates = 0.01 and 0.005 respectively). Given either a 5 year follow up (resulting prevalence 5%) or 10 year follow up (resulting prevalence 21%), the prevalence odds ratio would be 1.5, equal to the IRR and little different from the prevalence ratio of 1.4. Only with a much higher assumed incidence rate ratio [e.g. IRR= 5], would the prevalence odds ratio produces an overestimate (5.4) of the IRR.

Variables entered into the multivariate logistic model included all those of *a priori* interest, plus those identified as significant in bivariate analysis. The final model was refined with the help of stepwise regression with an entry p-value of 0.1, with the requirement that it contain at least one variable (each) reflecting smoking, damp and salt preference. Effect modification was examined by inclusion of interaction terms in the final model on the basis of *a priori* hypotheses, and effects were reported separately where significant.

The urinary cotinine creatinine ratio (CCR) was used (1) to examine the association between cotinine and covariates such as age, sex and number of household smokers, and (2) to define strata of cotinine for use as a categorical variable, including a cut-off above which CCR might reflect active as well as passive smoking. In multivariate regression analysis, log cotinine and creatinine were entered separately as continuous variables.

6.3. Results

6.3.1. Features of study group

Of the 662 children chosen for home interviews, 29 did not live in the study area and were excluded. Of the remaining 633 children, 620 home interviews were successfully concluded (348 cases and 272 controls), a response rate of 97.9%. Urine specimens were available for analysis in 576 of the interviewed sample.

In this phase of the study, boys comprised 51.2% of the sample. Of the children, 50.4% were 7 years of age, 37.6% 8 years, 8.1% 9 years, and the remaining 3.9% outside this range. The mother was identified as the respondent in most cases (79.7%), followed by grandmother (9.3%), father (6.0%) and other (5.0%).

There was no difference in age between cases and controls (both 7.6 years), nor in sex distribution (cases: 52.6% male, controls 50.2% male). **Table 6.4.** illustrates the symptom prevalences among cases, controls, and potential controls not sampled. The control group selected was representative of all potential controls.

Table 6.4 Symptoms and asthma prevalence* in cases, controls and remainder of potential sample (n=1736)

	Cases (n=348)** %	Controls (n=272) %	Remainder of potential sample (n=1093) %
Wheeze	94.5	10.5	10.9
Wheeze frequency ≥ 4	30.2	0.4	0.0
Sleep disturbed by wheeze	86.1	2.8	5.0
Speech disturbed by wheeze	42.4	1.5	0.7
Wheeze on exercise	80.2	6.7	5.5
Tight chest	86.7	9.0	8.4
Cough at night	81.4	12.5	12.4
Asthma ever	44.1	2.2	2.0
On regular asthma treatment	26.1.	1.5	1.5

*Past 12 months unless otherwise specified

**Excludes 20 cases not successfully interviewed

6.3.2 Bivariate associations

Tables 6.5 and 6.6 compare cases and controls with respect to a range of sociodemographic, medical history and environmental exposure variables. Household occupancy of more than 6 persons (against 6 or fewer) and lack of paternal contribution to income were the socioeconomic indicators associated with current asthma/wheeze. Of the medical history variables, eczema, hayfever, a paternal, maternal or sibling history of asthma, and recent chest illness in the respondent were significantly associated with current asthma/wheeze.

Among the environmental exposure factors, visible mould in the child's bedroom, all the maternal smoking measures, the number of current household smokers, and CCR were associated with current asthma/wheeze. Paternal smoking, pet ownership (cat or dog), energy/fuel source (i.e. paraffin or gas against electricity), and salt preference showed no significant association.

Table 6.5 Association of sociodemographic and medical history variables with current asthma/wheeze (n=620) *

Variable	Cases (n=348) %	Controls (n=272) %	Odds ratio	95% confidence interval
Socioeconomic				
Maternal education < 8 years	59.7	58.1	1.07	0.77 - 1.17
Father not formally employed	61.7	56.5	1.25	0.80 - 1.72
Paternal education < 8 years	60.5	57.8	1.12	0.81 -1.55
No paternal contribution to income **	38.9	30.6	1.44	1.03 - 2.03
>6 people in house	46.7	38.4	1.41	1.02 - 1.94
>3 children in house	33.3	30.9	1.12	0.80 - 1.57
>2 people share child's bedroom	52.0	48.2	1.17	0.85 - 1.60
<4 rooms in house	19.8	22.4	0.86	0.58 - 1.26
Child's history				
Eczema	25.6	12.6	2.40	1.55 - 3.69
Hayfever	33.5	8.2	5.69	3.48 - 9.28
Never breast-fed	12.6	15.7	0.78	0.49 - 1.22
Family history asthma				
Father	10.8	5.4	2.11	1.11 - 3.99
Mother	16.4	8.7	2.07	1.24 - 3.46
Sibling	20.9	12.2	1.90	1.22 - 2.97
Respondent				
Mother respondent	80.0	79.3	1.04	0.70 - 1.55
Recent chest illness	54.5	45.2	1.45	1.05 - 2.00

*See Table 6.2 for full list of variables tested
**Includes absence of male parent

Table 6.6 Association of enviromental exposure variables* with current asthma/wheeze (n=620) *

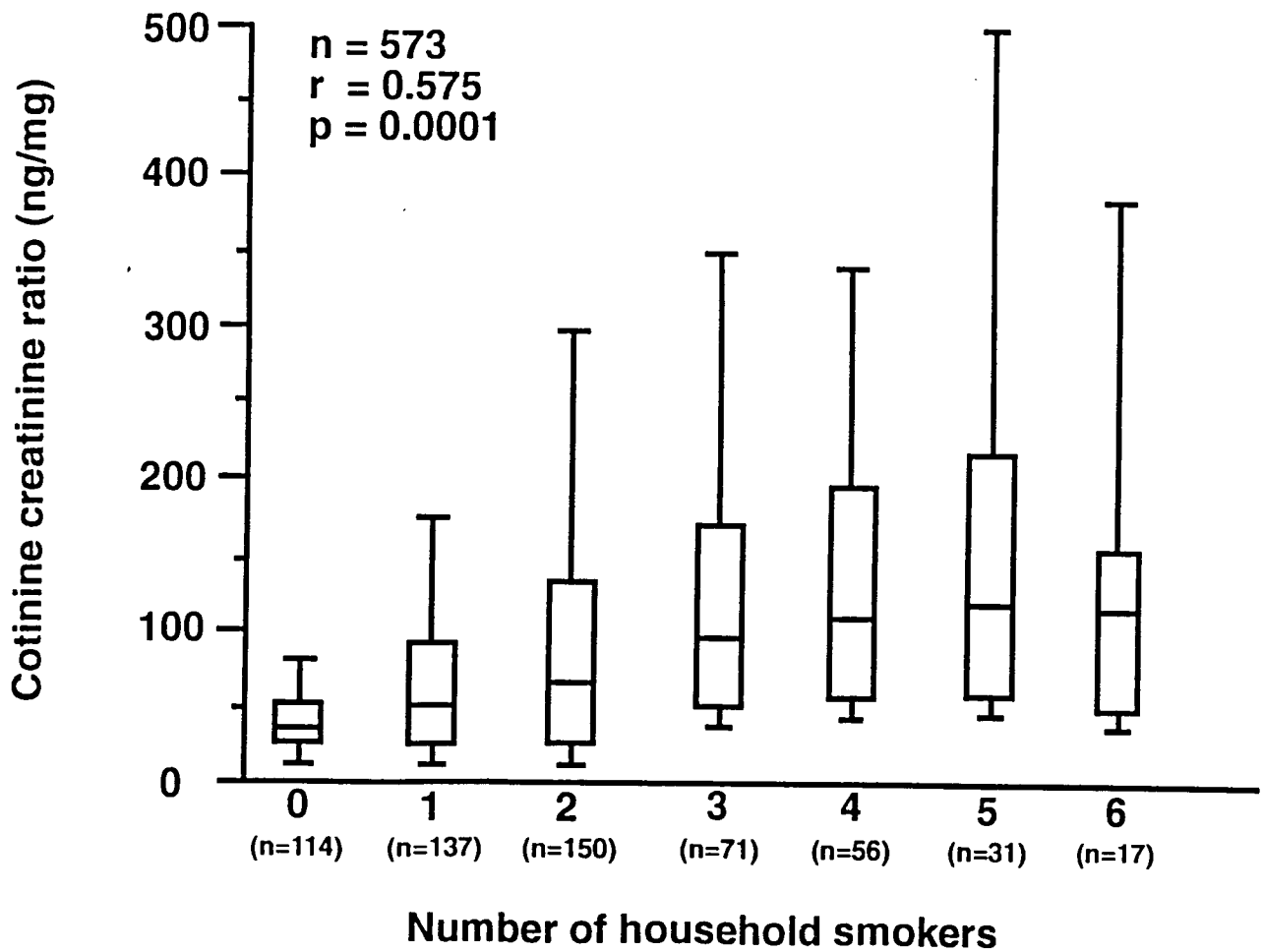
Variable		N	Cases (n=348) %	Controls (n=272) %	Odds ratio	95% confidence interval
Mould in child's bedroom			33.1	25.0	1.48	1.04 - 2.11
Pets (cat or dog)			55.5	55.5	1.00	0.73 - 1.37
Salt preferenence			68.4	64.7	1.18	0.84 - 1.65
Maternal smoking						1.29 - 2.50
Ever			68.2	54.4	1.80	1.42 - 2.73
In pregnancy			53.2	36.6	1.97	1.20 - 2.35
First year of child's life			55.8	42.5	1.70	1.23 - 2.34
Current			58.6	45.4	1.70	1.23 - 2.34
Cigarettes daily	0	291	41.4	54.6		
	1 - 5	108	19.4	15.1		
	6 - 10	122	20.6	18.8		
	> 11	99	18.8	11.5	1.19**	1.05 - 1.55
Parental smoking						
First year of child's life			70.0	164.0	1.31	0.93 - 1.85
Current			54.5	49.3	1.23	0.90 - 1.70
Other smokers in child's bedroom			23.3	18.0	1.38	0.93 - 2.05
Total household smokers	0	125	17.1	24.3		
	1	144	20.0	27.6		
	2	100	27.8	23.5		
	>3	188	35.0	24.6	1.21***	1.10 - 1.34

*See Table 6.2 for full list of variables tested
**Odds ratio for an increment of 5 cigarettes in logistic model
***Odds ratio for an increment of one household smoker in logistic model

6.3.3. Urinary cotinine

Overall (n = 576), the median CCR was 63.5 ng/mg (interquartile range 30.6 - 130.1). Of this total, 4 values exceeded 1 000 ng/mg and 72 fell between 200 ng/mg and 1000 ng/mg. The median CCR among cases [73.2 ng/mg (interquartile range 34.4 - 137.7)] was significantly greater than among controls [55.2 ng/mg (interquartile range 22.5-124.30)] (Wilcoxon test, p = 0.02). The CCR increased with the number of smokers at home (Spearman's r = 0.57; p = 0.0001) (**Fig. 6.1**).

Fig 6.1 Cotinine creatinine ratio by number of household smokers



The median CCR (and unadjusted cotinine) was higher among children over seven years of age than among those six or seven years of age, but the trend by age was not significant.

To assess an exposure response relationship, the CCR was divided into quartiles, and the lowest quartile used as a reference group in a categorical analysis (**Table 6.7**). The data are consistent with an exposure response relationship with saturation of the effect in the highest quartile. One can allow for the possibility that high values of CCR included some active smokers, by assuming that all children in the stratum with a CCR above 130 ng/mg were active smokers. Exclusion of this stratum strengthens the exposure-response trend.

Table 6.7 Association between current asthma/wheeze and CCR by quartile, with lowest quartile as reference group (n=576)

CCR (ng/mg)	N	Odds ratio	95% Confidence interval
<30.6	144	1.00	-
30.6 - 63.5	144	1.21	0.76 - 1.93
63.5 - 130.1	144	1.66*	1.04 - 2.66
>130.1	144	1.61*	1.01 - 2.58

* Chi-square test for linear trend over first three strata = 62.9; p = 0.0001
** Chi-square test for linear trend over whole range = 5.4; p = 0.02

6.3.4. Multivariate logistic model

The associations between variables of interest and current asthma/wheeze after adjustment for potential confounders are displayed in **Table 6.8** (first column). The strongest predictors were hayfever and eczema. Parental asthma history (mother or

Table 6.8 Final model of predictors of current asthma or wheezing in multivariate analysis, using different case definitions *

	Asthma or wheezing (n=575) 325 cases	Asthma reported (n=396) 146 cases	No asthma reported (n=429) 178 cases	More severe wheezing (n=429) 179 cases
Hayfever	5.30 (3.16 - 8.89)	7.37 (4.04 - 13.44)	4.28 (2.40 - 7.61)	7.26 (4.14 - 12.76)
Eczema	2.19 (1.33 - 3.62)	3.26 (1.79 - 5.92)	1.51 (0.84 - 2.73)	2.29 (1.28 - 4.08)
Parental history of asthma	1.77 (1.11 - 2.84)	3.07 (1.76 - 5.38)	1.07 (0.60 - 1.91)	1.43 (0.80 - 2.53)
Sibling history of asthma	1.54 (0.93 - 2.56)	1.33 (0.70 - 2.54)	1.71 (0.97 - 3.05)	1.55 (0.85 - 2.80)
No parental contribution to income**	1.72 (1.17 - 2.54)	1.85 (1.11 - 3.08)	1.68 (1.08 - 2.63)	1.85 (1.16 - 2.95)
Maternal smoking in pregnancy	1.87 (1.25 - 2.81)	2.20 (1.28 - 2.85)	1.79 (1.14 - 2.85)	2.04 (1.25 - 3.34)
Number of household smokers***	1.15 (1.01 - 1.30)	1.07 (0.91 - 1.25)	1.20 (1.04 - 1.38)	1.17 (1.003 - 1.35)
Bedroom mould	1.19 (0.79 - 1.79)	1.35 (0.80 - 2.28)	1.07 (0.66 - 1.72)	1.11 (0.68 - 1.83)
Salt preference	1.03 (0.70 - 1.52)	0.92 (0.56 - 1.51)	1.20 (0.76 - 1.88)	1.08 (0.68 - 1.71)

*See text for definitions
**Includes absence of male parent
***Odds ratio for an increment of one household smoker

father) was also positively associated with asthma/wheeze, with sibling history being marginally significant. Of the socioeconomic variables, only the absence of paternal contribution to family income remained a significant predictor. Among the environmental risk factors, maternal smoking in pregnancy and number of smokers at home were independently associated with asthma/ wheeze. Log cotinine adjusted for creatinine (OR = 1.23; 95% C.I.= 0.82-1.84) was not significant when substituted for number of household smokers in the final model.

As a number of the smoking measures were closely related to one another, the final model was re-examined by entering, separately, these smoking variables (or combinations of variables) into the model. Of 288 currently non-smoking mothers, 253 had also not smoked in pregnancy. Of 321 currently smoking mothers, 243 had also smoked in pregnancy. Smoking in pregnancy and current smoking were thus highly correlated (concordance = 81.4%). When various maternal smoking variables were entered separately into the model predicting current asthma/wheeze, only those variables which included pregnancy smoking remained significant (**Table 6.9**).

Table 6.9 Effect of using different definitions of maternal smoking on its contribution to final model of predictors of current asthma/wheeze (n=575)

Variable	Reference Level	Improvement Chi square	P	Odds ratio	95% Confidence interval
Smoked in pregnancy	Did not smoke in pregnancy	9.27	0.002	1.87	1.25 - 2.81
Smoked first year of life	Did not smoke first year of life	2.72	0.09	1.40	0.94 - 2.10
Smoking currently	Not smoking currently	1.53	0.21	1.33	0.85 - 2.00
Smoked but not in pregnancy*	Never smoked	9.88*	0.007	0.79	0.43 - 1.44
Smoked in pregnancy*	Never smoked			1.72	1.09 - 2.72

*Entered together into model

6.3.5. Interactions

Interactions of environmental factors with sex, hayfever, eczema and maternal education in their association with current asthma/wheeze were examined. An interaction was found between reported bedroom mould and hayfever, i.e. while no association between bedroom mould and asthma/wheeze was detectable in the absence of hayfever (OR = 1.01, 95% C.I. 0.65-1.59), this association was strong when hayfever was reported (OR = 2.91, 95% C.I. 1.98-4.29).

A further interaction was demonstrable between current maternal smoking (but not smoking in pregnancy) and maternal education. Current maternal smoking was a predictor of asthma/wheeze among children whose mothers had eight years of education or less (OR = 1.76, 95% C.I.= 1.01-3.05), but not among children whose mothers had more than eight years of education (OR = 0.92, 95% C.I.= 0.50-1.70). Maternal education was itself inversely related to the child's nicotine absorption, in that the median urinary CCR among children of mothers with eight years of education or less (73.1 ng/mg) was significantly greater than that among children of mothers with more than eight years of education (55.3 ng/mg; p = 0.02).

Finally, the interaction term between salt preference and sex was significant when entered into the model, with boys tending to show a greater association between salt preference and asthma/wheeze (OR = 1.50; 95% C.I.= 0.87-2.59) than girls (OR = 0.71, 95% C.I. = 0.41-1.24).

6.3.6. Alternative case and control definitions

The effect on the final model of using three alternative case definitions was examined (**Table 6.8**): column 2: cases whose parents reported asthma, column 3: cases whose parents did not report asthma, and column 4: cases with more severe symptoms, viz. children reported as having had either four or more wheezing episodes or an episode of wheezing which interfered with speech, in the past year. There was some variation in the odds ratios: in particular, the reported asthma group tended to show stronger associations with hayfever, eczema, parental asthma history, and maternal smoking in pregnancy, but weaker associations with sibling asthma history and number of houshold smokers.

Since the control group contained some subjects (n = 73) with a few current symptoms, the final model was also re-examined by limiting the controls to currently asymptomatic children (n = 199). Such restriction did not materially alter the findings.

6.4. Discussion

The case definition in this study of children aged predominantly 7 to 9 years was based on parental reporting of asthma or of symptoms, mainly wheezing, typical of asthma. In the ISAAC based questionnaire used in this study, the asthma question does not refer to a doctor's diagnosis. However, since asthma is more likely to be underdiagnosed than overdiagnosed in this population (see Chapters 5 and 8) parental reporting of asthma is probably specific. To overcome the problem of underascertainment, children not labelled asthmatic by the parent but with multiple manifestations of wheeze, tight chest, or night cough (without a cold) were also included in the case group in the initial analysis.

Wheezing children with a label of asthma may, however, differ from other wheezing children in a number of respects. These include a greater likelihood of severe symptoms, a parental history of asthma, presence of other atopic disease such as hayfever, actions taken to avoid environmental triggers, and less likelihood of wheezing only with viral respiratory infections. Restriction of the case definition in the final model to children labelled as asthma by their parents increased the strength of most but not all of the associations.

The factors associated with current asthma/wheeze in this study can be grouped into three types. The first category reflects the atopic and familial components of childhood asthma, i.e. hayfever and eczema in the child, a history of asthma in either parent and to a lesser degree in siblings. With the exception of sibling history, these variables were stronger predictors among children with reported asthma than among wheezing children without asthma. Children labelled asthma are thus more likely to have a cluster of atopic or allergic manifestations than wheezing children not so labelled. Also, asthmatic parents are presumably more likely to identify wheezing in their children as asthma.

The second category includes variables indicative of socioeconomic status. The risk of diagnosed asthma as inferred from cohort studies has not been clearly related to socioeconomic status (Horwood 1985, Martinez 1992). In contrast, wheezing symptoms

(Leeder 1976), severe asthma (Mielck 1996) and asthma complications tend to be more common among children of lower socioeconomic status, reflecting the lesser access to diagnosis and good quality asthma care among poorer children (Halfon 1993, Mielck 1996). In this study, the only predictive socioeconomic variable (of a list including medical insurance, maternal and paternal education and occupation, family size, numbers of household and bedroom occupants), was the lack of paternal contribution to family income. This held whatever the case definition. Female headed households may thus reflect some characteristic of poverty not captured by the categories of occupation or education used.

Low maternal education did, however, enhance the association between current maternal smoking and asthma/wheeze, as has been found elsewhere (Martinez 1992). This implies that one of the routes by which low maternal education contributes to asthma or wheezing is through its association with increased smoking activity in the household, confirmed in this study by the inverse association between cotinine in the child's urine and maternal education.

The third category of risk factor is exposure to environmental agents. Sensitisation to specific antigens was not measured directly in this study, which relied on reporting of exposures. Pet ownership (whether of a cat or dog) was very similar among the two groups, and was thus unrelated to current asthma/wheeze. Damp and/or mould, one of the household factors of interest in this study, has elsewhere been linked to respiratory symptoms and reported asthma or wheezing (Verhoeff 1995, Brunekreef 1989, Dijkstra 1990) probably via sensitisation to moulds or house dust mite (Verhoeff 1995). Although the association of asthma/wheeze with visible mould in the child's bedroom in this sample was not significant after adjusting for covariates, bedroom mould was a risk factor among the subgroup of children with hayfever. These children with both hayfever and asthma symptoms are presumably more likely to be the group sensitised to the allergens associated with damp.

There was too little use of energy sources other than electricity, such as gas or paraffin (household kerosene), to be able to examine their association with asthma/wheeze. Salt preference, another factor of *a priori* interest, did not differ overall between the case and control groups. However, there did appear to be some difference between the sexes, in that salt preference showed a stronger association with current asthma/wheeze among boys than among girls. Despite the crude questionnaire definition of salt intake used, this sex-specificity accords with findings in adult studies of asthma or BHR (Burney 1986, 1987, 1989, Pistelli 1993), and remains intriguing even if difficult to explain.

In multivariate analysis, two environmental exposure variables remained independently associated with current asthma/wheeze under most of the case definitions: maternal smoking in pregnancy, and number of household smokers.

Potential confounders of the association between maternal and household smoking and asthma or wheezing include active smoking by the child, socioeconomic status, household fuels other than electricity, and possibly the respondent's own symptoms (see Chapter 3). All of these potential confounders, other than active smoking by the child, could be controlled to some degree in the analysis.

The urinary cotinine levels may be of some interest in evaluating the role of active smoking. Cotinine levels were high in this population, even among children with no reported smokers at home. The most likely explanation is the high background exposure of these children in the homes of friends and relatives and perhaps in other enclosed spaces such as on transport and in shops. There was no direct way to identify actively smoking children, as the questioning of young schoolchildren at school is likely to be ineffectual in obtaining such information. However, if active smoking in the sample of children were important enough to influence mean cotinine levels, it would be expected that cotinine levels would rise with age, and that the active smokers would tend to be clustered in the children with the highest cotinine levels. There was a tendency for CCR to be higher in older children, but exclusion of children with urinary CCR > 130 ng/mg

strengthened rather than weakened the association between CCR and asthma/wheeze.

The mechanism for the association between ETS and asthma or wheezing in this age group remains unknown. It is difficult in cross-sectional studies of schoolchildren to distinguish an effect of *in utero* exposure which lays the anatomic or physiologic basis for later wheezing illness from a postnatal effect which induces or aggravates its clinical appearance. In this study, maternal smoking in pregnancy was closely correlated with postnatal maternal smoking, whether in the first year of life or at the time of the study. However, it was possible to distinguish statistically mothers who smoked both in pregnancy and postnatally from those who smoked postnatally only, while controlling for smoking by other household members and for nicotine absorption by the child. The results imply that maternal smoking in pregnancy may be necessary to the association between maternal smoking and current asthma/wheeze, either alone or in combination with postnatal smoking.

However, the finding in this study that independently of maternal smoking, the number of current household smokers was associated with asthma/wheeze, is consistent with a postnatal effect of ETS exposure. Validation of the questionnaire measure of household smoking was obtained by measurement of urinary cotinine, which was correlated most closely with the number of smokers in the household. Cotinine was associated also with current asthma/wheeze in bivariate analysis, showing an exposure-response relationship. Limitation of the case group to children with an asthma label, while strengthening the association with maternal smoking, resulted in disappearance of the association with number of household smokers. A possible explanation for this is that an asthma diagnosis leads to smoking restriction in such households.

In conclusion, this phase of the study has demonstrated that both maternal smoking and number of household smokers are independently significant risk factors for current wheezing illness, with some variation depending on whether asthma is reported or not. The findings are thus consistent with the hypothesis that there may be at least two

mechanisms at work in the association between household or familial smoking and wheezing illness in young schoolchildren, one operating *in utero* and the other postnatally.

The prevalence of wheezing was shown in Chapter 5 to be high in this population, with probable underdiagnosis of asthma. Crude smoking rates in the population of which the study community is a part are the highest in South Africa, with 58% of men and 59% of women in surveys admitting to smoking (Reddy 1996). This includes a smoking rate in pregnancy of 44% (Steyn 1997). The high cotinine levels recorded in this study confirm the considerable exposure of these children to ETS from all sources. Based on estimates of attributable fraction (see section 3.1.6.), a substantial proportion of childhood wheezing illness in this population could thus be prevented by targeting smoking by mothers and other household members as a public health priority.

6.5. References

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CHAPTER 7

HOUSEHOLD SMOKING AND BRONCHIAL HYPERRESPONSIVENESS AMONG CHILDREN WITH ASTHMA/WHEEZE

7.1 Background and objectives

The study described in Chapter 6 found an association between maternal and household smoking and the occurrence of asthma and wheeze in a population of primary school children. This is in accordance with the body of population studies reviewed in Chapter 3 which supports the hypothesis that maternal tobacco smoking is associated with an increased frequency o asthma and wheezing illness in young children. In addition, some but not all general population studies of children have shown a positive association between ETS exposure and bronchial hyperresponsiveness (O'Connor 1987, Martinez 1988, Strachan 1990, Frischer 1992, Soyseth 1995, Cook 1998).

In contrast to studies of general populations of children, investigations or analyses of samples of asthmatic or wheezing children address the question of *exacerbation* of the condition by ETS rather its initiation or induction. Studies of asthmatic children have shown positive associations between ETS and symptoms (Murray 1986, 1988, 1989) daily peak flow variability (Meijer 1996) and frequency of emergency room visits (Evans 1987), and a negative association between ETS and lung function (Murray 1986, 1988, 1989, Sherrill 1992, Chilmonczyk 1993). Some of these studies have also found an association between ETS exposure and BHR, a possible mechanism underlying the aggravation of asthma by ETS in susceptible children (O'Connor 1987, Martinez 1988, Murray 1986, 1988, 1989).

The objective of the study described below was to test the aggravation hypothesis, viz. that exposure to household ETS is associated with increased bronchial hyperresponsiveness in children identified as having asthma/wheeze.

7.2. Methods

7.2.1. Selection of study subjects

The current study drew for its sampling frame on the case group defined in section 6.2.1. in the previous chapter. In summary, cases with "current asthma/wheeze" (n = 368) were defined as those children with (1) parent reported asthma, plus at least one symptom in the past 12 months (n = 162), or, (2) in the absence of reported asthma, affirmative

responses to four or more symptom questions referring to the past 12 months (n = 206). This resulted in a score with a scale of 0 to 10 (see **Table 6.1**). Case status was based on a score of 4 or more.

Resources available to the study did not permit BHR testing of every child meeting the case definition. Accordingly, for BHR testing, the 368 case children were randomly ordered in lists by school, and selected with the aim of achieving as large a sample as practicable, in this case a minimum of a 70% sample per school (n = approximately 258). Any unavailable subject was replaced by the child next on the random list for that school.

7.2.2. Smoking and other covariates

Information on household smoking and other covariates was obtained from the home interviews. Items in the home interview questionnaire of interest in this phase of the study included information on: sociodemographic features; the child's medical history; household smoking; visible damp and mould; dietary salt preference and family history of asthma.

"Atopic history" was defined as a history of hayfever or eczema in the child. "Asthma recognition" was defined by a yes answer to the question: "Has your child ever had asthma?". Symptom score was treated as a binary variable (7-10 vs 4-6). Urinary cotinine was measured as described in section 6.2.3. in the previous chapter.

7.2.3. Bronchial hyperresponsiveness testing

Histamine challenge tests were carried out using the long challenge protocol of Yan (1983). A Vitalograph S wedge-bellows spirometer was used, calibrated daily with a 3 litre syringe. Any child judged clinically by the medical practitioner present to have a significant respiratory infection on the day was not tested. Parents were requested to withhold routine asthma medication on the morning of the test unless the child was ill, but it was not possible to evaluate compliance with this request. Each child was also asked privately at the time of the test

whether he or she had ever tried cigarettes; none admitted to having done so. Temperature and humidity readings were obtained for each day of the study from the metropolitan weather station.

Each child carried out a standing forced expiratory manoeuvre without a noseclip until 2 reproducible tracings, i.e. within 100 ml of each other, were obtained. The baseline measurement was repeated after an inhalation of normal saline. Any child found to have a pre or post-saline forced expiratory volume in one second (FEV1) of less than 75 percent of predicted for sex, age and height was not challenged with histamine. Instead, the child inhaled 200 ug salbutamol from a metered dose inhaler and repeated the expiratory manoeuvre after 10 minutes. A positive bronchodilator test was defined as one in which the FEV1 increased by 15 percent or more post bronchodilator.

In the children whose baseline FEV1 was 75 percent or more of predicted, the test consisted of inhaling doubling doses of histamine solution delivered with a series of De Vilbiss No. 40 handheld nebulisers which dispense an average of 0.003 ml solution with each squeeze. The exact amount per squeeze delivered by each of the nebulisers used in the study was measured at the beginning and again in the middle of the study to calculate the delivered dose for the coming phase of testing. The test was ended when a fall in FEV1 of 20 percent or greater from the post-saline value was recorded (a positive test), or when a cumulative dose of approximately 7.8 umol histamine been reached without such a fall (a negative test).

Any child who experienced a fall of 10 percent or more in the course of the challenge was given 200 ug salbutamol at the end of the testing and observed until the FEV1 had returned to its baseline value.

7.2.3. Statistical analysis

The principle of bronchorovocation tests such as histamine challenge is to start with a very low inhaled dose, measure any fall in FEV1 from baseline, and increase the dose until a 20 percent or greater fall in FEV1 occurs or until the limit dose is reached. There are different methods available to analyse information obtained from such bronchoprovocation tests (O'Connor 1987b, de Marco 1998). The most commonly used method has been to treat BHR as a binary variable, with positive responders defined by a 20 percent or greater fall in their FEV1 ("hyperresponsiveness") within the dose range of the test.

A more quantitative scale can be obtained from estimation of the actual dose of histamine required to provoke a 20 percent fall in FEV1 among positive responders. This is done by interpolating between the last dose at which the FEV1 decline is less than 20 percent and the first dose at which the fall in FEV1 exceeds 20 percent.

Another way of examining the effect of ETS exposure and other variables on BHR while making maximal use of histamine dose-response data is by means of survival analysis (Sunyer 1996, Sunyer 1997, de Marco 1998). The principle of this method is to treat the "effective concentration" of histamine at which a positive response is attained as the chronological time to failure, i.e. as a hazard function (with the covariates of interest at their baseline values). Censored observations are those from negative or incomplete tests.

In the above methods, there is censoring of the information of negative responders, i.e. of subjects whose FEV1 does not fall by 20 percent by the time the highest test dose is reached. An alternative is to estimate the slope of the dose-response curve drawn through the points defined by successive FEV1 measurements (O'Connor 1987b). This can be estimated by either the slope of the linear regression line through all data points of the individual's dose-response curve, or by the percentage fall in FEV1 divided by the total dose administered (Peat 1991). An advantage of this method is that an estimate of BHR can be obtained for every subject, including the minimal responders. This method has

been criticised, however, for assuming a linear relationship between FEV1 fall and the bronchoprovocation dose (de Marco 1998).

In modelling BHR to methacholine against a variety of covariates, the method based on survival analysis has been shown to perform better than either logistic regression based on a binary definition of response or linear regression making use of the dose response slope (de Marco 1998).

For purposes of this study both logistic regression using a binary definition of BHR and survival analysis were used to model the data. The results of the two analyses were essentially the same. Since the output of survival analysis is somewhat unfamiliar, for ease of exposition only the analysis based on a binary definition of BHR is presented, viz. a 20 percent or greater fall in FEV1 within the test dose range. Subjects who underwent a bronchodilator test because their baseline FEV1 was less than 75 percent were included in the BHR group in the reported analysis. However, the analysis was repeated after excluding them. As the design effect of sampling schools rather than individuals was found to be small, no adjustment for this effect was made.

The association between BHR and a range of covariates was first examined in bivariate analysis, expressed as the prevalence ratio (of a positive BHR test using one of the levels of exposure as the reference). These covariates included socioeconomic, medical history, and ETS exposure variables, as well as baseline FEV1, asthma recognition and symptom score (see section 7.2.2. above for definitions).

The association between BHR and covariates of interest was then modelled in multivariate analysis using logistic regression, with the prevalence odds ratio as the measure of effect. The variables entered into multivariate analysis included ETS exposure variables of interest, covariates that were statistically significant in bivariate analysis, and potential confounders.

Effect modification, i.e. variation of the ETS-BHR association across subgroups in the population, was tested by examining interaction terms in the model. Effect modifiers of interest were sex, atopic history, asthma recognition and symptom score.

Besides BHR, the other association of interest was that between baseline FEV1 and ETS. FEV1 was analysed as a continuous variable, after adjusting for age, sex and height, and mean adjusted FEV1 compared across different levels of the exposure variables.

7.3. Results

7.3.1. Final sample

A total of 263 children attempted the BHR test. Of another 33 children invited to the testing but replaced by the child next on the list, 14 were absent on the day, 14 were judged at the test site to have a respiratory tract infection, and 5 were no longer at the school. Of those who attempted the test, 8 were unable to perform an adequate test and 2 tests were curtailed because of time. There was insufficient or no questionnaire information on 4 of the children who completed the test, leaving 249 subjects for analysis. Of these, 240 successfully completed the histamine challenge test (115 positive, 125 negative). Of the positives, 23 responded by the fifth histamine dose of 0.49 umol, 61 by the seventh dose of 1.95 umol and 115 by the last dose of 7.8 umol. A further nine children had bronchodilator tests only (6 with positive, 3 with negative tests).

CCR results were available for 248 children of these children. The median cotinine creatinine ratio (CCR) was 74.2 ng/mg (interquartile range 33.9 to 137.7 ng/mg). The CCR increased with the number of smokers at home (Spearman's r=0.5, p=0.0001).

Median daily temperature on the testing days was 18 degrees C. (range 12 - 22), and median daily humidity 69 percent (range 46 - 95).

7.3.2. Predictors of BHR

The symptom and maternal smoking profiles of the children who underwent BHR testing are listed in **Table 7.1** and compared to those children with asthma/wheeze who were not tested (n=99). There were no significant differences between the tested and untested group in symptoms, asthma recognition, hayfever or maternal smoking prevalence. There was also no difference between the groups in a range of other demographic, socioeconomic and domestic exposure variables (not shown).

Table 7.1 Group that completed bronchial hyperresponsiveness testing compared to untested group (n=348)

Symptoms*/ diagnosis	Tested (%) (n=249)**	Not tested (%) (n=99)
Wheeze	97.4	93.8
Wheeze frequency ≥4	29.0	33.3
Sleep disturbance	85.6	87.5
Speech disturbance	40.3	47.9
Night cough without a cold	81.9	80.0
Post-exercise wheeze	81.0	78.4
Tight chest	85.5	89.6
Asthma ever	44.4	43.4
Hayfever ever	31.9	37.8
Selected exposure characteristics		
Mother smokes currently	57.8	60.4
Mother smoked in pregnancy	46.4	47.9
Mother smoked ever	69.0	66.3

*Past 12 months unless otherwise indicated.
**Includes 9 children who underwent bronchodilator rather than histamine test.

Table 7.2 compares BHR with respect to a number of sociodemographic and medical history variables. There was no association between age or sex and BHR. There was a positive association between medical insurance and BHR (prevalence ratio [PR] = 1.30, 95% confidence interval [C.I.] 1.03 - 1.66).

Of the medical history variables, children with an atopic history also showed greater BHR (PR = 1.46, 95% C.I. 1.14 -1.81). This was also the case for a history of hayfever or eczema separately. Symptom score was positively associated with BHR (PR = 1.45, 95% C.I. 1.01 - 2.09), while asthma recognition was somewhat less so. Higher baseline FEV1 was inversely associated with BHR (PR = 0.57, 95% C.I. = 0.39-0.81).

Table 7.2 Bronchial hyperresponsiveness by demographic, socioeconomic, medical history and lung function variables (n=249)

Variable	Category	N	Positive BHR test %	Prevalence ratio (95% CI)
Age (yrs)	6 – 7	109	50,5	0.98 (0.76 – 1.26)
	8 – 11	124	51.6	
Sex	Female	119	52.9	0.94 (0.74 – 1.2)
	Male	130	50.0	
Medical insurance	No	172	47.1	1.30 (1.03 – 1.66)
	Yes	75	61.3	
Mother's education (yrs)	0 – 8	152	53.3	0.91 (0.71 – 1.18)
	> 8	96	49.0	
Mother contributes to income	No	153	49.7	1.11 (0.88 – 1.40)
	Yes	94	55.3	
Father's education (yrs)	0 – 8	151	55.0	0.85 (0.66 – 1.10)
	> 8	94	46.8	
Father contributes to income	No	95	53.7	0.94 (0.74 – 1.19)
	Yes	153	50.3	
Hayfever	No	169	45.6	1.44 (1.14 – 1,81)
	Yes	78	65.4	
Eczema	No	186	48.4	1.25 (0.97 – 1.60)
	Yes	63	60.3	
Atopic history	No	135	43.0	1.46 (1.14 – 1.85)
	Yes	112	62.5	
Parental asthma	No	170	50.6	1.08 (0.83 – 1.40)
	Yes	68	54.4	
Sibling asthma	No	191	51.8	1.04 (0.78 – 1.38)
	Yes	54	53.7	
Asthma recognition	No	142	45.8	1.28 (0.90 – 1.81)
	Yes	106	58.5	
Symptom score *	4 – 7	183	45.9	1.45 (1.01 – 2.09)
	8 - 10	66	66.7	
Baseline FEV1	650 - 1420	125	65.6	0.57 (0.44 – 0.74)
(ml)	1420- 2150	124	37.1	

Table 7.3 compares BHR at different levels of a number of ETS exposure measures as well as reported household damp or mould. In general, exposure to maternal smoking was associated with less BHR in the children, although not reaching statistical significance, (i.e. the confidence interval included one).

The most suggestive effect was among children of mothers who smoked 15 or more cigarettes a day, who showed considerably less BHR compared to children whose mothers smoked none (PR = 0.60, 95% C.I. 0.34 - 1.08). A similar pattern was evident for the number of smokers in the household, where the highest stratum (> 3 smokers) showed somewhat less BHR than the intermediate or unexposed stratum.

There was no association between paternal smoking and BHR. Although the higher quartiles of urinary CCR were associated with less BHR than the lowest stratum, there was no exposure response trend. There was no association between reported household damp and BHR. There was also no association between BHR and temperature or humidity on the test day (not shown).

Table 7.3 Bronchial hyperresponsiveness by household smoking and other environmental variables (n=249)

Variable	Category	N	Positive BHR test (%)	Prevalence ratio (95% CI)
Mother's smoking				
Current	Never	76	61.8	1.00
	Ex	27	44.4	0.72 (0.38 – 1.36)
	Current	144	47.9	0.78 (0.54 – 1.12)
Daily cigarettes	0	104	56.7	1.00
	1 - 14	102	53.9	0.95 (0.66 – 1.37)
	15 - 35	41	34.2	0.60 (0.34 – 1.08)
In pregnancy	No	114	53.5	0.93 (0.73 – 1.18)
	Yes	133	49.6	
First year of child's life	No	109	54.1	0.91 (0.72 – 1.16)
	Yes	140	49.3	
Father's smoking				
Current	No	115	51.3	0.99 (0.78 – 1.27)
	Yes	131	51.2	
First year of child's Life	No	71	46.5	1.12 (0.84 – 1.50)
	Yes	167	52.1	
Number of Smokers in house	0	41	53.7	1.00
	1 - 3	154	55.8	1.04 (0.76 – 1.43)
	>3	52	36.5	0.68 (0.43 – 1.08)
CCR (ng/mg)	0 – 33.8	60	56.7	
	33.9 – 74.2	64	48.4	0.86 (0.61 – 1.20)
	74.3 – 137.7	62	53.2	0.94 (0.68 – 1.30)
	>137.7	61	45.9	0.81 (0.57 – 1.15)
Household damp or Mould	No	161	49.1	1.14 (0.89 – 1.45)
	Yes	88	55.7	

BHR: Bronchial hyperresponsiveness. CI: Confidence interval. CCR cotinine creatinine ratio.

To explore whether the child's symptoms or perception of the child's condition by parents might cause them to reduce the child's exposure to ETS, the relationships between urinary CCR and atopic history, asthma recognition and asthma score were examined. This is shown in **Table 7.4**. Urinary cotinine was in fact lower among children with an atopic history and with asthma recognition than those without. Children with a higher symptom score showed a slightly lower level of urinary CCR.

Table 7.4 Association of urinary cotinine with various features of asthma or atopic status in children with asthma/wheeze (n=249)

Variable	Category	N	Cotinine creatinine ratio/(ng/mg)	p-value
Atopic history	No	134	84.4 (2.70)	
	Yes	110	56.1 (2.91)	0.002
Asthma recognition	No	140	81.5 (2.64)	
	Yes	105	58.9 (3.00)	0.015
Symptom score	4 – 7	181	72.8 (2.58)	
	8 – 10	65	64.1 (2.58)	0.4

Table 7.5 shows the results of multivariate analysis. Among the ETS variables current smoking by the mother in the form of number of cigarettes smoked daily was entered into the model. This was adjusted for medical insurance, atopic history, baseline FEV1, asthma recognition, and symptom score (treated as confounders) in multivariate analysis. There was no change in the negative association between maternal daily cigarette consumption and BHR compared to the bivariate analysis.

No significant effect modification was found. In particular, the associations (or lack of them) between BHR and maternal smoking, paternal smoking, number of household

smokers or CCR did not vary significantly by atopic history, asthma recognition, higher symptom score, or parental or sibling history of asthma.

Table 7.5 Predictors of bronchial hyperresponsiveness in multivariate analysis in children with asthma/wheeze (n=249)

Variable	Categories	Odds ratio (95% confidence interval)
Mother's daily Cigarettes	0	1.00
	1 – 14	0.97 (0.67 – 1.41)
	15 – 35	0.62 (0.34 – 1.11)
Atopic history	No	1.27 (0.88 – 1.83)
	Yes	
Baseline FEV1 (ml)	650 – 1420	0.60 (0.42 – 0.86)
	1420 - 2150	
Asthma label	No	1.06 (0.72 – 1.58)
	Yes	
Symptom score	4 – 7	1.34 (0.89 – 2.01)
	8 – 10	
Medical insurance	No	1.32 (0.87 – 2.00)
	Yes	

The analysis was repeated excluding the children who underwent the bronchodilator test only, with no change in the results.

ETS exposure and FEV1

Table 7.6 shows mean baseline FEV1 adjusted for age, sex and height in relation to smoking exposure variables. The significant associations were a lower mean FEV1 among children whose mothers currently smoked compared to children whose mothers did not,

and similarly for children whose parents both smoked. Children whose fathers smoked had a higher mean FEV1 than those of nonsmoking fathers, but this difference was not statistically significant. There was no association between FEV1 and CCR.

Table 7.6 FEV1* by household smoking variables and CCR (n=247)

Variable	Mean FEV1 (SE) (ml)		Mean difference (ml)	
	Yes	No	(Yes - No)	95 % CI
Mother's smoking				
Current	1409 (19)	1641 (115)	-232	(-461, -2)
Ever	1526 (69)	1467 (48)	59	(107, 225)
In pregnancy	1464 (60)	1557 (83)	-93	(-296, 110)
First year of child's life	1463 (57)	1560 (88)	-97	(-305, 110)
Father's smoking				
Current	1561 (91)	1449 (32)	112	(-78, 302)
First year of child's life	1518 (72)	1502 (47)	16	(-154,186)
Mother and father smoke	1385 (32)	1591 (62)	-150	(-286, -131)
Two or more smokers in household	1455 (53)	1591 (102)	-137	(-366, 92)
	Mean FEV1 (SE) (ml)		Mean difference from lowest category	
CCR (ng/mg)				
0 - 33.8	1467 (96)		-	
33.9 - 74.2	1466 (96)		2	(-320,325)
74.3 – 137.7	1653 (101)		190	(-139,520)
>137.7	1423 (97)		-40	(-363,282)

*Adjusted for age, sex and height
FEV1: Forced expiratory volume in one second. SE: Standard error.
CI: Confidence interval. CCR: Cotinine creatinine ratio.

7.4. Discussion

Bronchial hyperresponsiveness can be interpreted as a marker of current asthma severity, or alternatively, susceptibility to acute asthmatic episodes, in children identified on questionnaire as having asthma or wheeze. BHR is not a fixed nor a defining characteristic of asthma, however. It may vary over time in the same child or vary considerably between asthmatic children, i.e. it shows intra- and inter-individual variability (Phelan 1991). In clinical settings a single measurement of BHR must be interpreted with caution. However, as long as this variability is distributed equally across the groups of interest, BHR remains useful as an objective outcome in epidemiologic analysis of exposure factors contributing to asthma or its severity.

This study has failed to show that household ETS exposure is associated with increased BHR in a population based sample of children with a recent history of wheeze or diagnosis of asthma. This was so whether ETS exposure was defined in terms of urinary cotinine, reported parental smoking or number of smokers in the house. Unexpectedly, BHR was lowest in the highest stratum of each of three ETS variables, viz. more than 15 cigarettes smoked daily by the mother (compared to fewer or none), four or more smokers in the house (compared to fewer or none) and CCR > 137.7 ng/mg (compared to any of the lower strata of CCR).

The only expected association (Murray 1988, Sherill 1992, Chilmonczyk 1993) demonstrated in this group of schoolchildren with asthma/wheeze was an FEV1 deficit among children whose mothers currently smoked, or whose parents both smoked, compared to children whose mothers (or parents) were current nonsmokers.

The findings were also surprising in view of the findings in Chapter 6, namely a robust association (odds ratio of the order of 1.7 to 2.0) between maternal and other household smoking and asthma/wheeze when the whole population, i.e. including the controls (scores 0 to 3), was analysed. The results of the two studies suggest a model in which maternal

smoking contributes to the induction of asthma, and to its chronicity as measured by FEV1, but not to the worsening of BHR in children already identified with asthma/wheeze.

Of other covariates examined, the known association between atopy and BHR from population studies (Martinez 1988, Peat 1987) was confirmed. However, no significant variation in BHR by age, sex, reported household damp or mould, or socioeconomic markers (other than medical insurance) could be demonstrated. The increased BHR among children with medical insurance is interesting but ambiguous, as medical insurance is both an indicator of better socioeconomic circumstances and greater access to private sector medical care.

Possible explanations for the unexpected findings include lack of power, bias, negative confounding or effect modification. Lack of power is evident from the wide confidence intervals. However, the measures of effect estimates for the smoking variables were consistently either close to one or smaller than one. While a larger study would have reduced the size of the confidence intervals, it is unlikely to have resulted in substantial reversal of the direction of the estimates.

Bias (due to the cross-sectional study design) away from finding an effect of current ETS exposure on BHR would occur if parents of children with correlates of BHR (such as more active or severe asthma or multiple manifestations of atopy such as rhinitis and eczema) avoided smoking around the children or reduced their smoking altogether. This was suggested by Frischer (1992) who found an association between ETS and peak expiratory flow rate variability (assumed to reflect BHR) in non-atopic asthmatic children but not in atopic asthmatic children, and by Chen (1996) who found an association between ETS and diagnosed asthma in non-allergic but not in allergic children.

A seemingly protective effect of current smoking on current BHR among 8 year old asthmatics was also found by Meinert (1994), in contrast to positive associations between

smoking by the mother in pregnancy and during the child's first year of life and current BHR. This suggested that mothers reduced their smoking over time (or did not take it up) in response to having a child with BHR. The authors called this the "healthy passive smoker" effect.

In this study asthma recognition, atopic history and symptom score were associated with increased BHR. In addition, urinary CCR was significantly lower in children with asthma recognition and atopic history than those without, and slightly lower in those with a higher asthma/wheeze score. These covariates thus qualify as potential confounders. A strong selection effect based on these correlates of BHR could possibly produce a spurious inverse association between ETS and BHR, with the more bronchially responsive children having less ETS exposure.

However, when these potential confounders were entered into multivariate analysis together with current maternal smoking activity, there was no change in the inverse association between maternal smoking and BHR.

Other forms of negative confounding were considered. Meijer (1996) measuring circadian peak flow variation in allergic asthmatic children, found an association of ETS with peak flow variation among children with mild to moderate BHR as measured by histamine challenge, but not among those with severe BHR. Those authors postulated that the effect of ETS in the group of children with severe BHR was masked by the impact of other exogenous stimuli. The only marker of environmental allergen exposure measured in the current study was household mould or damp, which was not associated with BHR. While house dust mite sensitisation is the most common form of atopy in this population (Van Niekerk 1977, Potter 1991) it is implausible that house dust mite exposure would be inversely related to ETS exposure.

Effect modification may result in an effect that occurs in a subgroup of the population being diluted if the whole population is studied. In this study there was no effect modification by

atopy, in contrast to the findings of Chen (1996) and Frischer (1992). Effect modification of the association between ETS and BHR among asthmatics by age, sex and season has been noted in some studies. Murray (1988, 1989) found in their series that a positive

association was demonstrable mainly in boys, among adolescents compared to the age group 7 to 11 years (the age range of this study), and during testing in the cold, wet season rather than in the warm, dry season. In the current study, there was no sex difference in the findings. All the testing was done in spring and early summer when the child's household ETS exposure would conceivably be lower than in the wet winter months. It has also been suggested by some authors that there may be a susceptibility factor, as yet uncharacterised, making some asthmatics more sensitive to ETS than others (O'Connell 1974, Lehrer 1984, Menon 1992).

The findings regarding ETS and BHR are in conflict with a number of other studies of children with asthma/wheeze, in which BHR was greater in the children of smokers (O'Connor 1987, Martinez 1988, Murray 1986, 1988, 1989). One of these study populations, (Murray 1986, 1988, 1989)] in which histamine challenge was also used, consisted of diagnosed asthmatics attending a clinic and may have represented a selected group with more severe asthma. The sample in the current study was a group of children described as having symptomatic asthma or multiple symptoms of asthma in the previous 12 months. In this study, the spectrum of disease would be different from studies of clinic asthmatics, in that the sample included both children with current active asthma, and those whose asthma might have been episodic, seasonal or mild. However, the findings also contradict those studies in which children the asthma group were identified from population based samples in a similar way (O'Connor 1987, Martinez 1988), although the methods of BHR testing were different.

Chamber studies, in which asthmatic subjects are subjected to ETS under controlled conditions, have reproduced acute symptoms of upper and lower respiratory tract irritation, but have produced conflicting results with regard to changes in BHR. Oldigs (1991)

studied asthmatic children, and found no consistent change in lung function or BHR after one hour of exposure to ETS. Some chamber studies of adult asthmatics have shown lung function decline and increased BHR on ETS challenge (Knight 1985, Menon 1992), although in the latter study subjects were pre-selected for previous "sensitivity" to ETS.

Other chamber studies of asthmatic adults failed to show these responses to ETS (Shephard 1979, Weidemann 1986, Jorres 1992). In general, these studies are able to reproduce only acute ETS exposures in small samples of mainly adult volunteers, and the relevance to chronic exposure of children in home environments is limited.

In conclusion, this study does not support the hypothesis that ETS aggravates asthma by increasing BHR. If anything, an inverse association between heavier maternal smoking and BHR was found. It is difficult to conceive of a biological basis for an inverse association. An attempt was made to adjust for factors which might induce parents to modify their smoking in response to manifestations of asthma in their child, but the effectiveness of such adjustment is difficult to judge in a cross-sectional study. Further cross-sectional studies cannot solve this problem. Only prospective studies with measurement over appropriate time periods of both the child's ETS exposure and BHR are likely to answer the question.

The findings of this study should be considered in the light of the conclusion of a recent systematic literature review by Cook and Strachan (1998). Reviewing studies of passive smoking and BHR both in general populations and in asthmatic populations or subgroups, the authors concluded that there was insufficient evidence for an effect of ETS on BHR at the general population level. They cited selective reporting of results in published studies and publication bias in favour of positive studies as having produced a spurious a positive association in the literature. In addition, the relatively few studies of asthmatic children were contradictory or inconclusive.

In contrast to the findings regarding BHR, the results of this study are consistent with an effect of maternal smoking, and combined maternal and paternal smoking, on lung function deficit (as reflected in FEV1) among symptomatic children. ETS exposure may thus be an added risk factor for long term lung function loss in wheezy or asthmatic children (Sherrill 1992).

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CHAPTER 8

UNDERRECOGNITION AND UNDERTREATMENT OF ASTHMA

8.1 Background and study objectives

Although asthma is not curable, the quality of life of asthmatic children can be greatly improved by appropriate management. Elements of such management include appropriate anti-inflammatory and bronchodilator medication, education of caregivers about the disease, home monitoring and a self-management plan, allergen control, and attention to psychosocial obstacles to treatment (British Thoracic Society and Others 1993, Bosley 1996). Guidelines for the treatment of childhood asthma have been published in South Africa in recent years (South African Childhood Asthma Working Group 1992, 1993a, 1993b, 1994). Doubt has been expressed, however, about the extent of their application in practice (Morris 1994, Green 1998).

Appropriate management of childhood asthma requires acceptance of the diagnosis by parents or caregivers, which in turn requires recognition by medical practitioners. Underrecognition and/or undertreatment of childhood and adolescent asthma have been studied and identified as problems in the United Kingdom (Speight 1983, Duran-Tauleria 1996), Australia (Bauman 1992), the Netherlands (Kolnaar 1994), the USA (Davidson 1994) and Denmark (Siersted 1998). Differences between socioeconomic and ethnic groups in the recognition and treatment of childhood asthma have also been noted (Duran-Tauleria 1996, Bauman 1992, Davidson 1994, Evans 1992). The common finding is that poorer, inner city or minority status children, depending on the society, tend to suffer more from their asthma and receive worse care than better off children.

It was shown in Chapter 5 that primary school children in Mitchell's Plain have a relatively high prevalence of wheezing by published international standards. The aim of the current study was to determine, based on parental reporting, the degree to which asthma is recognised and appropriately managed in this population. The influence of socioeconomic and other factors on the recognition and treatment of asthma was also examined.

8.2. Method

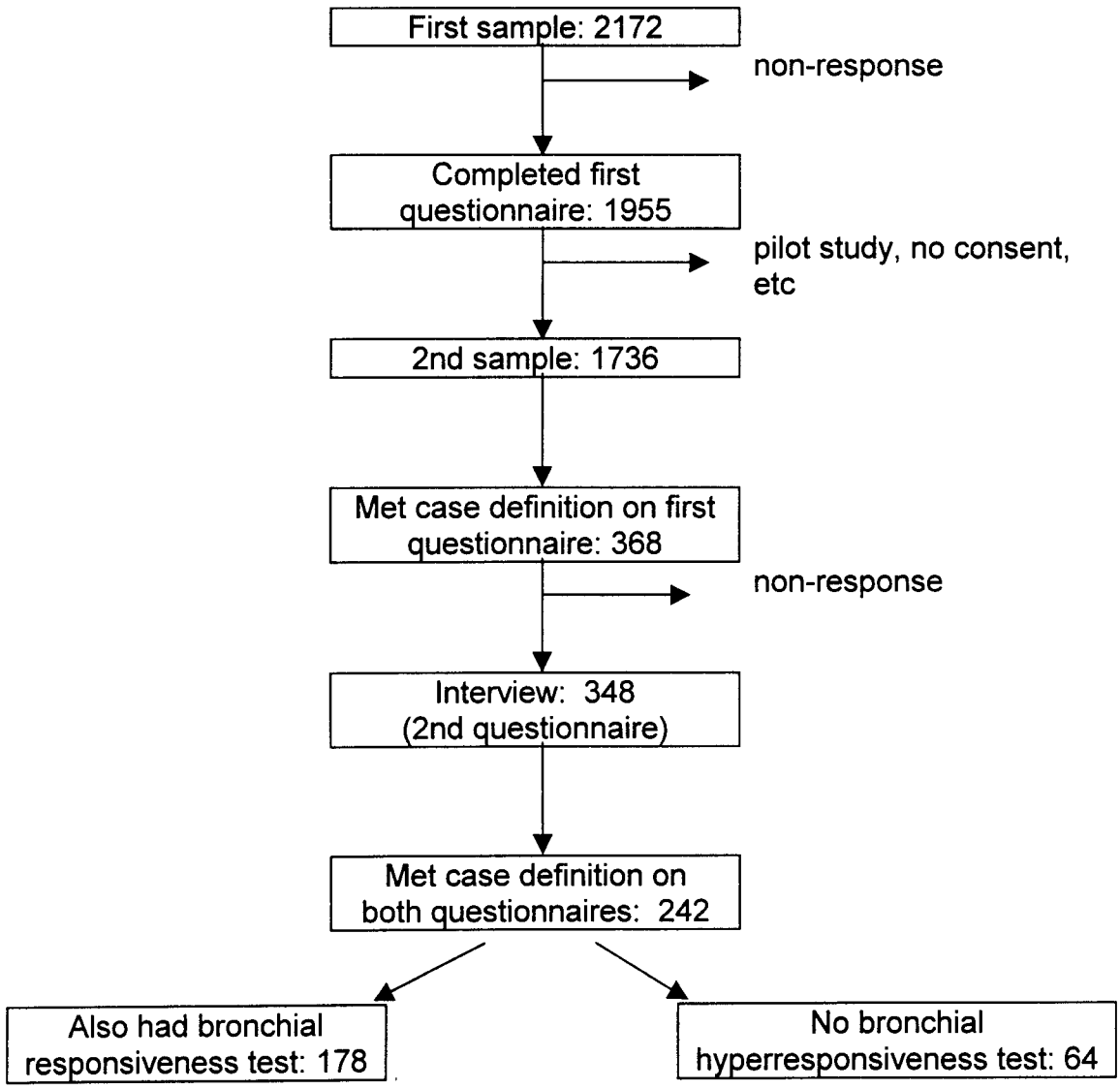
8.2.1. Selection of group for study

Because the focus of this phase of the study was on diagnosis and treatment, in order to increase the validity (Kelsey 1986) of the case definition of asthma, responses to both questionnaires were used in the case definition. Thus only children who met the criteria for asthma (see section 6.2.1. and **Table 6.1**) on *both* the self-administered and interview questionnaire were regarded as having asthma.

Fig. 8.1 illustrates how the groups for analysis in this part of the study were obtained. A total of 243 children qualified as asthmatic by meeting the criteria for case status on both the initial and repeat questionnaires, of whom 242 had sufficient information for analysis.

Because of the sampling for BHR testing (see 7.2.1.), among the group that completed BHR tests, only 178 also met the criteria for case status on both questionnaires. As a result, for 64 of the asthma cases in this phase of the study, BHR status was unknown. (See **Fig. 8.1**). Of the 178 children who had undergone the test, 100 showed positive BHR.

Fig. 8.1 Sampling pathway to case group in study of underrecognition and undertreatment of asthma



8.2.2. Measurement of descriptive and predictive variables of interest

Items on the home interview of particular relevance to this phase of the study were sociodemographic characteristics, the child's respiratory medical history, history of treatment for chest symptoms, knowledge of asthma management, and terms used by the parent and medical practitioner to describe the child's condition (**Table 8.1**). If the child was on current treatment, the respondent indicated the medication used by the child with the aid of a chart with photographs of the most common oral and inhaled medication in local use. The name and mode of delivery of the medication were recorded by the interviewer if the information could be obtained.

The primary division of interest in this study sample was into those children for whom the respondent answered yes to the question "has your child ever had asthma" (*recognised asthma*) on the interview questionnaire, and those for whom the respondent answered no (*unrecognised asthma*).

Current treatment was defined as affirmative response to the question "is your child currently on treatment from a doctor for any of the following symptoms: wheezing/whistling in the chest, tight chest, night cough or asthma?" *Appropriateness* of treatment was inferred qualitatively by comparing patterns of reported treatment against the recommended South African 1991 consenus guideline published in 1992 (South African Childhood Asthma Working Group 1992). Of particular interest was conformity with recommendations that short acting beta-2 agonist therapy is preferable to theophylline as front line medication, and that children with moderate or severe asthma should be on daily anti-inflammatory treatment. (Later guidelines emphasised the benefits of inhaled over oral therapy).

Table 8.1 Questions used in interview questionnaire on asthma recognition and treatment

1. Has the child ever had asthma?

   1.1 Does s/he still have asthma?

2. In talking about these symptoms (wheeze, tight chest, night cough) with your doctor, family or friends, what name do *you* use to describe the problem? (record)

3. During the past 12 months, has the child received any treatment from a doctor for any of the following symptoms? (wheezing/whistling in the chest, tight chest, difficulty sleeping because of cough)

   3.1 What name(s) did the doctor use to describe the child's chest problem? (record)

   3.2 Where did the child go for treatment for this chest problem? [private doctor, day hospital, Red Cross Hospital, other hospital or clinic, other (specify)]

4. Is the child *currently* on any treatment for any of the following: wheezing/whistling in the chest, tight chest, night cough or asthma?

   4.1 If *yes* what treatment? [tablets, syrup, inhaler, nebuliser (oxygen), injection, other (specify)]

5. Do you know of anything you can do *inside the child's bedroom* to prevent allergy or breathing problems? (specify)

6. Do you know of anything your child can avoid *eating or drinking* so as to prevent allergy or breathing problems? (specify)

7. Has the child ever been asked by a doctor or nurse to blow into a peak flow meter? (show picture of meter)

Socioeconomic status was measured by a number of variables including highest educational standard reached by mother and/or father, employment and occupational status of mother and/or father, number of people in the household in relation to number of rooms, number of other children in the household and, less directly, membership of a

medical aid (insurance) scheme and use of a private doctor. In addition, the school was rated by a Department of Education official on a relative scale of "high, medium or low socioeconomic status".

8.2.3. Statistical analysis

Symptom proportions in the two "recognition" subgroups as well as the proportions of the two groups reporting various aspects of management and knowledge of asthma were compared using the likelihood ratio chi-squared statistic.

The associations of sociodemographic, medical and family history factors and symptom severity with asthma recognition, current treatment and use of an inhaler were tested in bivariate analysis. (As the objective was exploratory, multivariate analysis was not carried out). The measure of effect presented in this analysis is the prevalence ratio. The Cox proportional hazards model was used obtain the point estimates and the corresponding 95% confidence intervals (Lee 1994) of the prevalence ratios.

8.3. Results

8.3.1. Features of recognised versus unrecognised asthma

Of the 242 children identified as asthmatic using the case definition, only 129 (53%) had recognised asthma. Even in this group, only 88 (37% of total) were acknowledged as "still" having asthma (**Table 8.1**: question 1.1). Even on a stricter criterion requiring case status on both questionnaires plus BHR (n=100), recognition of asthma occurred in only 62 percent, with only 45 percent acknowledged as current.

The majority of children in the sample in this phase of the study were aged 6 to 8 years. Boys made up just over half of both the recognised and unrecognised asthma groups. The mother was identified as the respondent in 85 percent of both groups.

The unrecognised group had significantly higher prevalences of wheeze, sleep disturbance and night cough compared to the recognised group (**Table 8.2**). By contrast,

a higher proportion of the recognised asthma group had a positive BHR test (62% vs 48.1%, p = 0.07).

Table 8.2 Reported symptoms and bronchial hyperresponsiveness by asthma recognition (n=242)

Symptoms (past 12 months)	Asthma recognised (n=129) %	Asthma not recognised (n=113) %
Wheeze	95.3	100.0[a]
Wheeze ≥4 episodes	45.7	44.3
Sleep disturbance by wheeze	76.6	87.6[b]
Speech disturbance by wheeze	43.4	52.2
Night cough	71.1	85.8[a]
Exercise wheeze	68.2	71.7
Tight chest	83.7	79.7
Bronchial hyperresponsiveness test (n=178)		
Positive	62.0	48.1[c]
Negative	38.0	51.9

[a] *P*=0.005. [b] *P*=0.002. [c] *P*=0.07

Table 8.3 describes the terms offered by the respondent to describe the child's respiratory problem, as well as the terms attributed to the child's doctor (**Table 8.1**: questions 2 and 3). The term "asthma" was offered by only 31.0 percent of the recognised group, and 2.7 percent of the unrecognised group (the latter thus contradicting the response to the direct question about asthma). The largest proportion in both groups preferred "tight chest" ("toebors" in Afrikaans). "Wheeze/wheezing chest" was rarely used. In describing what term the doctor used, "asthma" was reported by the

majority (71.9%) of the recognised group. In the unrecognised group, "bronchitis" (49%) and "cold" ("verkoue op die bors" in Afrikaans) (20%) were the majority responses.

Table 8.3 Terms to describe child's symptoms* used by respondent or attributed to doctor, by asthma recognition (n=242)

	Asthma recognised (n=129) (%)	Asthma not recognised (n=129) (%)
Name used by respondent		
Tight chest	31.0	28.3
Asthma	31.0	2.7
Cold	7.8	16.8
Bronchitis	7.0	15.0
Sore chest	5.4	12.4
Short breath	2.3	2.7
Wheezing chest	5.4	4.4
Other	5.4	9.7
None	10.1	8.0
Name attributed to doctor (n=215)		
Asthma	71.9	7.0
Bronchitis	11.4	49.0
Cold	2.6	20.0
Tight chest	3.5	9.0
Other	4.4	7.0
None	6.1	8.0

*See Table 8.1, questions 2 and 3.1

Almost all of the children in both groups had received some treatment for asthma symptoms in the previous 12 months (**Table 8.4**). However, while 23.2 percent of the recognised group were on daily treatment, and a further 42.9 percent on treatment as needed, only 3 percent in the unrecognised group were on daily treatment, with a large proportion (63%) on no current treatment. Children in the recognised group were more likely to have been treated privately and/or at Red Cross Children's Hospital, the regional paediatric teaching hospital. By contrast, day hospitals (public sector community outpatient clinics) were a more common site of treatment of children in the unrecognised group.

With regard to types of medication currently used, syrups (sweetened liquid preparations) were mentioned by a large majority of the respondents to this question (90.5% and 88.9% respectively), with pills the next most common mode of treatment reported. Inhalers were used by 44.6 percent of the recognised group and only 8.3 percent of the unrecognised group. Nebulisers were as commonly used as inhalers (the question did not distinguish between nebuliser use in a clinic or doctor's surgery and at home). Only 46.8 percent of the recognised group and 13.2 percent of the unrecognised group reported that the child had ever used a peak flow meter.

Response rates to the questions about home preventive measures were low (**Table 8.4**). Of the 114 who answered the question about preventive bedroom measures, a minority (16.4% in the recognised asthma group, 8.7% in the unrecognised group) mentioned avoidance of smoking in the child's bedroom. Even fewer respondents (60) answered the question about dietary avoidance. Among these, the most common reference was to cooldrinks (synthetic or fruit based sweet drinks). There were no significant differences between the two groups in these responses.

Table 8.4 Treatment and parential knowledge of home management, by asthma recognition (%) (n=242)

	Asthma recognised (n=129) %	Asthma not recognised (n=113) %
Treatment in past 12 months (yes = 215)	90.5	89.3
Source of treatment (n=215)*		
Private doctor	67.5	49.0[a]
Day hospital	28.1	47.0[b]
Red Cross Hospital	43.9	22.0[b]
Other hospital	7.0	5.1
Other	8.8	16.0
Current treatment (n=215)		
Every day	23.2	3.0
As needed	42.9	34.0
No	33.9	63.0[c]
Type of current treatment (n=112)		
Pills	54.8	25.0[b]
Syrup	90.5	88.9
Inhaler	44.6	8.3[b]
Nebuliser	44.6	13.9[b]
Inhaler or nebuliser	64.9	21.6[b]
Injection	6.9	2.8
Other	1.4	8.3
Peak flow meter (ever used) (n=242)	46.8	13.2[b]
Knowledge of bedroom prevention (n=114)**		
Clean room	22.4	26.1
No smoke	16.4	8.7
Sleep with fresh air	16.4	30.4
No soft furniture/carpets	17.9	10.9
Other	17.9	17.4
Did not specify	9.0	6.5
Knowledge of dietary avoidance (n=60)**		
Drinks	43.8	33.3
Dairy	10.4	22.2
Preservatives/colourants	6.3	5.6
Other	22.9	27.8
Did not specify	16.7	11.1

[a]$0.005<P<0.01$ for difference between two groups; [b]$P<0.005$ for difference between two groups; [c]$P<0.000$ for difference between two groups across all 3 categories
*Respondent could choose one or more
**See Table 8.1, questions 5 and 6. Numbers are those who answered yes.

A total of 101 of the 242 respondents provided more detail about the treatment the child used currently, either daily or as needed (see **Table 8.1**: question 4.1.). (Non-response implies either that the child was not on current treatment or no response to that question). Based on these responses, the number of times a specific medication/mode of delivery was mentioned is listed in **Table 8.5**. (A given respondent could mention more than one medication). Salbutamol was most commonly mentioned, with a syrup preparation the most frequent mode of administration. Other beta-2 agonists, including fenoterol, were mentioned much less commonly. The next most popular medication were the theophyllines, again with syrups the most common form. Anti-inflammatory medication was identified relatively few times: inhaled corticosteroids 9 times, oral corticosteroids 11, and sodium cromoglycate 12. The remainder of the medications mentioned included antihistamines, antibiotics and various cold and flu' preparations.

8.3.2. Predictors of recognition and treatment

Variables examined in relation to asthma recognition, current treatment and inhaler use were: demographic (age, sex); medical history (hayfever, eczema, parental asthma); socioeconomic (school, household crowding and size, maternal and paternal education and occupational/employment status); health care (medical aid, use of private doctor or day hospital); and severity (frequent wheeze, speech disturbance, positive BHR). Covariates reaching statistical significance in any association (i.e. for any of the three outcomes), plus those of *a priori* interest are presented in **Table 8.6**.

Table 8.5 Number of times asthma medication class mentioned for children on current medication (n=101)

Salbutamol	71
Syrup	32
Inhaler	15
Pills	7
Unspecified	17
Fenoterol	14
Syrup	8
Inhaler	1
Pills	0
Unspecified	5
Other beta-2 agonist	2
Theophylline	66
Syrup	21
Pills	10
Unspecified	35
Steroids	20
Inhaled	9
Oral	11
Sodium cromoglycate	12
Ketotifen	3
Antihistamines	12
Syrup	0
Pills	1
Unspecified	11
Other	27

(n=101) refers to the number of respondents who gave information about current medications. As a single respondent could mention multiple medications, numbers in table do not refer to respondents.

Table 8.6 Predictors of asthma recognition, current treatment and inhaler use (n=242)

	Asthma recognition (n=242)		Current treatment (n=242)		Inhaler use (n=112)	
	%	Prevalence ratio (95 % CI)	%	Prevalence ratio (95 % CI)	%	Prevalence ratio (95 % CI)
Age (yrs)						
6-7	62.3	1.3 (1.03 - 1.66)	50.9	1.13 (0.86 - 1.48)	33.9	1.08 (0.63 - 1.87)
8-11	47.8		45.1		31.4	
Hayfever						
Yes	62.1	1.29 (1.02 - 1.62)	67.4	1.93 (1.48 - 2.51)	40.3	1.83 (1.00 - 3.35)
No	48.3		34.9		22.0	
Eczema						
Yes	60.3	1.19 (0.94 - 1.52)	59.4	1.41 (1.09 - 1.84)	36.6	1.24 (0.72 - 2.12)
No	50.6		42.1		29.6	
Parental asthma						
Yes	69.1	1.45 (1.16 - 1.81)	49.7	1.15 (0.84 - 1.57)	31.3	0.91 (0.50 - 1.65)
No	47.7		43.3		34.5	
Medical Aid						
Yes	65.5	1.4 (1.11 - 1.76)	56.1	1.35 (1.03 - 1.76)	30.4	0.89 (0.51 - 1.54)
No	46.8		41.7		34.9	
Treated by private doctor						
Yes	60.2	1.45 (1.09 - 1.92)	58.6	1.39 (1.05 - 1.85)	29.3	0.75 (0.44 - 1.29)
No	41.6		42.1		38.9	
Treated by day hospital						
Yes	40.0	0.67 (0.49 - 0.90)	38.8	0.65 (0.48 - 0.89)	30.3	0.90 (0.48 - 1.69)
No	59.9		59.6		33.3	
Socio-economic status of school						
High	57.9	1.23 (0.96 - 1.58)	53.3	1.37 (1.03 - 1.83)	32.4	0.98 (0.56 - 1.72)
Low	47.1		38.8		32.5	
Other children in household						
$\leq$ 3	59.8	1.23 (0.94 - 1.61)	52.2	1.42 (1.03 - 1.97)	37.4	2.17 (0.93 - 5.04)
> 3	46.3		36.7		17.2	
BHR test						
+	62.6	1.29 (0.98 - 1.69)	58.2	1.97 (1.35 - 2.89)	33.3	1.53 (0.65 - 3.62)
–	48.7		29.5		21.7	

CI: confidence interval. BHR: bronchial hyperresponsiveness

Younger children, and those with hayfever or a parental asthma history were more likely to be in the recognised asthma group. Having medical aid (insurance) and attendance at a private doctor were also associated with recognition, while day hospital attendance was associated with non-recognition.

Similar factors were associated with being on current treatment, with the addition of eczema and some socioeconomic variables (higher socioeconomic status school, and "smaller" households [fewer than 4 other children]). A positive BHR test was also significantly associated with current treatment.

Among the smaller group of 112 children on current treatment, the only predictors of inhaler use were hayfever and smaller households.

8.4. Discussion

The results of this study show that asthma, a common disease, is underrecognised and undertreated in this population of Cape Town schoolchildren. This confirms, using a more thorough analysis including a home interview, the conclusion arrived at in Chapter 5 based on the self administered questionnaire. A recent study of child and adult clients of pharmacies in Cape Town, a large proportion of whom came from the study area, reached a similar conclusion (Bheekie 1998).

There are certain limitations in a study of this nature. Diagnosis of asthma and assessment of its severity are clinical processes; epidemiological definitions can make only approximate classifications. Epidemiologic studies may, for example, identify infrequently symptomatic children who would not merit diagnosis or treatment because of the mildness of their condition.

For these reasons, a stricter epidemiologic definition than that used in Chapters 5 and 6 was employed in an attempt to make the group as specific to asthma requiring treatment as possible. To qualify, respondents had to acknowledge multiple symptoms typical of

asthma and/or a diagnosis of asthma on *both* of two questionnaires 6 weeks to 3 months apart. A positive BHR test was not used to define asthma, as it is relatively insensitive in detecting asthma in population studies (Pattemore 1990, Jenkins 1996). (See also **Fig. 1.1**). In this study a positive BHR test could, however, be regarded as a marker of severity of asthma and of current activity of the child's asthma.

The first finding was that only about half of the respondents for these symptomatic children acknowledged any asthma history, while only a third acknowledged current asthma. Recognition should (appropriately) be a function of severity. Surprisingly, while the recognised asthma group had a higher proportion of children with a positive BHR test, symptom prevalences were equivalent or higher in the unrecognised group. An explanation for this may be that the children with greater BHR come to medical attention more readily and are treated more vigorously than asthmatic children without BHR. The net "treatment effect" may thus be lower prevalences of symptoms among the recognised group.

Labelling of ill-health is a complex phenomenon, reflecting medical practice, parental education, parental willingness to accept the diagnosis or the management of the problem and explanatory constructs held by parents of cause and natural history (Peterson 1991, Jones[1]). Practitioners may use less specific diagnoses or be reluctant to use the term asthma for fear of alarming parents. "Bronchitis", and to a lesser extent "verkoue op die bors" (chest cold) were the terms other than asthma most commonly attributed to medical practitioners by parents in both groups, reflecting belief in an infective cause of the symptoms.

Alternatively, even if asthma is diagnosed by the practitioner, the implications may not be effectively conveyed to parents by the medical practitioner, or parents may be reluctant to accept the diagnosis or the chronicity of the condition. Fear of prognosis or guilt over

[1] Jones S, Weinberg M, Ehrlich RI, Roberts K. Knowledge, attitudes and practices among parents of asthmatic children (unpublished manuscript).

perceived neglect of the child may underlie this reluctance. When asked what terms they used to describe the child's chest condition, the majority of parents who had acknowledged asthma in a direct question, instead offered one of a number of symptoms such as "tight chest" or other terms, rather than asthma.

The importance of diagnosis rests on the hypothesis that specific asthma management is more likely to follow if the correct diagnosis is made. This study lends support to this hypothesis in that children with recognised asthma were considerably more likely to be on current treatment, and especially on daily treatment, than if asthma was not acknowledged. The importance of recognition is further borne out by the somewhat lower symptom prevalences among these children compared to children in whom asthma was not acknowledged.

The existence of a published guideline based on a graduated approach to treatment allows for evaluation of the management items reported by respondents. Although the latest guideline (South African Childhood Asthma Working Group 1994) postdates the study, earlier guidelines have been published (South African Childhood Asthma Working Group 1992). While approximately 90 percent of all symptomatic children had received some form of treatment in the last 12 months, this did not appear to conform to the recommended protocol. Although the protocol recommended beta-2 agonists as first line therapy rather than theophyllines, a sizeable proportion of children on whom specific information was provided were on a theophylline preparation. In addition, inhaler therapy was used by less than half of the children in the recognised group, and by less than 10 percent in the unrecognised group. The large majority of children were on some form of oral medication, particularly syrups. This preference for oral treatment may be because of a fear of inhaler therapy (e.g. a perception that it is addictive or weakens the heart [Moosa 1996]) or a preference for compound linctuses or syrups offering "broad-spectrum" symptomatic treatment. Also, oral medication, although less cost effective, appears cheaper per unit purchase. Later guidelines have emphasised that inhaled therapy is preferable to oral therapy. Use of syrups, in particular, may make it difficult to

achieve the correct dose.

In the 1991 consensus guideline (South African Childhood Asthma Working Group 1992) bronchodilator therapy was recommended only as *prn* medication, with the addition of maintenance inhaled cromoglycate for moderate asthma and steroids for severe asthma. In the recognised asthma group, 23 percent were on daily medication. While this would include a proportion appropriately on anti-inflammatory treatment such as cromoglycate or steroids, given the medications cited in **Table 8.6** and the underuse of inhalers, it is likely that a sizable proportion of this daily therapy was bronchodilator medication. Similarly, it can be inferred that anti-inflammatory treatment was uncommon in the unrecognised group. Underuse of anti-inflammatory medication has been associated elsewhere with increased morbidity (Gottlieb 1995), and may be one of the factors contributing to high asthma morbidity in this population.

A majority of children overall (59.1%) reported access to treatment from a private general practitioner, despite the fact that only 34.9 percent came from families on some form of medical aid and that a high proportion were of lower socioeconomic status as reflected by education and household variables. A substantial fraction (43%) in the recognised group and 22 percent in the unrecognised group had been treated at some time at Red Cross Children's Hospital. This accords with other findings that even in low income areas, patients may use some combination of private practitioners and the teaching hospital in preference to local day hospitals (Mahomed 1995). Treatment at the hospital may reflect greater severity of asthma and appropriate referral, but may also include inappropriate use of the hospital for primary care (Davidson 1994).

Although the management of asthma should include the use of a peak flow meter in diagnosis, assessment and monitoring of airways obstruction, only about half the recognised group and 13.2 percent of the unrecognised group of respondents could recall the child ever using a peak flow meter, even with a photographic prompt. With regard to home use, however, these meters are relatively expensive (average price as of early

1997: approximately R120) and their purchase is not reimbursable by all medical aid schemes.

The home and bedroom environment merits attention in managing asthma because of the importance of house dust mite (Van Niekerk 1977, Potter 1991) and environmental tobacco smoke in contributing to asthma in this population. Diet is another requisite area of management in some cases because of the role of sulphited drinks and foodstuffs in triggering asthma in susceptible children (Steinman 1993). The lack of any significant difference between the two groups in their responses on the open-ended questions about preventive measures may partly be due to the low response rate to these questions, but may also reflect a low priority given by medical practitioners to these measures even in diagnosed children.

Amongst potential barriers to recognition and treatment, the absence of medical aid was a strong predictor of non-recognition and non-treatment. Medical aid is a marker of socioeconomic status and access to private medical care. Such access typically, although not invariably, implies better quality care. Apart from medical aid, current treatment and inhaler use were less likely in children with some but not all indicators of lower socioeconomic class. Overall, these findings seems to confirm the association of poor asthma control with lower income status. American studies have suggested that children from lower income homes are more likely to use multiple health care providers and make heavier reliance on hospital emergency facilities, resulting in fragmented care and absence of asthma management plans (Davidson 1994, Evans 1992). Children from poorer areas may also be less likely to be on anti-inflammatory medication, contributing to greater morbidity and hospitalisation (Gottlieb 1995). Similar factors are likely to operate in this population.

In conclusion, these findings have important implications for a public health asthma strategy in South Africa, whether at local or national level. These implications are developed in further detail in the next chapter.

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CHAPTER 9

CONCLUSIONS

9.1 Implications of study findings

This thesis is the record of a study that was conceived in the early 1990s and carried out in 1993. The research was part of a growing programme of epidemiologic inquiry into childhood asthma, stimulated by rising measures of asthma occurrence and complication throughout the developed world, and in some cases where documented, the developing world.

Most of the research published has been from developed countries, although the populations studied range from rich to poor. Cape Town, in common with many other cities in both developed and developing countries, has rich and poor inhabitants. The population studied in this thesis is urban, generally poor, but has access to a well developed health care infrastructure including immunisation and medical treatment.

The questions asked in this thesis have both global and local interest. Global in the sense

of contributing pieces to a puzzle that is the same everywhere: what determines asthma incidence and severity? Local in the sense of helping to shape indigenous clinical and public health efforts: what is the size of our problem, and where should we be putting our efforts to solve it?

Since the classic study comparing children in Cape Town to those in the Transkei in the late 1970s, very little population based research into asthma in South Africa has been published. Some of the possible reasons for this paucity of asthma research in the public health context of South Africa are discussed in section 9.2.1. below. The study making up this thesis is thus the most extensive attempt thus far to use epidemiologic tools to add to our knowledge about childhood asthma in South Africa: its prevalence, risk factors and quality of care.

The study consisted of four parts, each asking different questions, with part 1 covering two questions. Although the findings of each part were discussed critically in the relevant chapter, each of these questions is briefly re-visited below in the light of the findings as a whole.

9.1.1. Reliability of questions about wheezing and asthma.

The reliability in this population of the questions derived from the International Study of Asthma and Allergies in Childhood (ISAAC) varied somewhat. The results are reassuring to the extent that in practice most questionnaire studies have relied for inferences about prevalence on the questions that proved the most reliable. These questions were: "has your child ever had asthma" (not including a doctor's diagnosis, although this is a common variant in other studies) and "in the last 12 months, has your child had wheezing or whistling in the chest?". The other symptom questions, which are likely to become widespread through their use in the ISAAC project, proved somewhat less reliable.

The imperfect reliability of the various symptom questions implies misclassification (Kelsey 1986) in the asthma scoring system used to define case status for the purposes

of Chapters 6, 7 and 8.

The effect of using only the self-administered questionnaire for case definition in Chapter 6 would thus have been some degree of misclassification of non-asthmatics as asthmatics and vice versa. To the extent that this misclassification was non-differential with respect to ETS, its effect would have been to reduce the power of the case control study in Chapter 6 to find associations. If anything, the positive findings regarding ETS could thus be stronger.

In Chapter 7, the effect of misclassification would have been to "dilute" the case group used for BHR testing with non-asthmatics (who presumably would have had less BHR). However, it is difficult to predict the effect of such misclassification in contributing to the null or unexpectedly inverse findings.

An attempt was made to minimise misclassification in Chapter 8 by including only subjects meeting the case definition on both questionnaires. Inclusion of non-asthmatics would have overstated the degree of underrecognition and undertreatment.

9.1.2. Prevalence of asthma and wheezing

The prevalence of asthma or of "asthma/wheeze" depends on the definition, and a number of such definitions could be inferred from this study (**Table 9.1**). The strictest definition would be one derived from Chapter 8, viz. case status on both questionnaires plus a positive BHR test (n = 100; see section 8.3.1.). Adjusting for the sampling that was done for the challenge testing, this prevalence (presumably of more severe or active asthma associated with a positive BHR test) can be calculated as 7.8%. Without the requirement of a positive BHR test, the prevalence based on case status on both questionnaires rises to 13.9% (242 / 1 736).

If one limits the case status to that derived from the self-administered questionnaire only (i.e. on one occasion only, as per Chapter 6) the prevalence of asthma rises to 21.1

percent (368 / 1736). The highest values are obtained using single symptom prevalences, for example any wheeze in the previous 12 months (26 to 34 percent or so of children - depending on questionnaire).

Finally, about 11 percent of children were reported as "ever" having had asthma , the variable De Marco (1998) found in an adult population to correlate best with independent clinical evaluation of current asthma.

Table 9.1 Summary of prevalence of asthma/wheeze in whole sample using various definitions derived from study

Self-administered questionnaire	Interview questionnaire	BHR test	Prevalence (%)
Score ≥ 4	Score ≥ 4	Positive	7.8*
Score ≥ 4	Score ≥ 4		13.9*
Score ≥ 4			21.1
Ever had asthma			10.8
Wheezing in past 12 months			26.8
	Wheezing in past 12 months		34.4

BHR: Bronchial hyperresponsiveness

*Adjusted for sampling fractions in selecting case and control groups, and in doing BHR testing.

These high prevalence figures entail a large burden of disease in this community, with many dimensions, mostly unmeasured. Despite underdiagnosis, almost all the cases identified in Chapter 8 had required treatment from the health care system in the previous year. Other than doctor visits, medication costs, much of it for suboptimal treatment, are likely to be substantial (Clark 1995). School absence attributable to asthma has been shown elsewhere to be considerable (Anderson 1983, Hill 1989), and asthmatic children may in turn produce poorer academic performance (Anderson 1983, Fowler 1992). The family anxiety and stress associated with having an asthmatic child add further to the true burden of the disease (Clarke 1992).

The question of generalisability of prevalence figures to elsewhere in South Africa is a difficult one to answer as there are geographic, environmental, medical care, socioeconomic and migration history variables which might affect the expression of asthma, its recognition or severity in different populations. Generalisability to populations with reasonably similar distributions of these modifying variables in Cape Town and other coastal cities is probably justified. More caution is required in regard to inland populations because of the influence of climate first identified by Ordman (1971). This "coastal hypothesis", viz. that asthma is more common at the coast, particularly under of the impact of house dust mite allergy, remains to be tested using standardised methods.

9.1.3. Environmental tobacco smoke and asthma/wheeze

The main aetiologic hypothesis in this thesis pertained to environmental tobacco smoke. The literature was reviewed in some detail in Chapter 3. The findings of this study are mostly in accordance with the conclusions of Strachan and Cook in the most comprehensive recent review of the question (Cook 1997, Strachan 1998a, Strachan 1998b). Specifically, the association in this study between maternal smoking and asthma or asthma symptoms was robust. The prevalence nature of the study makes conclusions about temporality difficult, but statistical modelling of different "windows" of reported maternal smoking suggests that smoking in pregnancy is important. An additional postnatal effect is suggested by the association between number of smokers in the

household (confirmed by urinary cotinine) and asthma/wheeze, a finding also in accord with Strachan and Cook's conclusions.

The mechanism of these effects at the population level remains elusive. However, one can repeat the conclusion of Chapter 3, viz. that there is now enough evidence for public health purposes to accept the causality of an association between maternal and probably other household smoking and asthma in children.

9.1.4. Environmental tobacco smoke and bronchial hyperresponsiveness among children with asthma/ wheeze (exacerbation hypothesis).

Among those children with asthma/wheeze, ETS exposure was not associated with greater BHR. If anything, the association appeared inverse. This was a surprising finding in view of the biologic plausibility of a positive association and the findings of some other studies of asthmatic children. However, as Cook and Strachan point out in their review, the evidence for an association in the published literature is weak, while there is evidence that this literature itself is subject to publication bias.

Cross-sectional bias may have been operating in this study if parents of asthmatics with greater BHR (or its correlates) had adjusted or reduced their smoking so as to decrease the child's exposure. This would in effect be confounding by time dependent variation in the exposure under the influence of the outcome. There was some limited evidence for this. Other possibilities were discussed in Chapter 7, but their effect remains speculative.

A stronger design would have involved carrying out BHR testing on the whole spectrum, i.e. including cases and controls. This would have enabled testing of the hypothesis of an association between ETS exposure and BHR across the whole population, while still allowing a separate analysis of children with asthma/wheeze only. The decision to do BHR testing only on children with asthma/wheeze (and thus to test the aggravation hypothesis) was an attempt to make best use of a more or less fixed sample size for BHR testing enforced by limited resources.

However, studying the whole spectrum of cases and controls would not have solved the cross-sectional problem of parents of asthmatic children altering their smoking behaviour. As pointed out in Chapter 7, a prospective study with multiple measurements of both ETS exposure and BHR is needed to answer this question.

9.1.5. Underrecognition and undertreatment in this population

This phase of the study was the most local as it addressed phenomena likely to reflect local belief and health service practice. The study confirmed the opinions of clinicians (Morris 1994, Green 1998) concerning the shortfall in asthma management practices, and had the advantage of doing so in a random population sample that included users of medical services in the private and public sectors. It also demonstrated that the diagnosis of asthma (or acceptance of the diagnosis) does make a difference to management and that the deficiencies are greatest in patients dependent on public sector facilities.

9.2. Public health application of the findings and related research needs.

9.2.1. Primary prevention of asthma in South Africa

Childhood asthma is clearly of great concern and interest to primary health practitioners and paediatricians in urban and rural areas in South Africa (Luyt 1994, Morris 1994, Green 1998, Syabbalo 1990). However, asthma occupies an uneasy position in the public health arena in South Africa. Public health in the sense of an organised state response to population health and disease has its origins in the need to control infectious disease epidemics (Phillips 1990). This is reflected in the list of notifiable diseases under the Health Act, 1977, which are primarily infectious (and of which tuberculosis, measles and malaria predominate in numbers among the notifiable diseases), and in the category of non-notifiable but priority diseases, of which AIDS and sexually transmitted diseases are the most prominent. In the face of large disparities in child survival and morbidity between rich and poor in South Africa (Bachmann 1996) state programmes directed at improving maternal and child health in South Africa have understandably focused on improving obstetric care and child survival, promoting optimal growth and reducing malnutrition. Amidst the many pressing problems in child health in South Africa, asthma

was not, for example, recognised as a priority in a recent policy document on child health (RSA 1995).

Asthma is a chronic disease of high morbidity and low mortality, affecting somewhat older children than those at greatest risk in the traditional child survival model. Various perceptions that asthma is primarily genetic, allergic or psychological, or a middle class disease, may have made the role for an organised public health response seem less important to policy makers. Where an environmental cause of asthma is considered, it is presumed to be ambient air pollution, responsibility for which was recently transferred from the Department of Health to the Environment ministry.

By contrast, as a result of the large role that pharmacological treatment plays in the management of asthma, the pharmaceutical industry has acquired a large stake in the organised societal response to asthma. This takes many forms, including funding the National Asthma Education Programme, the Allergy Society of South Africa, allergy and asthma research (including this study), the development of management guidelines, publications, conferences, public lectures, and, through sales representatives, the influencing of medical practitioners. This role of the pharmaceutical companies has resulted in an emphasis on correct medication regimens, and on mechanistic research to identify points in the immunochemical pathway amenable to modification by drugs. In comparison, there is little interest in developing effective non-pharmaceutical or public health measures to control asthma.

In considering a public health response, however, it has to be acknowledged that probably not enough is known at this stage to develop policies on primary prevention of asthma (Burney 1990, Peat 1994). Prospects for primary prevention are obviously limited by what is known about the causes of asthma, and among putative causes, by what is modifiable. If the "TH1/TH2 hypothesis", of the rise in asthma as a product of declining infectious disease and/or more widespread immunisation in infancy, proves correct (Cookson 1997, Strachan 1997, Shirakawa 1997, Hopkin 1997, Kemp 1997), the

increase in asthma will prove to be one of the costs of improving child survival in the modern era. Future solutions such as active modification of the immune system, e.g. through immunisation against asthma, have been mooted (Hopkin 1998).

More environmentally directed options for primary prevention of asthma are limited. Early allergen control in susceptible children (as measured by family history) is a prospect that has been investigated. An early trial suggested that the incidence of atopic disease in infancy can be reduced by measures to limit contact with dietary antigens and house dust mite (Arshad 1992). Recent reviews of trials restricting maternal diet in pregnancy (Kramer 1998a) and during lactation (Kramer 1998b) have concluded little or no benefit, however.

There is in addition the question of whether such approaches would be effective in the population setting of this study. The ability to modify the internal home environment, including furnishings, pets and to provide special (or even broadly "healthy") diets presupposes a degree of economic comfort, planning of daily household activities and continuity of medical support that is probably beyond most of the families of the children in this study.

The one clearly definable and achievable public health measure to prevent asthma is the reduction of ETS exposure in children. The attributable fraction for ETS with respect to asthma of 14 percent cited for the United States in Chapter 3 was based on a relative risk estimate of 1.4. If one takes the prevalence odds ratio of 1.8 from this study as a proxy for the relative risk and a background female smoking prevalence of 45% (based on smoking in pregnancy [Steyn 1997]), the attributable fraction would be 26 percent (Rothman 1986).

Estimates of attributable fractions overstate the prospects of prevention. If ETS exposure causes certain types of asthma, e.g. wheezing with infection, rather than other types, the fraction may be lower. Also, total elimination of exposure is utopian, which sets a lower

limit on the proportion that could be prevented.

Better understanding of the mechanism whereby ETS exposure affects the risk or expression of asthma will enable a better estimate of impact of prevention. However, ETS exposure *in utero*, early infancy and childhood has so many other adverse effects (US Department of Health and Human Services 1993), that the justification for preventing exposure of children to ETS is heavily overdetermined.

Research is needed to answer the question about the best way to reduce exposure in this heavily smoking population. Global programmes to reduce the burden of tobacco are still in development (Mackay 1994), and national efforts have borne fruit in the form of tougher legislation (RSA 1999). Local application is still lacking, however.

A separate study arising out of this research (Jordaan, in press) showed that the largest contributor to the variance in urine cotinine creatinine ratio among these primary school children was maternal smoking. Maternal smoking in fact accounted for 21.8 percent of the variance in CCR, equivalent to that from all other sources combined, viz. paternal smoking, other smokers and "community contribution" (crudely estimated from overall smoking prevalence of parents of children attending the child's school).

Efforts at reducing ETS exposure among asthmatic children, i.e. secondary prevention, have been shown to be effective (Hovell 1994, Whalgren 1997). These interventions directed at parents include counselling and monitoring of smoking. With regard to primary prevention, i.e. before the child develops asthma, target populations for anti-smoking measures within the ambit of the health services include pregnant women attending antenatal clinics (Dolan-Mullen 1994) and mothers attending well baby and child growth clinics. Outside the health services, workplace programmes may offer a prospect for reducing smoking among mothers, as 42 percent of the workforce in the Western Cape is female (RSA 1996). Simple advice by medical practitioners has also been shown to have some beneficial effect, although small, on cessation by patients (Silagy 1999).

Prevention measures need to be based on an understanding of the complexities of smoking behaviour by mothers, however. Since a smoking mother often implies the presence of a smoking father, smoking in the household rather than that of one member needs to be targeted. Sociologically oriented approaches have also shown that smoking is a response to role stress and lack of social networks among women (Romano 1991, Doyal 1995).

In the context of schools, pupil education is needed to reduce uptake among the young, the parents of tomorrow. Education of teachers is clearly needed as well, since judging by what the study team observed during the many school visits, the smoking example is all too common among teachers in this community.

9.2.2. Secondary prevention of asthma

In the public health model, secondary prevention of asthma includes early diagnosis and appropriate management to limit progression of the disease and its complications.

While underdiagnosis and undertreatment of childhood asthma are real, the reasons are speculative. Research is needed to identify barriers to early diagnosis and appropriate management. These may include ignorance of or resistance to the diagnosis or some aspect of treatment on the part of practitioners, or resistance to the diagnosis or treatment on the part of patients. Systemic barriers may include cost of medication, the time demands of patient education and follow up care and the difficulty for patients in following treatment and avoidance regimens. Such a study of barriers and determinants is currently underway in this population (A. Bheekie - personal communication).

Despite improvements in medication regimens, various aspects of treatment remain controversial. The shift from bronchodilators to corticosteroids for maintenance treatment is widely accepted in expert guidelines but may still be a source of uncertainty among practitioners and patients (Green 1998). Publicity about the danger of bronchodilators in certain circumstances may have added to popular perceptions that inhaled therapy is

addictive, or weakens the heart or lungs (Moosa 1996, Lim 1996). Uncertainties surrounding the effectiveness of specific allergen avoidance measures may make practitioners and patients reluctant to invest time and effort in achieving avoidance regimens, for example with respect to house dust mite allergen.

Cost barriers are frequently mentioned with respect to medication, particularly anti-inflammatory treatment (Watson 1997). In this study, medical insurance, which implies access to private practitioners, was a predictor or recognition and treatment. While inhaled corticosteroid medication is available at public sector clinics in Cape Town, there are constraints on its use. For example, the medication may not be prescribed on weekends or after hours, requiring the patient to return during normal clinic hours. Only very recently have 100 ug metered dose inhalers, which makes step-up therapy easier, been made available in addition to 50 ug dose devices.

Research done elsewhere suggests that good control on maintenance corticosteroids is cost effective (Perera 1995), a lesson to be emphasised in the stocking of public sector service dispensaries. Effectiveness of anti-inflammatory treatment requires good follow up medical care, however, and pressures of poverty, family disorganisation, and overburdened state services may form a significant barrier even where the medication is freely available.

A start to a national strategy of secondary asthma prevention in South Africa has been made with the National Asthma Education Programme (Luyt 1994). This needs to be supported by local research. A local cost-effectiveness analysis of asthma management would be useful for assessing the likelihood of achieving compliance with recommended management protocols in low income communities. Also, while there is evidence from elsewhere that targeted house dust avoidance measures can reduce symptoms in asthmatic children (Durham 1996), the effectiveness of these measures on a large scale have yet to be confirmed in this population (Manjra 1994).

There is current interest in methods of changing practitioner diagnosis and treatment behaviour. Research suggests that simple publication of expert guidelines is ineffective (Grimshaw 1993). Outreach education ("academic detailing") visits hold out more promise (Soumerai 1990, Grimshaw 1993) and a trial of such intervention is currently under way in this population, building on the findings of this thesis. Reorganisation of private medical care under the pressure of managed care organisations may be one way in which the practice of cost effective asthma management is promoted.

The findings of this study also have implications for the organisation of primary care services. It appears that many families in this population try to cope with the child's asthma symptoms through a combination of approaches. These include recourse to traditional remedies[1] and broad spectrum chest medications (typically theophylline containing syrups), urgent visits to the local general practitioner or an after hours service, and occasional referral visits to the children's hospital.

Currently, the cornerstone of state policy for reorganisation of public health care in South Africa is the district based primary health care strategy (RSA 1997). Such a strategy is likely to include more primary care facilities offering 24-hour medical care in proximity to where people live. While acute asthma care is an essential part of this service, it is not enough. To avoid the fragmentation of asthma care that appears to be a feature in this community, adequate follow up of acute cases at routine services and better communication between private and public sector facilities are needed.

The high degree of cooperation received from the school system in this study suggests that schools may have a role to play in asthma education and care. A school of 600 pupils is likely to have 60 asthmatic pupils, or alternatively a teacher with 40 pupils in her class will have 4 asthmatics among them. There have been initiatives in Australia to develop a schools policy for asthma (Thoracic Society of Australia and New Zealand

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1994). This recognises a role for asthma education at schools focused on improved recognition of asthma by staff, encouragement of participation in sport by asthmatic children, the initial management of acute attacks by teachers and provision of support for parents.

Finally, continued epidemiologic research is needed to monitor the asthma epidemic, to suggest or test hypotheses about causes, and to evaluate the effectiveness of health care delivery. In the face of competition for research money and effort, the place of such epidemiologic research in keeping asthma in the public eye, in improving the quality of life of asthmatic children and, in time, in solving the puzzle of its increase, needs to be secured.

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UNIVERSITY OF CAPE TOWN

APPENDIX 1

Department of Community Health

Medical School
Observatory 7925
South Africa
Telephone: 47-1250
Fax No: (021) 47-8955
Head of Department: Professor J.M.L. Klopper, OBE

DEAR PARENTS:

SURVEY OF BREATHING PROBLEMS IN CHILDREN: PART 1

The University of Cape Town and the Medical Research Council are doing a survey of breathing problems among sub-B children in Mitchell's Plain.

The *purpose* of the study is to measure how many children are affected by chest or breathing problems, and what treatment they are receiving.

We are also interested in factors in the *environment* which may be causing these problems.

The survey has two parts. In this part (*PART I*), we are asking you please to fill in this short questionnaire.

In *PART II*, we shall be coming to the schools to examine some of the children and our nurses will be interviewing these parents at home.

All of this information is completely confidential to the survey team and parents. Participation is voluntary.

The results of the survey will be used to improve the treatment of breathing and chest problems in children. It will also help us to understand the main causes of these ailments, so that we can try to prevent them.

Thank you for spending a few minutes on this questionnaire.

Yours sincerely

Signed

DR R. EHRLICH
Department of Community Health

PART I:

Please answer all the questions by making a **TICK** in the right box. If you make a mistake put a cross in the box and tick the correct answer. *Only tick one box for each question.*

They all apply to your child in Sub-B.

Examples of how to mark your questionnaire

	Yes	No
To answer "yes"	☑	☐
To answer "no"	☐	☑
If you make a mistake	☑	☒

For office use only

1. Child's age at *last* birthday ☐ — 7 ☐☐

2. Is your child a: Boy ☐ Girl ☐ — 9 ☐

3. You are the child's: Mother ☐ Father ☐ Grandmother ☐ Other ☐ — 10 ☐

PLEASE THINK BACK OVER THE LAST 12 MONTHS

4. Has your child had *wheezing or whistling* in the chest in the last 12 months? Yes ☐ No ☐ — 11 ☐

5. *How many* attacks of wheezing or whistling in the chest has your child had in the last 12 months?

None	1-3 attacks	4-12 attacks	More than 12 attacks
☐	☐	☐	☐

12 ☐

Please go to the next page

For office use only

6. In the last 12 months how often, on average, has your child *woken up due to* chest wheezing or whistling?

Never	Not every week	Every week	
☐	☐	☐	13 ☐

Yes	No	
☐	☐	14 ☐

7. In the last 12 months, has wheezing or whistling in the chest ever been so bad that your child *couldn't talk properly or had to whisper*?

Yes	No	
☐	☐	15 ☐

8. In the last 12 months, has your child's chest sounded wheezy or whistly, *during or after running or playing hard*?

Yes	No	
☐	☐	16 ☐

9 In the last 12 months has your child had a troublesome *dry cough* in the night *that was not from* a cold or chest infection?

Yes	No	
☐	☐	17 ☐

10. In the last 12 months, has your child had a *tight chest*?

THE NEXT QUESTIONS ARE ABOUT ANY TIME (EVER) IN THE PAST

Yes	No	
☐	☐	18 ☐

11. Has your child *ever* had wheezing or whistling in the chest at any time in the past?

Yes	No	
☐	☐	19 ☐

12. Has your child ever had *asthma*?

Yes	No	
☐	☐	20 ☐

13. Is your child at present taking any *regular asthma treatment*?

21 ☐ status

22 ☐ 1 language

Please go to the next page

PLEASE MAKE SURE YOU HAVE TICKED EVERY QUESTION.

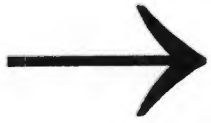
PLEASE GIVE THE COMPLETED QUESTIONNAIRE TO YOUR CHILD

TO RETURN TO HIS/HER TEACHER TOMORROW.

THANK YOU

End of Part I

****

Please read on 

SURVEY OF BREATHING PROBLEMS IN CHILDREN: PART 2

This second part of the survey will take place in September and October. It will involve some but not all of the children from Part 1. This part is also entirely voluntary.

Interview

Our nurses would like to visit some of the parents at home to ask you some questions about the child's health and home environment. This will take about 20 minutes and will be at a time convenient to you.

Examination of the children at school

We shall also be coming to the schools to examine some of the children. The examination has three steps:

1. A doctor will listen to each child's chest.

2. Each child wil be asked to pass some urine. This specimen will be analysed in our laboratory for "cotinine". This comes from nicotine, and gives us an idea of how much cigarette smoke (if any) the child has absorbed from the environment.

3. The child will have a "histamine breathing test". In this test the child is first asked to blow into a breath recorder. We have found that sub-B children have no problem doing this blowing.

   The child then breathes in a puff of air with a small amount of histamine in it, and blows again. This step is repeated 1 or more times if needed with slightly more histamine each time.

   Most children will not show positive on this test. However, children with an asthmatic tendency on that day will blow out less air. This is a positive test. These children will be given two puffs of medication to remove any effects of the test.

   This is a safe procedure, and is widely used in many countries as a test for asthmatic tendency. Some children may feel a little hoarse and may cough from the breathing in and blowing out, but this passes after a short while.

Letting you know

Each parent will receive a letter with the full results of the examination. The letter will also contain advice for parents and the child's doctor if necessary. Parents will also be able to get further advice from our allergy specialist if they want to.

Please turn over the page

IF YOU HAVE ANY QUESTIONS, PLEASE PHONE DR R. EHRLICH, UNIVERSITY OF CAPE TOWN TEL: 406 6483 OR YOUR PRINCIPAL

CHILD'S NAME:

NAME of parent or guardian with whom child lives:

ADDRESS: (where child lives all or most of the time during term)

PHONE NUMBER: Day: Night:

If we need to interview the mother (or person who looks after the child), what is the best day and time to find you/her at home?

CONSENT:

I hereby give ☐ **I hereby do not give** ☐

permission for my child to participate in the survey of breathing problems:

Signed: (parent or guardian)

Date today:

THANK YOU ONCE AGAIN

CONSENT TO APPROACH DOCTOR

1. Which doctor(s) usually treats the child for wheezing/whistling, night cough, tight chest or asthma?

RECORD MORE THAN ONE IF NECESSARY

Name _____ _____

Address _____ _____

_____ _____

_____ _____

2. We would like to contact your doctor and ask him/her some questions about the treatment of the child.

All the information obtained will be strictly confidential.

Do you have any objections to us doing this?

If not, respondant is asked to sign below

I hereby authorise Dr R. Ehrlich to contact the child's doctor to obtain information about the child's history of respiratory symptoms and treatment. This information will be treated as confidential.

Signed _____

Dated _____

Thank you for allowing me to visit you and for spending time answering these questions.

APPENDIX 2

MITCHELL'S PLAIN CHILD HEALTH STUDY

INTRODUCTION TO PARENTS

1. Thank you for participating in the study by the University of Cape Town and the Medical Research Council.

2. The aim of the study is

   2.1 to measure how many sub B children in Mitchell's Plain have chest problems and

   2.2 what factors in the environment may be causing these problems.

3. Today I would like to ask you some questions about your child's health and household environment.

4. We shall also be visiting schools to do a histamine test and urine test.

5. All information is strictly confidential.

6. All answers are voluntary - if you feel you would prefer not to answer any question, please say so.

7. If your child is found to need medical attention, we will inform you.

8. The results of the study will be given to the schools and will be available to any parent and doctor.

INTERVIEWER'S COMMENTS:

Card Number [1] 1

A. IDENTITY

1. Study number [ ][ ][ ][ ][ ][ ] 7
2. Name of child _____
3. Date of interview (DD MM YY) _____ _____ _____ [ ][ ][ ][ ][ ][ ] 13
4. Interviewer no. 1 2 3 4 5 6 [ ] 14
5. Address of child _____

   _____

   _____
6. Full name of respondent _____
7. Tel. number of respondent _____
8. Zone (area to be divided up) _____ [ ] 15
9. Respondent's relationship to child

mother	1	
father	2	
grandmother	3	
other (specify)_____	4	[ ] 16

10. In the past 12 months, has the child lived with *someone other than the respondent for more than* one *month*?

Yes = 1	No = 2	[ ] 17

11. How much time does the respondent at present spend at the child's home during a week?

Away from the home mornings only	1	
Away full weekdays	2	
Away weekday nights or weekends or both	3	
At home all or most of the time	4	[ ] 18

12. Is the child covered by any medical aid or fund?

Yes = 1	No = 2	Don't know = 9		19

12.1 If Yes is it a

Private Medical Aid	1	
Medical Fund	2	
Don't know	9	20

B. DEMOGRAPHIC AND HOUSEHOLD

1. Sex of child — Male = 1 | Female = 2 | 21

2. Date of birth (DD MM YY) _____ _____ _____ | | | | | | | 27

3. Where was the child born? _____ | 28

4. Number of years child has lived in Mitchell's Plain _____ | | 30

5. How many adults and children usually live *in* the same house as the child? (Include the child) _____ | | 32

6. How many children (under 14 years) live *in* the house? (Include the child) _____ | | 34

7. How many people sleep in your child's sleeping room? (Include the child) _____ | | 36

8. How many rooms are there inside the house? (not counting bathrooms) _____ | 37

9. Do you do anything to heat the home?

Yes = 1	No = 2	Don't know = 9		38

9.1 If YES do you use:

	Yes	No		
1. Heater plugged into electricity?	1	2		39
2. Gas?	1	2		40
3. Paraffin?	1	2		41
4. Charcoal, anthracite or wood fire?	1	2		42

10. What source/fuel is used to cook with?

	Yes	No		
1. Electricity?	1	2		43
2. Gas?	1	2		44
3. Paraffin?	1	2		45
4. Charcoal, anthracite or wood fire?	1	2		46

11. Is there a pet in the child's home?

	Yes	No		
1. Cat	1	2		47
2. Dog	1	2		48
3. Bird	1	2		49
4. Other	1	2		50

C. THE CHILD' SYMPTOMS AND MEDICAL TREATMENT

THE NEXT QUESTIONS COVER THE LAST 12 MONTHS

1. In the last 12 months, has the child had *wheezing or whistling* in the chest?

Yes = 1	No = 2		
			51

If Yes

1.1 Was this ONLY with a cold, or sometimes when s(he) did NOT have a cold?

Only with a cold	1	
Sometimes without a cold	2	
Don't know	9	52

1.2 *How many attacks* of wheezing or whistling in the chest has the child had in the last 12 months?

None	1	
1-3 attacks	2	
4-12 attacks	3	
More than 12 attacks	4	53

2. In the last 12 months, how often, on average has your child *woken up due to* chest wheezing or whistling?

Never	1	
Not every week	2	
Every week	3	54

3. In the last 12 months, has wheezing or whistling in the chest ever been so bad that your child *couldn't talk properly or had to whisper*?

Yes = 1	No = 2		
			55

4. In the last 12 months, has the child's chest ever sounded wheezy or whistly, *during or after running or playing hard*?

Yes = 1	No = 2		
			56

5. In the last 12 months, has the child had a troublesome *dry cough* in the night, *that was not from* a cold or chest infection?

Yes = 1	No = 2		
			57

6. In the last 12 months, has the child had a *tight chest*?

Yes = 1	No = 2		
			58

If NO to ALL the questions under section C (nos C.1-6), skip to 9

If YES to any of the questions in the above section C, continue

7. In talking about these symptoms (wheeze, tight chest, night cough) with your doctor, family or friends, what name do you use to describe the problem?

		60

_____

THE NEXT FEW QUESTIONS ARE ABOUT TREATMENT

8. During the past 12 months, has the child received any treatment from a doctor for any of the following symptoms?

	Yes	No		
1. Wheezing/whistling in the chest	1	2		61
2. Tight chest	1	2		62
3. Difficulty sleeping because of cough	1	2		63

If NO to all three above, skip to 9

If YES to treatment of any symptoms, continue

8.1. What name(s) did the doctor use to describe the child's chest problem?

	64

_____

8.2. Where did the child go for treatment for this chest problem?

	Yes	No		
1. Private doctor	1	2		65
2. Day Hospital	1	2		66
3. Red Cross Hospital	1	2		67
4. Other hospital or clinic	1	2		68
5. Other (specify) _____	1	2		69

8.3 Is the child *currently* on any treatment for any of the following: wheezing/whistling in the chest, tight chest, night cough or asthma?

Yes, every day	1	
Yes, some days, when s/he needs it	2	
No	3	
Don't know	9	70

If NO, DON'T KNOW skip to 9

8.4 **If YES** what treatment? **(Interviewer shows card)**

	Yes	No	Don't know		
1. Tablets	1	2	9		71
2. Syrup	1	2	9		72
3. Inhaler	1	2	9		73
4. Nebulizer (oxygen)	1	2	9		74
5. Injection	1	2	9		75
6. Other (specify) _____	1	2	9		76

_____

_____

Card Number 2 1

Study number | | | | | | | 7

9. Do you know of anything you can do *inside the child's bedroom* to prevent allergy or breathing problems?

Yes = 1	No = 2		8

If Yes specify _____ 10

_____

10. Do you know of anything your child can avoid *eating or drinking* so as to prevent allergy or breathing problems?

Yes = 1	No = 2		11

If Yes specify _____ 13

_____

11. Has the child ever been asked by a doctor or nurse to blow into a peak flow meter?
(show picture of meter)

Yes = 1	No = 2	Don't know = 9		14

THE NEXT TWO QUESTIONS ARE ABOUT ANY TIME (EVER) IN THE PAST

12. Has the child ever had wheezing or whistling in the chest *at any time* in the past?

Yes = 1	No = 2		15

13. Has the child ever had *asthma*?

Yes = 1	No = 2		16

If NO skip to 14

If YES continue

13.1 At what age did the asthma begin? _____ 17
(birth-1yr = 0, don't know = 9)

13.2 Does s/he still have asthma?

Yes = 1	No = 2	Don't know = 9		18

If YES go to 14

If NO continue

13.3 At what age did the asthma stop? _____ 19

THE LAST QUESTION IS ABOUT THE PAST TWO WEEKS

14. In the past *two weeks*, has the child had to go to a doctor or clinic with any illness or injury?

Yes = 1	No = 2	Don't know = 9		20

D SALT INTAKE AND DAMP

1. When food is cooked for the family, *how much* salt (Aromat/Fondor) is added?

2 or more teaspoons	1		
1 teaspoon	2		
Just a pinch or one shake	3		
None	4		
Don't know	9		21

2. Does the child (or anyone else) *add extra salt* or Aromat/ Fondor to the food the child eats?

No, no extra salt or Aromat/Fondor is added	1		
Yes, but the child's food is tasted first before adding	2		
Yes, even before the food is tasted	3		
Don't know	9		22

3. How often did the child eat salty snacks during the last week (i.e. chips, niknaks, salted peanuts, salty biscuits, biltong, dried sausage)?

Never	1		
1-2 times	2		
3 or more times	3		
Don't know	9		23

4. How often did the child eat cold meats (polony, viennas) during the *last week*?

Never	1		
1-2 times	2		
3 or more times	3		
Don't know	9		24

5. Within the past year has there ever been wet or damp spots *on surfaces* inside the child's present home (e.g. walls, ceiling, carpets)

Yes = 1	No = 2	Don't know = 9		25

6. Have you ever noticed *mould or mildew* growing on any surface (walls, ceiling, carpets)

	Yes	No		
1. In the child's bedroom?	1	2		26
2. In the living room?	1	2		27
3. In the kitchen?	1	2		28
4. In the bathroom?	1	2		29
5. In any other inside area of the child's home?	1	2		30

7. Has there been a leak, flooding or water damage in the child's home *in the past year*?

Yes = 1	No = 2	Don't know = 9		31

E SMOKING

Mother or female "parent"

1. Is the female parent the

Child's natural mother	1		
Other (specify) _____	2		32

THE NEXT FEW QUESTIONS APPLY TO THE WOMAN WHO IS THE MOTHER OR ACTS IN PLACE OF THE MOTHER

2. What was the highest standard completed by the mother (female parent)

_____ | | | 34

(Code no. of years of schooling)

3. Does she *currently* work?

Yes = 1	No = 2	Don't know = 9		35

3.1 **If NO,** is she (a)

Housewife	1	
Unemployed (looking for work)	2	
Other (specify) _____	3	36

4. Describe her *present or last* permanent job _____ 39

_____

Never worked = 0, 00

5. Does the mother/female parent *currently* smoke regularly (at least one cigarette a day)?

Yes = 1	No = 2	Don't know = 9		40

If NO, skip to 6.

If YES, continue

5.1 What year did she start smoking? _____ 42
(Don't know = 99)

5.2 How many cigarettes does she smoke daily? _____ 44
(Don't know = 99)

GO TO QUESTION 7

6. Did she ever smoke *in the past* while living in the home with this child?

Yes = 1	No = 2	Don't know = 9		45

If NO, skip to 7.

If YES continue

6.1 What year did she start? _____ 47
(Don't know = 99)

6.2 What year did she stop? _____ 49
(Don't know = 99)

6.3 How many cigarettes did she smoke daily in the past? _____ 51
(Don't know = 99)

THE NEXT TWO QUESTIONS ARE ABOUT THE PERIOD JUST BEFORE AND AFTER THE CHILD WAS BORN.

7. Did the *natural mother* smoke at any time *during her pregnancy* with this child?

Yes = 1	No = 2	Don't know = 9		52

8. Did the natural mother (or female parent) smoke *during the first year of life* of this child?

Yes = 1	No = 2	Don't know = 9		53

Father or "male parent"

9. Is there a male parent in the household?

Yes = 1	No = 2		54

If NO, skip to question 15

If YES continue

9.1 How many years has he been living in the household? (less than 1 yr = 0) | | | 56

10. What was the highest standard completed by the father (current male parent)

_____ | | | 58

(Code no. of years of schooling)

11. Does he *currently* work?

Yes = 1	No = 2	Don't know = 9		59

11.1 If NO, is he

Unemployed (looking for work)	1		
Other (specify) _____	2		60

12. Describe his *last* or *present* permanent job

_____ | | | 63

_____

13. Does he *currently* smoke regularly (at least one cigarette, cigar, pipeful) a day?

Yes = 1	No = 2	Don't know = 9		64

If NO, skip to 14

If YES, continue

13.1 What year did he start smoking?_____ (Don't know = 99) | | | 66

13.2 How many cigarettes does he smoke daily? _____ (Don't know = 99, pipe/cigar smokers = 88) | | | 68

GO TO QUESTION 15

14. Did he ever smoke *in the past* while living in the home with this child?

Yes = 1	No = 2	Don't know = 9		69

15. Did the/a male parent smoke in the child's home *during the first year of the child's life*?

Yes	1		
No	2		
No male parent during 1st year of life	3		
Do not know	9		70

Other household or family members (excluding female and male parent of the child)

16. How many *other* people are there who live in the house (sleep there at least 3 times a week) who currently smoke? | | | 72

_____
(Don't know = 99, none = 00)

17. If the child shares a sleeping room with anyone, do any of these people smoke in that room?

Yes = 1	No = 2	Don't know = 9		73

F FAMILY HISTORY

1. Has the childs' *natural* mother ever had asthma?

Yes = 1	No = 2	Don't know = 9		74

2. Has the child's *natural* father ever had asthma?

Yes = 1	No = 2	Don't know = 9		75

3. Has the child's *own brother or sister* ever had asthma?

Yes = 1	No = 2	Don't know = 9		76

Card Number | 3 | 1

Study number | | | | | | | 7

e past 12 months have *you (the respondent)* had any
e following?

	Yes	No		
Wheezing	1	2		8
Coughing up phlegm	1	2		9
Tight chest	1	2		10
Any chest illness	1	2		11

G CHILD'S PAST HISTORY

1. Has the child had his/her tonsils out?

Yes = 1	No = 2	Don't know = 9		12

2. Was the child breastfed?

Yes = 1	No = 2	Don't know = 9		13

3. Has the child ever had eczema?

Yes = 1	No = 2	Don't know = 9		14

4. Has the child ever had hayfever?

Yes = 1	No = 2	Don't know = 9		15

Status | | 16

CONSENT TO APPROACH DOCTOR

1. Which doctor(s) usually treats the child for wheezing/whistling, night cough, tight chest or asthma?

   RECORD MORE THAN ONE IF NECESSARY

   Name _____ _____

   Address _____ _____

   _____ _____

   _____ _____

2. We would like to contact your doctor and ask him/her some questions about the treatment of the child.

   All the information obtained will be strictly confidential.

   Do you have any objections to us doing this?

   If not, respondant is asked to sign below

   I hereby authorise Dr R. Ehrlich to contact the child's doctor to obtain information about the child's history of respiratory symptoms and treatment. This information will be treated as confidential.

   Signed _____

   Dated _____

****

Thank you for allowing me to visit you and for spending time answering these questions.