Risk factors precipitating exacerbations in adult asthma patients presenting at Kalafong Hospital, Pretoria

by

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DECLARATION

I, **M M Geyser**, hereby declare that the work which I hereby submit as partial fulfilment for the degree **MSc (Clinical Epidemiology)** on which this thesis is based, is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been submitted, or is being submitted for another degree at this or any other university.

Signed..... Date...27/01/2006

ABSTRACT

Objective. To determine if poor compliance with asthma treatment is independently associated with exacerbations requiring emergency room visits in adult patients seen at Kalafong Hospital, a secondary regional- and teaching hospital affiliated to the University of Pretoria.

Methods. A matched case-control study was undertaken – matched on age and gender, between December 2003 and May 2005. Known asthma patients with exacerbations presenting at the hospital's emergency unit were chosen as cases. Controls were stable asthma patients recruited from the outpatient departments. A structured questionnaire was used to interview patients concerning their possible exposure to certain triggers and risk factors. Univariate and multivariate analysis with conditional logistic regression was done to determine any significant exposures. Participants were between 18 - 65 years of age.

Results. Three hundred and fifty-six patients were evaluated. Fifty cases and 100 controls were enrolled. Cases were shown to be more non-compliant than controls (OR = 2.18; 95% CI 1.09 to 4.38, p = 0.03). Missing follow-up doctor appointments for the last six months was statistically significant with an OR of 2.39 (95% CI 1.08 to 5.27) and p = 0.03. Cases had more bacterial respiratory infections than controls (OR = 5.00; 95% CI 1.57 to 15.94, p = 0.01). More controls (50%) were exposed to dust- and environmental pollution than cases (38%) (OR = 0.60; 95% CI 0.29 to 1.23, p = 0.16). There was also an interaction between non-compliance and dust- and environmental pollution.

Conclusion. Non-compliance and bacterial respiratory infections were strong predictors of exacerbations in adult asthma patients at Kalafong Hospital.

ABSTRAK

Objektief. Om te bepaal of swak meewerkendheid ten opsigte van asmabehandeling, onafhanklik geassosieer is met akute asma-aanvalle deur volwasse pasiënte in Kalafong-hospitaal, 'n sekondêre streeks- en opleidingshospitaal geaffilieer aan die Universiteit van Pretoria.

Metodes. 'n Geval-kontrole studie is gedoen – gepas op ouderdom en geslag, tussen Desember 2003 en Mei 2005. Gevalle was bekende asmapasiënte wat met akute aanvalle presenteer het in die hospitaal se noodgevalle-eenheid. Kontroles was ook bekende asmapasiënte gewerf uit die buitepasiënte-afdelings. Onderhoude met pasiënte is gevoer met behulp van 'n gestruktureerde vraelys oor moontlike blootstelling aan risiko faktore en snellerfaktore. Univariaat en multivariaat analise met voorwaardelike logistiese regressie is gedoen om te bepaal of daar enige betekenisvolle blootstellings was. Kandidate was tussen die ouderdomme van 18 en 65 jaar.

Resultate. Driehonderd-ses-en-vyftig pasiënte is evalueer. Vyftig gevalle en 100 kontroles is in die studie ingesluit. Gevalle was minder meewerkend ten opsigte van asmabehandeling as kontroles (OR = 2.18; 95% BI: 1.09 tot 4.38, p = 0.03). Opvolg doktersafsprake wat gemis is die vorige ses maande was statisties betekenisvol met 'n OR van 2.39 (95% BI 1.08 tot 5.27) en p = 0.03. Gevalle het meer respiratoriese infeksies gehad as kontroles (OR = 5.00; 95% BI 1.57 tot 15.94, p = 0.01). Meer kontroles (50%) as gevalle (38%) was blootgestel aan stof- en omgewingbesoedeling (OR = 0.60; 95% BI 0.29 tot 1.23, p = 0.16). Daar was ook interaksie tussen nie-meewerkendheid en stof- en omgewingbesoedeling.

Gevolgtrekking. Nie-meewerkendheid ten opsigte van die gebruik van asmabehandeling en bakteriële infeksies is sterk voorspellers van aanvalle in volwasse asmapasiënte in Kalafong-hospitaal.

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Introduction and Literature Review

INTRODUCTION

Definition and Pathophysiology of Asthma

Asthma was first recognised by the Chinese about 4 000 years ago. It was certainly known to Hippocrates, who also described the use of an inhaler for its relief. In 1000 BC, the ancient Egyptians were treating asthma with an inhalation of camel and crocodile excrement mixed with herbs and heated over hot bricks – visitors to the bedside were probably not concerned by the effects of treatment on the ozone layer [1].

Asthma is defined as a chronic inflammatory condition of the airways which is usually allergic in origin and is characterised by hyperresponsive airways that constrict easily in response to a wide range of stimuli. These result in the characteristic symptoms of wheezing, tightness of the chest, a cough and dyspnoea, which are often worse in the early hours of the morning [2-5]. Asthma is characterised by a marked improvement after the use of a bronchodilator and/or a two-week trial of systemic corticosteroids. The improvement is 12% and 200ml in forced expiratory volume in the first second (FEV_1), or 15% in peak expiratory flow rate (PEFR) [2].

The main physiologic components of the asthmatic response include airway inflammation with wall thickening and increased vascular permeability, mucus hypersecretion and bronchial smooth muscle contraction [6]. Inflammation may lead to airway remodelling with a proliferation of the airway smooth muscle and the deposition of matrix proteins. There is emerging evidence that airway remodelling may be present very early in the disease, even in infancy,

and it may represent a risk factor for the persistence of symptoms and the development of asthma [4].

A stimulus triggers a cascade of inflammatory cell migration and activation involving resident cells (mast cells, macrophages and epithelial cells), and recruited inflammatory cells (lymphocytes, eosinophils and neutrophils). Histamines, leukotrienes, prostaglandins, kinins, cytokines and granular proteins are released by these activated cells leading to epithelial damage, increased mucus production, impaired mucus clearance, vasodilatation, mucosal oedema, smooth muscle contraction, and bronchial hyperresponsiveness. The final outcome is a narrowing of the airways and airflow obstruction [4,7]. Upstream obstruction causes premature closure of the airways with expiration, as pleural pressure becomes greater than the pressure inside the airway – the equal pressure point. Downstream airways become compressed with expiration, trapping air in the alveolar sacs [5]. The process may progress slowly over days (80 – 90% of adults) [6] or rapidly over a few hours (type 2 or asphyxic or hyperacute asthma).

Progressive airflow narrowing due to airway inflammation and/or increased bronchiolar smooth-muscle tone is the hallmark of an asthma attack and leads to increased flow resistance, pulmonary hyperinflation, and ventilation/perfusion (V/Q) mismatching [6]. Atelectasis (microscopic, segmental or lobar) also follows complete obstruction. These all manifest as arterial oxygen desaturation. Hypoxia triggers an increase in the respiratory rate, which decreases the dynamic compliance of the lungs [5].

If passive expiration is incomplete, it results in intrinsic or auto-positive end-expiratory pressure (PEEP*i*). While this correlates to the magnitude of hyperinflation, it is also influenced by the compliance of the respiratory system and can hence be increased by active expiratory muscle contraction, and increased elastic lung recoil [6].

Greatly increased intrathoracic pressure impedes venous return, thus decreasing the right and left ventricular preload. Hypotension and tachycardia

ensue and, in severe cases, tissue hypoperfusion and hypoxia can cause further cellular dysfunction [5].

When patients become asymptomatic, FEV1 tends to be at least 40 to 50% of predicted; when physical signs disappear, FEV1 is typically 60 to 70% of predicted or higher [6].

The characteristic symptoms of asthma are wheezing, coughing and dyspnoea. Wheezing ensues due to airflow limitation causing a high-pitched whistling sound, which is usually heard on expiration but may also be heard on inspiration. Coughing probably results from the stimulation of sensory nerves in the airways by inflammatory mediators [3,4]. During an asthma attack spasms, congestion and oedema produce wheezing, suprasternal and intercostal muscle retraction, flaring of the alae nasi, dyspnoea and coughing, although not all symptoms are present in all patients [8,9].

Epidemiology of Asthma

Research is proceeding at an unprecedented speed in all areas of asthma research, and yet, we live with a disease that escalates in prevalence and severity, despite a greater understanding of the pathophysiology and therapy thereof [10-14]. The total prevalence of asthma is estimated to lie at 7.2% of the world's population (6% in adults, 10% in children) [3]. In the United States, asthma is the 11th most frequent emergency department (ED) diagnosis and adolescents and young adults are the most affected age groups. Women visiting the ED for asthmatic complaints are hospitalised twice as often as men. The mortality in the US is about 5000 asthmatics across all age-groups per year [3,4,6]. Data from Australia, Canada and Spain reported that acute asthma accounted for 1 to 12% of all adult ED visits. In Britain the prevalence is about 10%. Asthma kills about 2000 people in Britain each year [1].

Twenty to thirty per cent of patients in the US visiting the ED for acute asthma required hospital admissions. Rates of hospital admission for female patients

and black patients were consistently higher than for male patients and whites [3,5,6]. This gender ratio reverses for children, where the prevalence of asthma is higher in boys than girls (3:2 ages 6-11 and 8:5 for ages 12-17) [3].

The reasons for rising rates of asthma morbidity and mortality are unclear. Case-control studies using retrospectively collected data have suggested that excess use of short-acting ß-agonists and under-use of inhaled corticosteroids may be associated with this phenomenon, although more recent data suggest that patterns of $ß_2$-agonist use may be markers of more severe asthma rather than a causal factor [1,10].

Results from a 1998 survey conducted by the American Lung Association highlight the following quality-of-life issues:

- Asthma significantly disrupts lives;
- Asthma is not under control;
- Asthmatics adapt their lifestyle to accommodate their asthma, they do not lead a "normal" life;
- Families of asthmatics adapt to accommodate asthma and lack a "normal" family life;
- Many asthmatics do not know the difference between the controller medication that keeps symptoms from occurring and the reliever medication that can alleviate an attack [3].

The prevalence of asthma is also impacted on by socioeconomic and environmental factors. These include the exposure to aeroallergens or air pollution. Links between heredity and asthma prevalence are further important. The term atopy has special significance and refers to the inherited predisposition to allergic diseases such as asthma, allergic rhinitis or eczema. Atopy underlies almost all asthma in children and most asthma in adults. The development of asthma in an atopic individual depends on exposure to specific allergens, infections, or other environmental influences [3].

Asthma in South Africa

The prevalence of asthma in South Africa lies at 5% for adults and 10% for children [15]. In 1993 a study done by the Medical Research Council's (MRC) Health Systems Research Unit and the Community Health Department at the University of Cape Town found a 12-month prevalence of asthma in children, diagnosed on the basis of symptoms, of 13% [16]. Another study on children in Cape Town, carried out in 1998, found a prevalence of clinically significant asthma between 7% and 13% [17]. According to Jeena [15] there is a significant increase in the number of people who have asthma amongst all races in South Africa. Hospital admissions for asthma increased 25 to 200 times over the past 25 years in Durban and Soweto [15].

A lower incidence of allergies in the family histories of blacks compared to other races was shown in recent studies. However, many more blacks who have a positive family history of allergy develop allergic diseases. The early exposure to foreign allergens from the newly adopted western lifestyle has contributed to the higher degree of sensitisation recorded amongst black infants than others. These factors account for the increased number of black children who have asthma [15].

In South Africa asthma appears to be associated with urbanisation, and it is likely that with its rapid urbanisation South Africa is also experiencing a rise in the prevalence of asthma [17]. Studies conducted on rural Transkeians have shown that migration to urban and peri-urban settlements results in a 20 times increased risk of developing asthma symptoms [15].

According to Weinberg, the most common indoor allergens in South Africa are animal dander, feathers, moulds, house dust mites and cockroaches. Environmental factors like air pollutants, cigarette smoking, motor vehicles' exhaust fumes and changes in fuels used for combustion (anthracites and coal) are also important triggers. South Africa has one of the largest floral kingdoms in the world (8000 species of flora found in the Cape Peninsula alone), including 947 indigenous and 115 naturalised grass species. All of

these produce pollen at different times of the year. The levels of pollen in the atmosphere depend on the season and the presence of wind or thermal currents [15].

A few studies highlight a real need for a greater level of patient education [17], especially in the rural areas [12]. Bheekie confirmed the under-diagnosis of asthma by general practitioners (GP), inappropriate use of drug therapy (43% of GP's felt that antibiotics improved an episode of asthma), poor compliance to preventive measures (52% of parents of asthmatic children did not adhere to advice on smoking avoidance) and delay in consultations in a survey [16].

The beneficial effects of inhaled steroids when used as maintenance therapy in chronic asthma are well known. When used regularly, inhaled steroids decrease the number of asthma exacerbations caused by most triggers, including exercise [9]. This fact was also recognised in a Cape Town study where it was concluded that practitioners should increase the use of current asthma guidelines, as under-treatment is a huge problem [17].

The National Asthma Education Programme in South Africa is actively engaged in the education of all asthmatic patients, urban and rural, and is probably the most active educational programme in South Africa that does not have government funding. Websites on the above programme and of the Allergy Society of South Africa are available to interested parties. Guidelines for the management of asthma are also available on internet: *Guidelines for the Management of Chronic Asthma in Adults – 2000 update* – by the South African Thoracic Society [2], *Global Initiative for Asthma (GINA)* and the *Guidelines for the Diagnosis and Management of Asthma – NIH (National Institutes of Health)* [Add3].

Asthma Exacerbations: Risk Factors/Triggers

Patients at any level of severity of asthma – from mild intermittent to severe persistent – can experience exacerbations. Each patient with asthma responds to a unique set of triggers. In some cases, exposures may be unavoidable (for example exposures to cold air, exercise or the asthma-inducing effects of pregnancy) [8].

Many triggers can provoke asthma exacerbations. According to the literature the following are possibilities:

Inhalant irritants: Dust as well as passive smoke (cigarette) exposure [1,8,10,14,15,18,19] were significant triggers according to a Canadian study [20] (avoidance of environmental tobacco exposure was found to be an important and statistically protective factor) [21]. Other inhalant irritants were diesel exhaust fumes [22,23], air pollution [24] (including ozone and various components of particulate matter such as sulphur dioxide and nitrogen dioxide) [15,25], gases, odours, insecticides, perfumes, hair spray, paint fumes [15], chemicals and strong cleaning agents [8]. A more recently appreciated trigger is the exposure to biologicals such as endotoxin and to transition metals such as copper and lead [15,23].

Inhalant allergens: Repeated exposure to allergens such as animal dander (from cats, dogs, rabbits, hamsters and even mice) [15], pollen, house dust mites [1,11,14,15,18,21,22], mould, cockroach antigens [8] and grass [24] lead to increased bronchial reactivity [9]. As regards cockroaches, their eggs, droppings and bodies are all common allergens [15]. Feathers also cause allergies, even if contained in a pillow [15]. It was recently reported that 54% of patients admitted to an intensive care unit (ICU) for asthma showed a positive result in skin tests for one or more fungal allergens (*Alternaria tenuis, Cladosporium cladosporoides, Helminthosporium maydis* or *Epicoccum nigrum)* [26].

Adverse drugs: Medications such as aspirin, indomethacin, ibuprofen, phenylbutazone, and other non-steroidal anti-inflammatory drugs (NSAID's) [8,27] and nonselective beta-blockers, such as propranolol can cause adverse events, as can food additives such as colouring and sulfites [8].

Adherence/compliance: According to Sawyer, poor adherence with the asthma treatment regimen is common [28]. Also, in a South African study done at seven rural health clinics by Green, only 43% of adults completed each step correctly in the use of inhaler devices [12]. The complexity of a multiple daily medication regimen is often a factor [8].

Seasonal and weather: Extremes in weather or temperature, for example very cold, windy, or dry air; moving from the hot outdoors to an air-conditioned room (and vice versa) may cause asthma exacerbations [8]. The effects of weather changes on asthma are probably largely related to the indirect effects on local allergens, e.g. fungal spores, pollens or house dust mite populations, rather than to the direct cold or irritant effects on the airways [26]. A time-trend analysis conducted by Johnston et al, comparing the seasonal patterns of respiratory infections and hospital admissions for asthma in adults and children, showed a strong correlation between the seasonal patterns of upper respiratory infections and hospital admissions for asthma [11].

Premenstrual and menstrual phases: Numerous case studies suggest that premenstrual declines in hormonal levels (from the late follicular to the late luteal phase) worsen asthma symptoms, and that exogenous hormone therapy, in reducing hormonal fluctuation, eliminates premenstrual asthma exacerbations. Stress exposure in the premenstrual or menstrual phase was associated with a significant decline in peak expiratory flow rate (PEFR) [13].

Pregnancy: This is a common trigger according to Reinke due to physiological changes [8]. However, Haggerty et al described a substantial variation [13]: 43% of women reported a worsening of symptoms [14], 43% reported no change, and 12 - 71% reported an improvement [13].

Exercise: [14] This has often been the first trigger for asthma attacks experienced by patients. It occurs in 40 to 90% of asthmatic cases. Exercise induced asthma (EIA) is usually preceded by at least 3 to 8 minutes of exercise. The increased amount of ventilation is the ultimate determinant leading to EIA and can be achieved by either exercise or hyperventilation. This means that any exercise can lead to EIA if it is performed hard enough or long enough to increase the amount of air being inhaled [9]. Vigorous activities such as basketball, soccer, distance running, tennis or the carrying of heavy loads [8] can cause more severe attacks than less vigorous ones such as baseball. Also, figure skaters and ice hockey players who have asthma are more prone to EIA in their particular sports because of the cold environment [9,27], – cool and dry air worsens airway cooling.

Respiratory infections:

Viral: Epidemiologic studies have detected viral upper respiratory infections in 80 to 85% [29,30] of childhood asthma exacerbations and in more than half [24,29,30] of adult exacerbations [17]. Of the viruses identified, 64% were rhinoviruses [11,25,29-32], 30% were coronaviruses [12,32] and the rest were influenza, parainfluenza and respiratory syncytial viruses [32].

Bacterial: Studies point to the possibility that in some patients acute Chlamydia pneumoniae infections may lead to acute exacerbations of asthma [33]. An Australian study adds the mycoplasma infection to this equation [32].

Heroin: A retrospective case-control study was done among drug using asthma patients requiring ICU care in Chicago. In 56% of these patients asthma exacerbations were associated with heroin insufflations [34].

Strong emotions: Excessive fear, excitement and anxiety [35] do not cause asthma but may aggravate it [36]. The mechanism of hyperventilation can subsequently dry the airways [8]. Laughter-induced asthma is strongly associated with exercise as a trigger [37].

Under-treatment: According to Samaria, in a country like India, one of the most important causes of acute severe asthma is the inadequate or maltreatment of bronchial asthma due to the high percentage of illiteracy [26].

Occupational asthma: A recent review of the relevant literature by a committee of the American Thoracic Society concluded that 15% of asthma among adults could be attributed to their occupation. The prevalence of workplace exacerbation of asthma has been investigated using a variety of data sources. In Ontario, Canada, the Worker Compensation Board reported that half of all asthma claims received between 1984 and 1988 involved exacerbation. It was concluded that workplace exacerbation of asthma is a relatively common occurrence identified in 23% of adult asthma cases [38].

Antic [39] suggested the following to prevent exacerbations:

- Identify and avoid allergen exposure;
- Give an annual influenza vaccination;
- Use antibiotics as appropriate;
- Avoid adverse drugs (e.g. beta blockers, salicylates, NSAID's);
- Identify and treat gastro-oesophageal reflux; and
- Avoid non-allergic triggers (smoke, exposure to irritants through occupation or hobbies).

Cost to Society

Green et al report that asthma takes up 1 – 2% of the total health budget in direct costs, with equally large indirect costs being incurred for time lost from work [25] and reduced productivity. Much of these costs come from hospital admissions. Osur states that approximately one third of the direct care costs of asthma are attributable to ED visits and hospitalisations [11].

According to Rodrigo US studies estimated that the total burden of asthma was approximately $6 billion per year. Direct costs represented almost 90% of the total societal costs. This is contrary to Green et al's report. Hospitalisations and ED visits account for almost 50% of the total cost overall. The average annual cost per patient who had an attack was $600, compared to $170 for those who did not. An increase of >3.5 times. Only 20% of asthmatics have ever been admitted to an ED or hospital, yet these patients account for >80% of total direct costs. The estimated annual per patient cost when admitted is $2500 versus $140 for the rest [6]. Outpatient visits account for 23% of total direct costs and medication for only 16% [3].

Motivation for Study

Many studies have been done in other countries on specific triggers, especially allergens and viral respiratory infections. However, circumstances differ in the public sector in South Africa, and other factors like compliance and under-treatment that may be as applicable should be studied in contention. Although a study had been done on asthma management and on perceptions in rural South Africa [12], no studies could be found about the reasons for exacerbations in the adult population and on interventional strategies.

Chapter 2
Study Methodology

METHODOLOGY

Study Design

Matched case-control study - matched on age and gender.

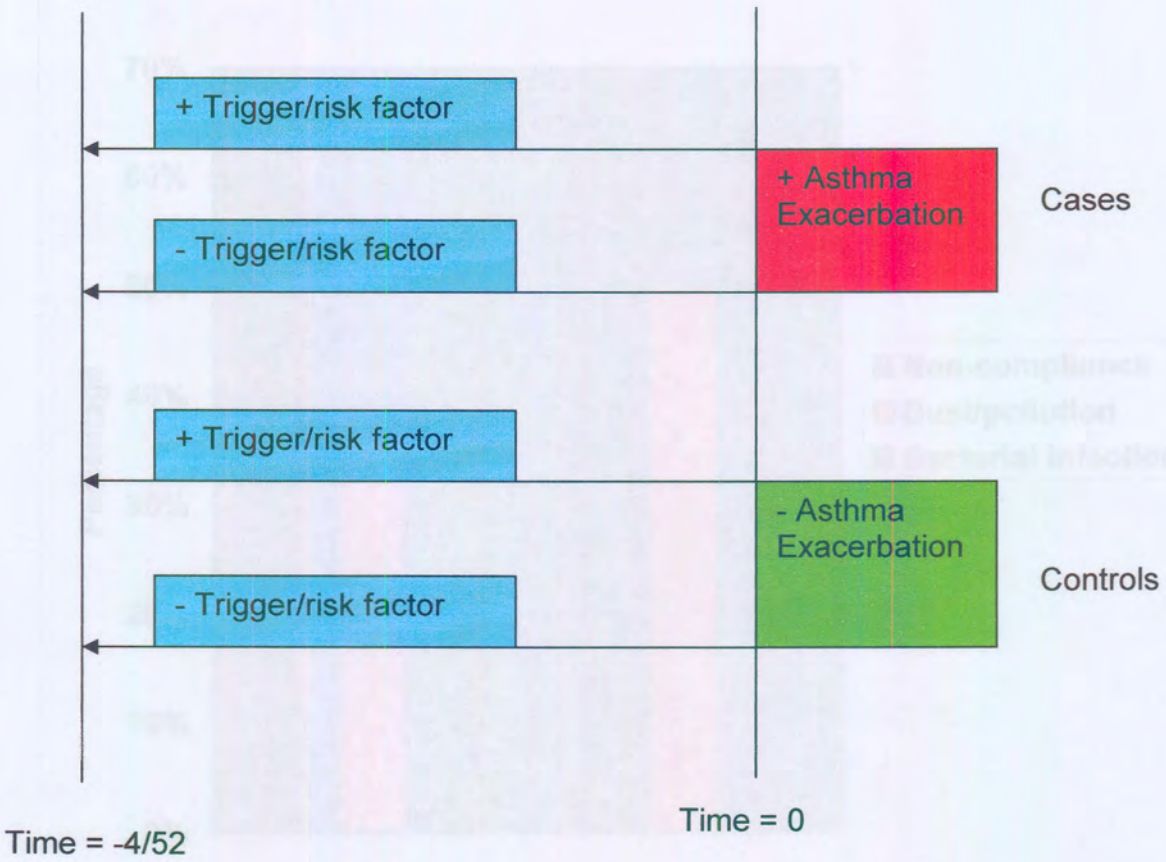

Figure 1 – Schematic presentation of a case-control study design

Study Setting and Population

The setting for this study was the emergency unit, the primary health clinic and the asthma clinics at the secondary family medicine and internal medicine outpatient departments at Kalafong Hospital, a secondary regional- and teaching hospital affiliated to the University of Pretoria. The population consisted of adult asthma patients between 18 and 65 years of age, which were homogenous and representative of the communities served by Kalafong, namely Atteridgeville, Saulsville, Brazzaville, Lotus Gardens and Pretoria West. Areas such as Centurion and Laudium were mostly excluded as these areas have their own clinics, except for a few patients attending specialist clinics at Kalafong.

Definition of Cases and Controls

Cases: Known asthma patients were considered cases if they developed an acute asthma exacerbation, defined as shortness of breath, chest tightness, wheezing and a peak expiratory flow rate (PEFR) that was at least 15 – 25% less than normal, requiring an ED visit, between December 2003 and May 2005.

Inclusion criteria:

- Diagnosis of asthma according to the National Guidelines of Management of Asthma in Adults at the Primary Level: Department of Health Directorate: Chronic Diseases, Disabilities and Geriatrics [40];
- Age of between 18 and 65 years;
- Duration of asthma of more than one year;
- Attendance of an asthma clinic at family medicine or internal medicine at Kalafong Hospital for six months or longer.

Exclusion criteria:

- Any history of smoking;

- Chronic obstructive pulmonary disease (COPD);
- Pulmonary embolism;
- Active pulmonary tuberculosis;
- Congestive heart failure;
- Cough secondary to medications (e.g. angiotensin-converting enzyme inhibitors);
- Laryngeal dysfunction;
- Mechanical obstruction (e.g. tumour);
- Pulmonary eosinophilic infiltration;
- Vocal cord dysfunction;
- Self-diagnosed asthma; and
- Newly diagnosed asthma.

Controls: Known asthma patients were considered controls if they had no exacerbations requiring emergency visits during the preceding month. Controls were recruited from the primary health clinic, secondary family medicine clinic and internal medicine outpatients.

Inclusion criteria.

- Age of between 18 and 65 years;
- Diagnosis of asthma according to the National Guidelines of Management of Asthma in Adults at the Primary Level: Department of Health Directorate: Chronic Diseases, Disabilities and Geriatrics [40];
- Duration of asthma of more than one year;
- Attendance of an asthma clinic at family medicine or internal medicine at Kalafong Hospital for six months or longer.

Exclusion criteria.

- Any history of smoking;
- Self-diagnosed asthma;
- Newly diagnosed asthma;
- COPD;

- Congestive heart failure;
- Cough secondary to medications (e.g. angiotensin-converting enzyme inhibitors);
- Laryngeal dysfunction;
- Mechanical obstruction (e.g. tumour);
- Pulmonary eosinophilic infiltration;
- Vocal cord dysfunction.

Sample Size and Selection

A complete sampling of all cases that fit the necessary criteria was done. On a confidence level of 95% and power of 80%, the sample size was determined using the Epi Info6 statistical package. With a ratio of 1:2 for cases versus controls, 20% exposure of controls and an odds ratio of 3.0, it was decided to use 56 cases and 112 controls. Due to time constraints only 50 cases and 100 controls were included.

The sampling frame of the cases was the emergency unit register. Four hundred and forty-four asthma patients were treated at the unit between December 2003 and May 2005. Of these 356 patients were evaluated by the investigator; 50 patients fitted the inclusion criteria and were included in the study as cases. That is a total of 14%.

Eighty eight patients could not be evaluated by the investigator due to leave, illness or other departmental and academic responsibilities. This resulted in 12 missed cases. In conclusion there was a 19.4% loss of patient cases.

Measurement of Exposure

The investigator used a structured questionnaire after obtaining informed consent to interview all participants. Information obtained included age, gender, compliance, literacy, allergic rhinitis, infections, exercise, passive smoking, dust- and environmental pollution, in-house coal fires, adverse drugs, stress/anxiety, exposure to household pets, premenstrual/menstrual phases, pregnancy, work-related exposures and under-treatment. Exposure to triggers was noted for the past four weeks in both cases and controls. Each trigger/risk factor was defined as followed:

Non-compliance

Non-compliance was identified as a trigger/risk factor when the participant missed one or more doctor appointments in the past six months, or missed one or more script appointments in the past six months or not taking medication as prescribed – the patient had to describe exactly how they used their medication and this was compared to the prescription in their file. The doctor and script appointments were available from each patient's file.

Literacy Level

The following four sub-groups were included:

1. No schooling;
2. Some primary schooling;
3. Some high school training; and
4. Matriculation.

A low literacy level would be seen as a trigger/risk factor.

Severity of the Chronic Phase of Asthma

The following four sub-groups were investigated according to the *Guidelines for the Management of Chronic Asthma in Adults – 2000 Update* [2]:

1. Mild intermittent;
2. Mild persistent;

3. Moderate persistent; and
4. Severe persistent.

A high level of severity of chronic asthma was seen as a trigger/risk factor.

Under-treatment

The prescribed medication of the patient was evaluated against the severity of the chronic phase of the patient's asthma according to the guidelines of the National Institutes of Health [Add 3]. All insufficient prescriptions were applicable.

Exercise/sport

Participation in any formal or informal sport activities were seen as a possible trigger/risk factor for an asthma exacerbation. This included walking distances of at least 1km.

Viral Infections

A viral infection was seen as a trigger/risk factor when at least three of the following five components on the questionnaire were marked positive:

1. Sore throat;
2. Fever;
3. Runny/blocked nose;
4. Muscle aches;
5. Exposure to others with a cold.

Household Pets

This trigger/risk factor was restricted to cats or caged birds in the house or in the direct working place.

Passive Smoking

Passive tobacco smoking indoors at home, at the working place or at any other institution was seen as a trigger/risk factor.

Strong Emotions

1. ***Anger***

   Anger was seen as a trigger/risk factor when a participant had any loss of temper.

2. ***Excitement***

   Excitement was seen as a trigger/risk factor when a participant was extremely excited or happy about something e.g. gifts, sports, finances or relationships.

3. ***Anxiety***

   Anxiety was seen as a trigger/risk factor when a participant was anxious due to e.g. crime, death of a relative, or having an anxiety attack.

Dust- and Environmental Pollution

Dust- and environmental pollution was defined as a trigger/risk factor when for example a participant stayed next to a dusty dirt road, carrying high volumes of traffic including heavy vehicles or near factories.

House dust was not included in this category due to its universality and difficulty to measure by the participants.

Coal Stoves

With exposure of participants to in-house wood burning or usage of coal stoves, this category was seen as a trigger/risk factor.

Weather

Weather was seen as a trigger/risk factor for all participants experiencing rainy weather conditions during their exposure assessment period.

Medication

Non-steroid Anti-inflammatory Drugs

Any orally ingested, rectally inserted or injected NSAID's received by participants were seen as a trigger/risk factor for acute asthma exacerbations.

β-blockers

Any β-blocker containing medication was seen as a trigger/risk factor. This included eye drops, intravenous preparations and tablets.

Allergic Rhinitis

Allergic rhinitis was seen as a trigger/risk factor when symptoms were present for more than one hour per day over two weeks. At least two of the following four components on the questionnaire were marked positive:

1. Blocked nose;
2. Sneezing;
3. Runny nose;
4. Seasonal symptoms.

Bacterial Respiratory Infections

A bacterial respiratory infection was seen as a trigger/risk factor when antibiotics were prescribed by the attending doctor for a clinically bacterial upper airway infection or a radiological confirmed lower tract infection.

Work-related

Work-related was seen as a trigger/risk factor when a participant was exposed to for example spray-painting, diisocyanate or employed at a pharmaceutical-, plastics- or platinum industry.

Pregnancy, Menopause, Premenstrual/menstrual

All female participants were evaluated regarding pregnancy, menopause or their menstrual cycles. Pregnancy was diagnosed with a positive β-human chorionic gonado trophins (β-HCG) blood test and menopause on a history of normal cessation of menstruation. Premenstrual/menstrual was seen as a possible trigger/risk factor for cases in their premenstrual or menstrual phase during an exacerbation and for controls with no amenorrhoea for the past four weeks.

Prescribed Medication

Prescribed medication was recorded from the patients' files. This included β-agonist-, ipratropiumbromide-, beclomethasone- and budesonide inhalers, oral theophylline, long-acting β_2-agonists and daily oral steroids. The cases were questioned during the interview with regard to the utilisation of their β_2-agonist inhalers: the number of dosages used in the past 24 hours and the average dosage used per day in the past seven days.

Ethical Considerations

The Ethics committee of the Faculty of Human Health Sciences of the University of Pretoria authorised the study. It was done according to the ethical principles of the Declaration of Helsinki and Geneva Declaration of World Medical Association. An informed consent form was available to every participant to sign. It spelled out the study objectives, information required, risks and benefits. Participants could withdraw at any stage and this did not affect their further care.

The investigator alone undertook all the interviews and research. Code numbers and patient names were kept separately and were destroyed as soon as all data had been collected in order to ensure anonymity.

Data Analysis

Univariate statistical analysis was done to assess the characteristics and risk factors of participants. Stata 8.1 software (Intercooled for Windows; STATA Corp, College Station, Tex; 2003) was used. Student's *t* test was used for continuous data. The *effmenu1* command for use in matched case-control studies was applied to determine odds ratios and interactions. For multivariate analysis conditional logistic regression was used to determine confounders, build a logistic model and test for interactions.

Chapter 3
Study Results

RESULTS

One hundred and fifty (150) patients were recruited: 50 cases with acute asthma exacerbations, from the emergency unit, and 100 controls with stable asthma, from the outpatient departments. Exposure assessment was done for the four weeks prior to recruitment on both the cases and controls. Each of the cases was matched with two controls. Matching was done on gender and age, and controls were recruited an average of 10.82 days (standard deviation of 12.73) after the cases. Univariate statistical analysis was done to assess the characteristics and risk factors of participants (Table I).

Cases were more likely than controls not to comply with treatment OR = 2.18 (95% confidence interval 1.09 to 4.38), p = 0.03, and to have had bacterial respiratory infections OR = 5 (95% CI 1.57 to 15.94), p = 0.01. Twenty per cent of cases were diagnosed with bacterial infections and treated with antibiotics, while 4% of controls were treated for respiratory bacterial infections in the preceding four weeks. Respiratory viral infections were present according to responses to the questionnaire in 32% of cases and 23% of controls.

The literacy level (matriculation) was higher in cases than controls – 34% versus 16%. Females were more likely to be included in the study, as 84% of participants were females and only 16% were males. The results also found more controls (50%) to be exposed to dust or pollution than cases (38%). Under-treatment was detected in less than 20% of cases and controls. Rainy weather was present in 82% of cases and also in 90% of controls. Birds as pets or in the working place were identified in 2% of cases and 12% of controls with the OR = 0.17 and p = 0.09. More female controls (46%) than cases (38%) were in their menopause. Although more cases than controls

were exposed to passive smoke (36% vs 26%) and to non steroid anti-inflammatory drugs (40% versus 34%), this was not statistically significant.

TABLE I - CHARACTERISTICS OF STUDY PARTICIPANTS

Character	Cases (n=50)		Controls (n=100)		OR matched	95% CI	p-val
	N	%	N	%			
Gender							
Male	8	16	16	16	N/A		
Female	42	84	84	84	N/A		
Age mean±SD[1]	43.6± 11.1		44.8± 10.2		N/A		0.49
Literacy							0.07
1. NS[2]	6	12	20	20			
2. SPS[3]	14	28	29	29	1.68	0.55 – 5.16	0.37
3. SHT[4]	13	26	35	35	1.36	0.42 – 4.46	0.61
4. M[5]	17	34	16	16	4.60	1.26 – 16.79	0.02
Severity							0.36
1.MI[6]	10	20	19	19			
2.MP[7]	18	36	32	32	1.14	0.43 – 3.02	0.79
3.Mod P[8]	19	38	48	48	0.79	0.30 – 2.07	0.64
4.SP[9]	3	6	1	1	5.77	0.51 – 65.86	0.16
Non-compliance	32	64	44	44	2.18	1.09 - 4.38	0.03
Undertreatment	8	16	11	11	1.57	0.57 – 4.33	0.38
Exercise	22	44	48	48	0.80	0.36 – 1.79	0.59
Viral infections	16	32	23	23	1.50	0.74 – 3.05	0.26
Pets: cats	4	8	10	10	0.79	0.24 – 2.61	0.70
Passive smoke	18	36	26	26	1.66	0.77 – 3.58	0.19

Emotions: *anger*	21	42	41	41	1.05	0.51 – 2.13	0.90
excitement	15	30	40	40	0.64	0.31 – 1.33	0.24
anxiety	11	22	23	23	0.95	0.42 – 2.11	0.89
Dust/pollution	19	38	50	50	0.60	0.29 – 1.23	0.16
Coal stoves	4	8	4	4	2.00	0.50 – 8.00	0.33
Weather: rain	41	82	90	90	0.00	0.00 – ∞	1.00
NSAIDS[10]	20	40	34	34	1.32	0.64 – 2.76	0.45
β-blockers	0	0	1	1	0.00	0.00 - ∞	1.00
Allergic rhinitis	4	8	11	11	0.70	0.21 – 2.35	0.56
Bacterial infections	10	20	4	4	5.00	1.57 – 15.94	0.01
Work-related	4	8	2	2	4.00	0.73 – 21.84	0.11
Females: *pregnancy*	2	4.8	1	1.2	4.00	0.36 – 44.11	0.26
menopause	16	38.1	39	46.4	0.38	0.10 – 1.49	0.17
menstrual/ pre menstrual	23	54.8	42	50	1.56	0.49 – 4.93	0.45

1 SD Standard deviation; 2 NS No schooling; 3 SPS Some primary schooling; 4 SHT Some high school training; 5 M Matriculation; 6 MI Mild intermittent; 7 MP Mild persistent; 8 Mod P Moderate persistent; 9 SP Severe persistent; 10 NSAIDS Non steroid anti-inflammatory drugs

The parameters used to determine non-compliance are shown in Table II. Only one of the three needed to be fulfilled in order to mark a participant as not complying. Missing follow-up appointments in the last six months was statistically significant with an OR of 2.39 (95% CI 1.08 to 5.27) and p = 0.03. The median for missed appointments by the cases was 0 (range 0 to 5), and 0 (range 0 to 4) by the controls; p = 0.01 (Mann-Whitney test). Script appointments were also missed by a median of 0 (range 0 to 4) for both cases and controls; p = 0.07.

TABLE II - EXPOSITION OF COMPLIANCE OF STUDY PARTICIPANTS

Parameters	Cases (n=50)		Controls (n=100)		OR Matched	95%CI	p-value
	N	%	N	%			
Missed f/u appointment(s) past 6 months	16	32	16	16	2.39	1.08 – 5.27	0.03
Missed script appointment(s) past 6 months	19	38	24	24	2.18	0.96 – 4.93	0.06
Meds not taken as prescribed	20	40	27	27	1.78	0.87 – 3.62	0.11

Analysis of the case-control data with individual matching was done using the change-in-estimate method of conditional logistic regression in a stepwise forward-selection fashion to assess clinically relevant and statistically significant variables identified in the univariate analysis. These included non-compliance, bacterial infections and literacy. Also included were birds, work-related, dust- and environmental pollution, menopause and passive smoke with p-values up to 0.2. Non-compliance was the forced-in variable in the model. A bacterial infection had an effect of more than 10% on the OR (18%), and was included in the model as a confounder. Menopause was not included with a change in effect of 10.42%, as it would restrict the model to females only and would result in the loss of too many study participants. The other variables had the following changes in OR and were therefore also not included: literacy (all four levels were investigated), work-related 2.6%, dust- and environmental pollution 5.8% and passive smoke 1.9%.

However, the backward-elimination algorithm was also applied to verify the possibility of missing possible confounders. The following variables were deleted from the model stepwise:

- Literacy (all four levels);
- Work-related p = 0.13; and
- Passive smoke p = 0.07

The final model (Table III) consisted of the dependant variable (case/control), non-compliance, bacterial infections and dust- and environmental pollution.

TABLE III - LOGISTIC MODEL FOR ASTHMA EXACERBATIONS

Case	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]
ncompliance	2.82	1.11	2.64	0.008	1.31 - 6.10
Bacterial infection	7.68	5.01	3.13	0.002	2.14 - 27.58
Dust exposure	0.44	0.19	-1.94	0.053	0.19 - 1.01

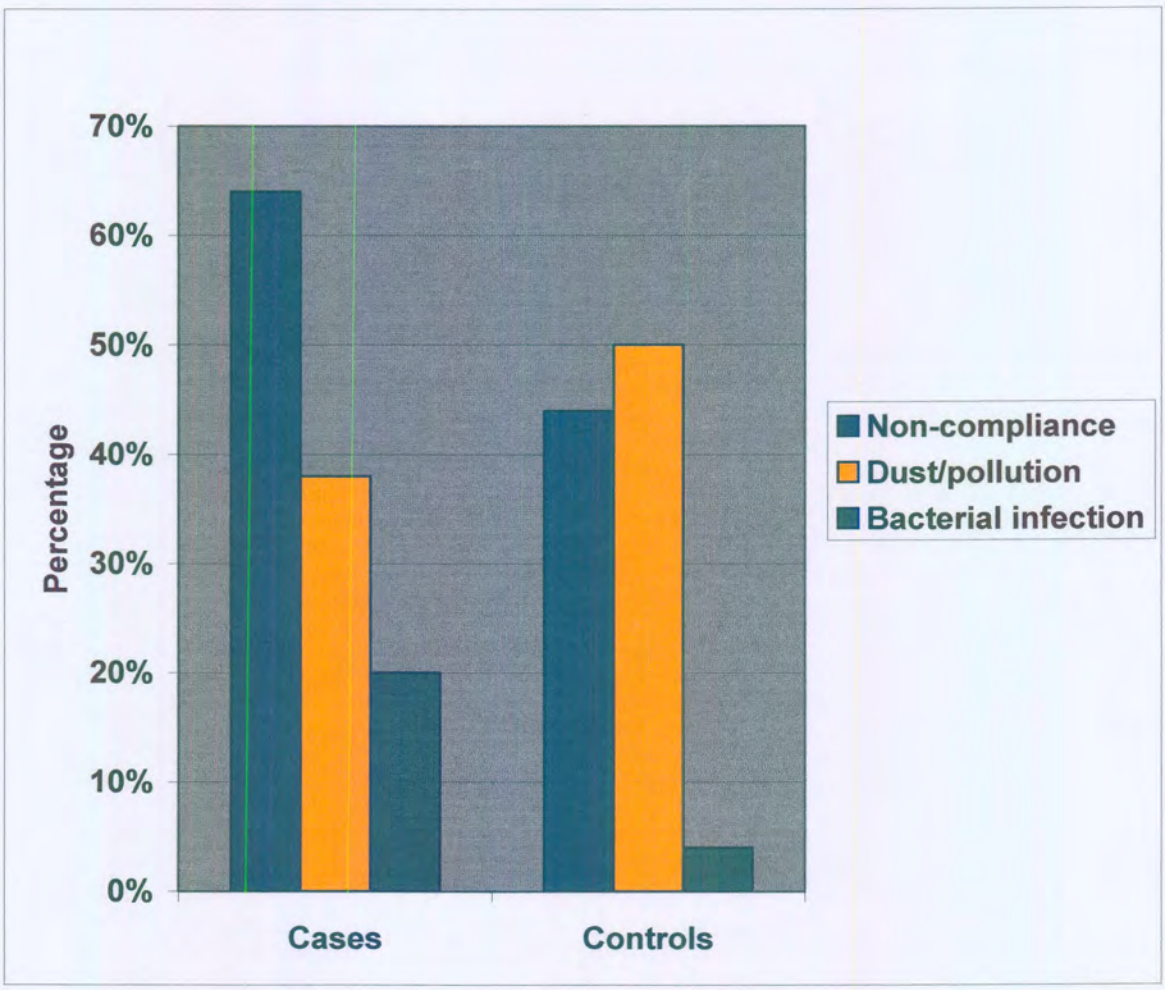

Figure 2 - Comparison between cases and controls concerning the most significant potential triggers/risk factors.

Interaction was further evaluated between non-compliance and the following variables: bacterial infections p = 0.56, literacy p = 0.53, dust- and environmental pollution p = 0.02, menopause p = 0.54 and passive smoke p = 0.63. An interaction between non-compliance and dust- and environmental pollution was found. There was no interaction between non-compliance and bacterial infections, or any of the other variables. There was also no interaction between bacterial infections and dust- and environmental pollution (p = 0.7).

Due to interactions between non-compliance and dust- and environmental pollution, the OR for non-compliance could only be calculated with respect to a given dust exposure. After stratifying on dust- and environmental pollution exposure and the interaction variable (non-compliance * dust/pollution), the following was found:

- OR (non-compliance) = 5.76, if dust/pollution = 0 (absent)
- OR (non-compliance) = 0.99, if dust/pollution = 1 (present)

In Table IV all the medications prescribed for the cases and controls are shown. There was no difference of note. Daily oral steroids were prescribed for six cases - only three of these cases had severe persistent asthma in the dataset, and for eight controls with only one severe persistent participant. One participant received two β-agonist inhalers and another participant did not receive a budesonide inhaler from the pharmacy although it was prescribed. The average dosages of β-agonist used per day by the cases, for the 24 hours before exacerbation (8.12±8.2) and for the seven days before exacerbation (3.64±2.8) differed in a statistically significant way: $p<0.001$, 95% CI 2.27 to 6.69.

TABLE IV - PRESCRIBED MEDICATION OF STUDY PARTICIPANTS

Prescribed medication	Cases (n=50)		Controls (n=100)		OR matched	95%CI	p-value
	N	%	N	%			
β_2-agonist inhaler	47	94	97	97	0.25	0.02 – 2.76	0.26
Dosages past 24h (mean ± standard deviation)	8.12±8.2		-		-		
Average dose past 7 days	3.64±2.8		-		-		
Ipratropiumbromide inhaler	1	2	2	2	1	0.09 – 11.03	1.00
Beclomethasone inhaler	11	22	29	29	0.69	0.31 – 1.54	0.36
Budesonide inhaler	33	66	64	64	1.23	0.65 – 2.32	0.52
Oral theophylline	31	62	64	64	0.92	0.45 – 1.86	0.81
Longactβagonist inhaler	1	2	3	3	0.67	0.07 – 6.41	0.73
Oral steroids	6	12	8	8	1.55	0.51 – 4.69	0.44

Chapter 4
Discussion of Results

DISCUSSION

This was a matched case-control study, investigating the potential triggers or risk factors causing exacerbations in known adult asthma patients in a hospital setting. A significant association between non-compliance and asthma exacerbations was shown. Compliance was determined by (1) evaluating the patients' records to decide whether they kept follow-up appointments, (2) evaluating the prescription chart for script follow-ups, and (3) interviewing each patient to assess whether they used medication as prescribed. According to the literature, poor adherence is a common phenomenon [28]. Social class might have been a potential confounding factor here, but the controls were selected from the same environment and communities. This effectively matched for social class and indicated that our results are unlikely to be due to misclassifications. Many of the patients who did not keep follow-up appointments complained about money and transport problems.

The literacy level (matriculation) was higher in cases than controls, therefore one can speculate that education would not decrease the number of asthma exacerbations. Under-usage of inhaled corticosteroids was one of the major elements that surfaced during interviews on the use of prescribed medication. This was also found in other studies [1, 10]. According to Green [12], patients didn't know the difference between controller- and reliever treatment.

Analysis also showed a significant association between bacterial respiratory infections in need of antibiotics, as concluded through clinical examination

and chest radiography, and asthma exacerbations necessitating the patient to attend the emergency unit. These findings confirmed results in previous studies [30,32,33].

Viral infections were, however, still more common in cases than bacterial infections – 32% viral infections versus 20% bacterial infections. According to some studies 40 - 50% of asthma exacerbations were caused by viral upper respiratory infections [11,30]. A British study undertaken by Green et al in a large district hospital, detected viruses in 26% acute asthma and 18% stable asthma control patients with polymerase chain reaction (PCR) assays. It was discussed that viral infection was noticeably less common in adults admitted to hospital with acute asthma than in children or adults having asthma exacerbations in the community [25]. In our study the odds ratio for viral infections in the exposure assessment was only 1.5 (p=0.26). This could be ascribed to the high occurrence (23%) of viral infections in the controls. Green et al explained this phenomenon, which also occurred in their study (controls of 18%), by stating that patients with asthma are more susceptible to viral infections than patients without asthma, but that such an infection may not necessarily induce a deterioration in asthma requiring hospital admission [25]. Tan et al confirmed this in their study where viruses were recovered from asymptomatic adolescents with asthma [30]. This corresponds with our study.

The definitive diagnosis of respiratory viral infections is complicated by the lack of commercial availability of a rapid and cost-effective laboratory test to confirm the presence of viral respiratory infections [30]. Questionnaires, and not cultures of nasopharyngeal swabs and serology were used to evaluate the presence of respiratory viral infections. According to Osur, PCR is only available in the research setting, so in the evaluation of typical viral infections, clinical signs and symptoms are the clinician's only tool for establishing the diagnosis of viral respiratory infections [11].

Further factors identified as being statistically significant in the analysis were dust- and environmental pollution. With an OR of 0.60 it seemed to be protective. There was also an interaction between non-compliance and dust-

and environmental pollution. The effect of non-compliance on increasing the risk for exacerbation was restricted to those who were not exposed to dust- and environmental pollution. The actual exposure to dust- and environmental pollution was not measured. The researcher relied on self-reported histories. Such an assessment was difficult in a community based study, particularly due to the absence of information about conditions such as enclosures, ventilation, indoor air exposure levels among different households, the duration of traffic exposures, etc. Thus the misclassification of exposures was highly likely in this study. This could explain the effect of dust- and environmental pollution as found in this study. According to Park et al, ambient air particles with a median diameter of <10 μm (PM_{10}), result in greater use of asthma medication and increased hospital admissions for patients with asthmatic symptoms. In contrast to the associations observed between PM_{10} and asthmatic symptoms in many studies, there have been studies that have shown weaker evidence for these associations. Other air pollutants, such as nitrogen dioxide (NO_2), sulphur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) have been studied in detail and have been shown to produce adverse effects on the pulmonary functions of both asthmatics and normal subjects [41].

Although the approach of self-administered questionnaires or interviews was cost-effective, the quality of this data was variable, in part because many exposures were inherently difficult to specify and quantify, and in part because of the difficulty in recalling events that occurred in the past by the participant. Some of these inaccuracies could be reduced with careful questionnaire design but even with the best design, considerable exposure misclassification could be expected.

The variable quality of self-reported exposure information indicated that although participants could reliably and accurately report exposures in certain circumstances, it was also possible for participants to provide exposure data of such low quality that true exposure-effect relations would be obscured or even reversed in direction [42,43].

Kennedy et al did an occupational medicine multi-centre case-control study in which asthma specific job exposure matrices were used. They showed that correction of subtle job title coding errors resulted in an increase of the OR for the risk of asthma associated with exposure from 1.0 to 1.5. Furthermore, when exposure misclassification was reduced by an expert review step, the OR increased to 1.8, and then increased even further to 2.2 when jobs still likely to be misclassified were excluded from the analysis [44].

Age and gender were excluded as confounders by matching. Only 16% of study participants were males. This corresponded with other literature [3,5,6] where females attended the ED more often than males.

One of the motivations for the study was to determine the level of under-treatment of patients. This was totally insignificant. According to the guidelines long-term daily oral steroids should be restricted to severe persistent asthma patients [2], however, a few participants with less severe disease did receive prescriptions for it.

Issues of Case-control Study Design

Our study design, a matched case-control study, allowed us to identify risk factors responsible for asthma exacerbations. The advantages of using this design were that the study was:

- Economical;
- Quick to carry out;
- Facilitated the use of a smaller sample size;
- Ideal for the study of a variety of exposures; and
- Ideal for the study of rare disease.

The disadvantages of the case-control study design were that the study:

- Did not allow for the inclusion of several diseases in the study;
- Did not allow for the direct estimation of the risk of a disease; and
- Brought with it many biases – selection, information and recall.

Recall biases might have occurred, as this is a major problem in case-control studies. It was suspected especially with the emotion variables, where controls seemed to be more exposed than cases. Fortunately none of these were statistically significant.

Information bias could also be a factor. This would be misclassification where unexposed participants could actually have been exposed or vice versa [45].

Selection of Controls

The selection of controls is always problematic in case-control studies. Controls must be representative of the source population. Although in hospital- and clinic-based populations controls are easily accessible and are less expensive, these controls are not representative of the source population. They are only representative of the people who "feed" the hospital with the cases of the disease which is being studied. Controls should further represent people who would have been designated study cases if they had developed the disease. Furthermore, controls must be sampled independently of their exposure status [42].

In this study controls were recruited an average of 11 (10.82) days after the cases due to the necessity for matching. Other restricting factors included the fact that most of the asthma patients attended the specific clinics on Thursdays, and many cases were recruited after hours and on weekends when the clinics were closed. Green et al applied the same principle where controls were recruited within two weeks of the index case during their matched case-control study [25]. Environmental factors, specifically rainy weather, were not different between the cases and the controls in the four week spectrums (p=1), and could be excluded as a potential confounder.

In accordance with a Canadian study [20], our controls were chronic asthmatics with no exacerbations during the preceding four weeks, selected

from the asthma clinics at Kalafong Hospital. The asthma clinic at internal medicine was a Thursday clinic, and consisted of asthmatics with or without heart failure, COPD or a smoking history. Patient files were arranged on a stack by the nursing staff according to arrival times. The first file matching the case on age and gender and with the correct inclusion criteria was used. That patient was finally selected as a control when informed consent was given. At the primary health and family medicine clinics asthma patients were not separated from the other patients. Files were also arranged according to arrival times. The same principle was followed where the first matching patient consenting to the study became a control. It was extremely difficult to find matching controls for the male cases, as most of them were smokers.

Controls were selected longitudinally throughout the course of the study (density sampling). This did not involve a random sample of the person-time in the study base since controls were only sampled for the "instantaneous" time periods in which cases occurred. Controls could become cases later during the study, but cases could not become controls.

Limitations

This study can probably not be generalised beyond the study population, as it involved patients within the public sector and at a single centre.

Critical limitations in most environmental and occupational studies involve problems in exposure assessment. Dust- and environmental pollution seem to have been misclassified in this study.

Definitive diagnosis of respiratory viral infections was not done with the use of laboratory tests such as serology, culture confirmation or PCR. Questionnaires on clinical symptomatology were used.

Recommendations

Self-management should be an important goal for an asthma patient. The key features would be a written action plan, the monitoring of asthma symptoms

and the scheduling of regular reviews [28]. Doctors should further learn how to improve patient's self-management.

Telephonic reminders or the rescheduling of follow-up appointments when necessary by a trained registered nurse may motivate patients to comply better with the management of their asthma. This may also produce long-term reductions in urgent care utilisation and improvements in quality of life [46].

A pharmacist care program in which the pharmacist monitors symptoms, provides medication counselling, helps resolve drug-related problems and facilitates communication with the patient's doctor may be able to enhance patients' adherence to therapy and outcomes [47].

Conclusion

To conclude, non-compliance and bacterial respiratory infections were strong predictors of exacerbations in adult asthma patients at Kalafong Hospital, which forms part of a third-world community.

Chapter 5
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Addendum 1

Questionnaire

Case number:

Control number:

1.Age:

2.Gender:

a) Male
b) Female

3.Literacy:

a) No schooling
b) Some primary schooling
c) Some high school training
d) Matriculation

4.Severity of asthma:

a) Mild intermittent
b) Mild persistent
c) Moderate persistent
d) Severe persistent

	Past 4 weeks	
	Yes	**No**
5 To which of the following were you exposed?:		
5.1 Exercise/sport		
5.2 Viral infections: Sore throat		
Fever		
Runny/blocked nose		
Muscle aches		
Exposure to others with a cold		
5.3 Household pets		
5.3.1 Cats		
5.3.2 Birds		
5.4 Passive tobacco smoke at home or work place		
5.5 Strong emotions: 5.5.1 Did you loose your temper?		
5.5.2 Were you extremely excited or happy about something?		
5.5.3 Were you very anxious or did you have an anxiety attack?		
5.6 Dusty conditions/air pollution		
5.7 In-house wood burning/coal stove		
5.8 Weather conditions e.g. cold air, rain		
5.9 Medication: 5.9.1 Non-steroid anti-inflammatory drugs		
5.9.2 β-blockers		
5.10 Hay fever/rhinitis: (symptoms for more than 1 hr/day over 2 weeks)		
5.10.1 Blocked nose		
5.10.2 Sneezing		
5.10.3 Runny nose		
5.10.4 Seasonal		
5.11 Bacterial respiratory infections – antibiotic treatment necessary		
5.12 Work-related eg. spray-painting, pharmaceutical manufacturing, plastics, platinum industries, diisocyanate		
5.13 Female patients only: 5.13.1 Pregnancy		
5.13.2 Menopause		
If no: 5.13.3 Premenstrual/menstrual		

MEDICATION (FROM PATIENT'S FILE):

6. β-agonist inhaler
   - YES
   - NO

   6.1 From the patient:
   - 6.1.1 Number of doses the past 24 hrs? _____
   - 6.1.2 Number of doses per day the past 7 days? _____

7. Beclomethasone inhaler
   - YES
   - NO

8. Budesonide inhaler
   - YES
   - NO

9. oral theophilline
   - YES
   - NO

10. long-acting β-agonist
   - YES
   - NO

11. daily oral steroids
   - YES
   - NO

12. Compliance:

   - 12.1 How many follow-up appointments did the patient miss in the last 6 months? _____
   - 12.2 How many script appointments did the patient miss in the past 6 months? _____
   - 12.3 Does the patient take medication as prescribed?
     - YES
     - NO

Addendum 2

Patient Informed Consent

AUTHORISATION TO PARTICIPATE IN A RESEARCH PROJECT.

TITLE OF STUDY: Risk factors precipitating exacerbations in adult asthma patients presenting at Kalafong hospital, Pretoria.

Dear Mr. / Mrs. .....date ...../...../.....

1. THE NATURE AND PURPOSE OF THIS STUDY

I understand that I am asked to take part in a research study. The aim of this study is to find out which factors are worsening asthma so much that patients need to come to casualties for emergency treatment. Asthma is a very dangerous illness that kills many people worldwide, by identifying these factors plans to prevent this can be proposed.

2. EXPLANATION OF PROCEDURES TO BE FOLLOWED.

This study involves answering some questions about possible factors that may concern you as an asthmatic during the past 4 weeks. Possible factors are hay fever, infections, cold air, etc. Information from your hospital file about medication and follow-up visits will also be used.

3. RISK AND DISCOMFORT INVOLVED.

There is no risk involved and the only discomfort would include spending a few minutes of your time answering questions posed by the investigator.

4. POSSIBLE BENEFITS OF THIS STUDY.

This study may enable us to identify your specific or potential risk factors. This knowledge may benefit you in the future by understanding your illness better.

It may also be of value for the management of your asthma by the hospital.

5. **I understand that if I do not want to partake in this study, I will still receive standard treatment for my illness.**

6. **I may at any time withdraw from this study.**

7. **INFORMATION** If I have any questions concerning this study, I should contact: Dr M.M. Geyser tel: 318-6563 or cell 0828511294.

8. **CONFIDENTIALITY**

All records obtained whilst in this study will be regarded as confidential. Results will be published or presented in such a fashion that patients remain unidentifiable.

9. **CONSENT TO PARTICIPATE IN THIS STUDY.**

I have read or have had the above information read to me in a language that I understand before signing this consent form. The content and meaning of this information has been explained to me. I have been given the opportunity to ask questions and am satisfied that they have been answered satisfactorily. I understand that if I do not participate it will not alter my asthma management in any way. I hereby volunteer to take part in this study.

I have received a signed copy of this informed consent agreement.

....

Patient / Guardian signature Date

....

Person obtaining informed consent Date

....

Witness Date

VERBAL PATIENT INFORMED CONSENT

(applicable when patients cannot read or write)

I, the undersigned, Dr ....., have read and have explained fully to the patient, named .....and/or his/her relative, the patient information leaflet, which has indicated the nature and purpose of the study in which I have asked the patient to participate. The explanation I have given has mentioned the possible benefits and risks of the study. The patient indicated that he/she understands that he/she will be free to withdraw from the study at any time, for any reason and without jeopardising their further treatment.

I hereby certify that the patient has agreed to participate in this study.

Patient's Name _____

(Please print)

Investigator's Name _____

(Please print)

Investigator's Signature _____ Date _____

Witness' Name _____

(Please print)

Witness' Signature _____ Date _____

Addendum 3
NIH Guidelines

Adaptation from the 1997 *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma*, provided by the National Institutes of Health [6].

A patient with **mild intermittent asthma** has intermittent, brief wheezes, cough, chest tightness, and/or dyspnoea up to twice a week and nocturnal symptoms up to twice a month. Peak flow is >=80% of predicted value at baseline.

Mild intermittent asthma requires only an inhaled short-acting $beta_2$ agonist taken as needed to relieve asthma symptoms. An inhaled short-acting $beta_2$ agonist or cromolyn or nedocromil prior to exercise or exposure to a known allergen may be taken if appropriate. If a $beta_2$ agonist is required more than twice a week, the patient should be evaluated for addition of a long-term control agent to decrease symptom frequency.

A patient with **mild persistent asthma** has symptoms that occur more than twice a week but less than once a day, and nocturnal symptoms more than twice a month. Exacerbations may affect activity. Peak expiratory flow is >=80% of predicted value at baseline, with 20% - 30% variability in peak expiratory flow.

The primary therapy is a daily dose of a long-term control agent, which can be either an inhaled corticosteroid or cromolyn or nedocromil (usually for children). Leukotriene modifiers, a new oral agent, may also be used to control symptoms. Leukotrienes are potent constrictors of bronchial smooth muscle which are released during an asthma attack. These drugs inhibit leukotriene synthesis by preventing leukotrienes from attaching to airway

receptors, thereby preventing asthma symptoms. An inhaled short-acting beta$_2$ agonist should be taken as needed for symptoms. Use of a beta$_2$ agonist on a daily basis or increasing use, indicates the need for additional long-term control therapy.

A patient with **moderate persistent asthma** has daily symptoms and nocturnal symptoms more than once a week. Exacerbations affect activity, occurring more than two or more times a week and sometimes lasting for days. Peak expiratory flow is 60% - 80% of predicted value at baseline, with a greater than 30% variability in peak expiratory flow.

The primary therapy is a daily medium dose of an inhaled corticosteroid, or a low to medium dose of an inhaled corticosteroid and a long-acting bronchodilator to control night time symptoms. An inhaled short-acting beta$_2$ agonist should be available to take as needed to relieve symptoms. Use of a short-acting beta$_2$ agonist on a daily basis, or increasing use, indicates the need for additional long-term control therapy.

A patient with **severe persistent asthma** has continual symptoms, limited physical activity, and frequent exacerbations. Peak expiratory flow is <=60% of predicted value at baseline, with a greater than 30% variability in peak expiratory flow. Control of asthma as defined by the Expert Panel Clinical Guidelines may not be possible. With severe persistent asthma, the goal of therapy becomes achieving the best possible results: the fewest symptoms, the least need for beta$_2$ agonists, the best peak flow rates, and the fewest side effects from medication. Therapy usually requires multiple daily medications. Primary therapy includes a daily high dose of inhaled corticosteroids, a long-acting bronchodilator such as an oral beta$_2$ agonist, or oral sustained-release theophylline, and corticosteroid tablets or syrup long-term. An inhaled short-acting beta$_2$ agonist should be available to take as needed to relieve symptoms. Use of a short-acting beta$_2$ agonist on a daily basis, or increasing use, indicates the need for additional long-term control therapy.