STRESS, UPPER RESPIRATORY SYMPTOMS AND THE 'COMMON COLD' IN CHILDREN WITH ASTHMA

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ABSTRACT

This study examined the relationship between life events and experiences, psychological adjustment and upper respiratory illness in 78 children, age 7-14 years, with moderate to severe asthma attending a specialist children's asthma clinic. Long-term experiences (LTEs) and acute life events (LEs), both positive and negative, were evaluated at baseline and after 9 months using an interview-based measure of psychological stress: PACE (Psychosocial Assessment of Childhood Experiences). Psychological adjustment was measured using Speilberger's State-Trait Anxiety in Children questionnaire and Harter's Self-Perception questionnaire. The occurrence and severity of upper respiratory (UR) symptoms were recorded daily by the parent using a specially designed symptom diary. At times of increased UR symptoms parents contacted the researcher who arranged to collect a throat swab for subsequent viral analysis.

A mean of 2 upper respiratory infections (URIs) per subject was recorded over the study period with a mean of 1.7 UR symptoms per day on 27% of study days. Girls, age 9-11 years, were at increased risk of reporting higher levels of URI ($p<0.05$). Children in lower social class groups were at increased risk of reporting higher levels of high negative LTEs ($p<0.05$) and lower levels of positive LTEs ($p<0.001$) compared to those in higher groups. High threat LTEs were negatively related to symptom measures in boys ($r=0.37$, $p<0.05$), with positive LTEs apparently playing a protective role. Those with high mean UR symptoms were at increased risk of reporting a higher number of high threat LTEs compared to those with low ($p<0.05$) or moderate UR symptoms ($p<0.05$) Self-perception scores were significantly higher in children with asthma compared to a normative Scottish sample of schoolchildren. Reported mean UR symptom levels were negatively correlated with self-perception scores but not anxiety measures. Boys reporting high mean UR symptoms perceived themselves as less well-behaved and had a lower sense of their own global self-worth compared to those with low UR symptom levels but after controlling for high threat LTEs (mean duration 40.9 months), this relationship disappeared. Girls, particularly

those aged 9-11 years, were at increased risk of reporting acute high threat LEs in the 6-week period before the start of a URI.

These findings show that high chronic stress levels are related to UR symptoms in boys with asthma, a relationship that might be moderated by self-esteem and mediated by inappropriate behaviours such as non-compliance with medication. In contrast, girls were at increased risk of URI or cold after the occurrence of an acute high threat life event.

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LIST OF ABBREVIATIONS

BHR	Bronchial hyperresponsiveness
HNI LE	High negative impact life event
HNI LE LT	High negative impact life event (long-term)
HNI LE ST	High negative impact life event (short-term)
HNI LTE	High negative impact long term experience
HRV	Human rhinovirus
IgE	Immunoglobulin E
LE	Life event
LT	Long term
LTE	Long Term Experience
MANOVA	Multivariate analysis of variance
NK	Natural Killer (cell)
PEF	Peak Expiratory Flow
PCR	Polymerase Chain Reaction
RE	Respiratory Episode
ST	Short Term
URI	Upper respiratory infection

"...If you can force your heart and nerve and sinew
To serve your turn long after they are gone,
And so hold on when there is nothing in you
Except the Will which says to them: 'Hold on!'..."

"If"- *Rudyard Kipling*

PART ONE

INTRODUCTION

CHAPTER 1

THE ENVIRONMENT AND CHILDHOOD ASTHMA

Background to Chapter

Asthma is an airways disease generally associated with an inherited predisposition towards atopy. Atopy is the ability to mount an increased immune response to environmental allergens. Atopy has been associated with persistent wheezing illness in infancy and later childhood but also with the development of late-onset wheezing illness at the age of 6 years. The association between this latter pattern of illness and atopy suggests that both genetic and environmental factors may play an important role in determining the age when symptoms begin.

Despite some methodological problems, reports generally conclude that the prevalence of asthma is increasing. Research indicates that in recent years prevalence increases have been greater for younger girls with asthma compared to boys and the boy/girl gap may be decreasing. However, prevalence increases in hay-fever like symptoms and eczema have been greater for boys than for girls. It has been suggested that the increase in asthma prevalence may be part of a more general increase in atopic illness. Some studies also report gender differences in these increases and it has been suggested that the mechanisms which mediate the relationships between asthma, hay-fever and eczema may be different for boys and girls and may not be attributed solely to genetic predisposition.

While genetic factors play an important role in the etiology of asthma, a number of environmental factors including allergens, irritants, viral infections and psychological stress also play a role. The aim of this first Chapter is to look at the definition and prevalence of asthma and to examine some of the genetic and environmental factors involved in asthma prevalence and morbidity. The role played by viral infection will be examined in Chapter 2 while the social and psychological impact of a chronic illness such as childhood asthma will be discussed in Chapter 3. The definition and measurement of both acute life events and long-term psychological stress and their role in childhood illness will be examined in Chapter 4, before discussing the contribution of such stress to childhood asthma in Chapter 5.

1.1 Clinical Definition and Prevalence of Childhood Asthma

Clinical definition of asthma

Asthma is a disease of the respiratory system. It is clinically recognised as a reversible obstructive lung disease and is usually associated with bronchial hyperresponsiveness (BHR) to physical or chemical challenges especially with increasing age. Reversibility, either spontaneously over time or with treatment, is an important feature of asthma and allows some differentiation of this condition from other respiratory illnesses such as bronchitis and upper respiratory tract infections (McFadden, 1984). Features used to define asthma clinically are recurrent (more than 2) episodes of bronchial obstruction partially or completely reversible through bronchodilators or steroids (Godfrey, 1985; Warner, Gotz, Landau, Levison, Milner, Pedersen & Silverman, 1989). Bronchial hyperresponsiveness (BHR) is a useful tool in the diagnosis of asthma. It can be measured by challenging the child with either a chemical or physical stimulus (Cockcroft & Berscheid, 1982; Chai, Farr, Froehlich, Mathison, McLean, Rosenthal, Sheffer, Spector & Townley, 1975). An exercise test may be used on children since this type of challenge is considered more acceptable to a younger age group. However, the relationship between bronchial reactivity and asthma in both adults and children is not a straightforward one (Clough, Williams & Holgate, 1992;. Ninian & Russell, 1993).

Clinical symptoms of asthma

The clinical manifestations of the disease are coughing, shortness of breath and tightness in the chest together with wheezing. In the child with asthma these symptoms may be perceived as an oppressive tightening or constriction of the chest. The clinical spectrum of asthma illness is wide and ranges from mild wheeze precipitated by viral infections to status asthmaticus or life threatening attack (Williams, 1980). Agreed guidelines are in place for the management of asthma in children and in adults, both in the long term and for acute exacerbations (Warner, Gotz, Landau, Levison, Milner, Pederson & Silverman, 1989; British Thoracic Society, 1990a,b; 1993).

Atopy

A parental history of asthma or atopic illness carries an increased risk to the offspring (Sherman, Tosteson, Tager, Speizer & Weiss, 1990). 'Atopy' generally refers to the diathesis which includes asthma, allergic rhinitis or 'hay-fever' and dermatitis or 'eczema'. While inheritance is an important determinant of asthma, what is inherited seems to be not a specific disease such as asthma or hay-fever but a propensity towards the development of increased immunological responses towards common allergens. Persistent wheeze in the first six years of life and late-onset wheezing illness later in childhood, just before the age of 6 years, have both been associated with atopy (Martinez, Wright, Taussig, Holberg, Halonen & Morgan, 1995). Martinez and colleagues reported that children with persistent wheeze at 6 years had more wheezing attacks early in life and were more likely to have mothers with asthma than those with no wheeze in early infancy or those with only transient wheezing. Early exposure to aero-allergens, together with maternal smoking, may be important risk factors for persistent wheeze in later childhood. However, the proposal of this early period as a crucial time for the aquisition and development of increased sensitivity is questioned by the finding of atopy in children with later-onset wheezing illness. A number of factors such as genetic factors, exposure to antigens, the season of birth, air pollution and viral infection may play a role in determining the age when symptoms begin (Bjorksten, 1994). Interestingly, the late-onset pattern of wheezing illness is reportedly the most common pattern among older children and young adults. Most individuals with asthma early in adult life have no history of childhood asthma (Strachan, Anderson, Bland & Peckham, 1988).

The class of antibodies particularly involved in the allergic or atopic response is immunoglobulin E (IgE) and the likelihood of development of atopic disease, including asthma, can be obtained by testing antibody levels of IgE in the blood of the umbilical cord. Determinants of the illness may already be operating at birth (Kjellman & Croner, 1984). An association between cord serum IgE and asthma has

been found at 6 years (Burrows, Martinez, Halonen, Barbee & Cline, 1989) and may be related to exposure to inhaled allergens early in life (Morgan & Martinez, 1992) such as house-dust mite antigens (Sporik, Holgate & Cogswell, 1991). The majority of children with asthma show reactions to allergy skin tests (Sears, Herbison, Holdaway, Hewitt, Flannery & Silva, 1989). Skin prick tests can be used to determine the allergen or range of allergens to which an individual might be hypersensitive.

Prevalence of childhood asthma

Since the relationship between asthma and bronchial reactivity in both adults and children is not a straightforward one, measures reflecting the frequency of wheezing and wheezing episodes have been incorporated into studies in addition to or in place of reports relating to the prevalence of diagnosed asthma. Such measures are also related to the fact that a number of methodological problems can also arise in studies investigating the prevalence and morbidity of asthma. In the main these problems involve the diagnosis or 'labelling', treatment and management of asthma which have changed over time and have also been shown to vary between medical practitioners (Burr, 1991; Usherwood & Barber, 1985; Bucknall, Robertson, Moran & Stevenson, 1988 a,b). For example, the findings of a number of studies have indicated an increase in the labelling of wheezing illness as asthma without any apparent increase in the prevalence of asthma (Strachan & Anderson, 1992; Hill, Williams, Tattersfield & Britton, 1989).

A recent national survey of asthma prevalence, severity and treatment in Great Britain was carried out on 5472 children, 5 to 17 years old (Strachan, Anderson, Limb, O'Neill, Wells, 1994). This survey reported that 23% of children had a history of wheezing at any age and that in the previous year 15% of children had wheezed, 2.2% had more than 12 attacks of asthma, 13.1% had doctor diagnosed asthma and 13.6% had been prescribed anti-asthmatic drugs. Despite methodological shortcomings relating to prevalence reports, the general trend of reports appears to tend towards an

increase in the prevalence of diagnosed asthma and wheezy illness (Burr, Butland, King & Vaughan-Williams, 1989; Burney, Chinn & Rona, 1990; Ninian & Russell, 1992; Gergen & Weiss, 1990; Robertson, Heycock, Bishop, Nolan, Olinsky & Phelan, 1991). Some investigators have concluded that increases are not due to changes in diagnostic labelling (Ninian & Russell, 1992) and some reports also point to an increase in the severity of asthma (Burney et al, 1990) particularly in the lower socio-economic groups (Strachan et al, 1994). Overall this data is also supported by evidence suggesting an increase in hospital admission rates related to asthma (Anderson, 1989; Hyndman, Williams, Merrill, Lipscombe & Palmer, 1994).

A number of reports have suggested that the increase in wheezing may be part of a more general increase in the expression of atopic disease (Britton, 1992; Ninian & Russell, 1992) since findings have also indicated increases in the prevalence of respiratory symptomatology commonly associated with hay-fever and eczema (Kelly, Brabin, Milligan, Reid, Heaf & Pearson, 1996; Ninian & Russell, 1992; Burr et al, 1989; Peat, Haby, Spijker, Berry & Woolcock, 1992). For example, in two surveys, 15 years apart, Burr and Colleagues (1989) reported an increase in the number of 12-year olds reporting eczema and hay-fever. A more recent survey conducted two years apart (1991 to 1993) on 5 to 11 year old children attending 15 Merseyside schools reported a significant increase in allergies (hay-fever and eczema) in children with cough, wheeze and breathlessness, 90% of whom had doctor diagnosed asthma (Kelly Brabin et al, 1996). These increases are also apparent in adults. A survey in Western Australia found a significant increase, in adults, of respiratory symptoms associated with allergy with the prevalence of hay-fever more than doubling over a 9-year period (Peat, Haby et al, 1992). Ninian & Russell (1992) have also reported an increase in the reporting of eczema and hay-fever-like symptoms. They found that the relative increase in eczema over a 25-year period was greater for boys than for girls and, similarly, between 1964 and 1989 the relative increase in hay-fever prevalence rates was greater for boys than for girls. However, the ratio increase for diagnosed asthma was slightly more for girls than boys. They have suggested that the mechanisms

which mediate the relationships between asthma, hay-fever and eczema may be different for boys and girls and may not be attributed solely to genetic predisposition. The figures reported by Ninian & Russell (Table 1) are generally consistent with the findings of other studies such as the odds ratio for asthma of 1.8:1 in boys compared with girls found by Weitzman, Gortmaker, Walker & Sobol (1990) and that of 1.6:1 found by Strachan et al, 1994.

The higher ratio increase in asthma in girls found by Ninian & Russell (1992) is also supported by the findings of another survey which examined symptoms in unlabelled wheezy illness and nocturnal cough (Powell & Primhak, 1996). This survey was conducted on 4406 Sheffield children, 8 to 9 years old, and repeated after a two-year period (1991 to1993). A standardised questionnaire was employed containing core wheeze questions from the International Study of Asthma and Allergies in Childhood (Asher, Keil, Anderson et al, 1995). Of those children with 'current wheeze' in the original study, there was an increased risk of females being 'labelled' as having asthma in the following two-year period.

A number of reports indicate that children can grow out of their symptoms with increasing age (Hill, Hosking, Shelton & Turner, 1991; Kelly, Hudson, Phelan, Pain, Olinsky, 1987; Martin, McLennan, Landau, Phelan, 1980; McNichol & Williams, 1973) but, again, there is an effect of gender differences in these illness processes over time. Asthma and early childhood wheeze, usually associated with viral infection, are reported to be more common and more severe in boys than in girls (Dodge & Burrows, 1980; Morgan & Martinez, 1992). This increased risk in males has been attributed to the relative size of airways compared to lungs in males, a condition which changes with puberty. However, this male 'disadvantage' continues into middle adolescence. In Strachan et al's (1994) report on morbidity related to wheezing, they found a general decrease in the male predominance in preadolescent children in that this predominance over females equalises out by the later teenage years (14 to 17 years). Thereafter, at 20 years of age, asthma incidence is greater in

females than in males (Dodge & Burrows, 1980) with morbidity rates in women being greater than in men after 40 years (Skobeloff, Spivey, St. Clair & Schoffstall, 1992). However, this changing male:female morbidity ratio during late childhood or early adolescence has also been recorded for overall levels of other chronic illness, neurotic disorders and the utilisation of health services (Sweeting, 1995).

1.2 The Role of Physical Environmental Factors

Although a number of studies have investigated the role of various risk factors in the development of asthma in infancy and later childhood, the environmental factors responsible for causing or precipitating episodes of asthma in children have remained relatively poorly understood. Stimuli commonly considered to be involved in the pathogenesis of asthma include physical environmental factors (allergens; irritants; exercise and cold air), viral respiratory infections and psychological factors (situations and emotional responses) (Reed & Townley, 1983). The role of viral infection and the psychological contribution to childhood asthma will be examined in later chapters.

Allergy

Allergy can produce a number of symptoms including runny nose, watery eyes, sneezing, skin irritation, coughing and wheezing. Repeated exposure to the allergen can result in sensitisation whereby the child may exhibit a heightened response in that small amounts of the allergen may then be capable of producing significant episodes of asthma (McFadden, 1984). Some of the more common allergens in asthma include house-dust mites, animals, pollen and food and these are detailed below together with the role played by irritants, exercise and cold air.

A defining characteristic of the 'true allergic response' is an 'early' response resulting in the release of chemical mediators and further processes resulting in the migration of cells to the lungs which can result some hours later in inflammation and tissue destruction. This inflammatory process is termed the 'late response'. A hay-fever

sufferer exposed to pollen may immediately experience itching, sneezing and runny nose, as the result of (mast) cell degranulation and the release of histamine, but many hours later as the result of further inflammatory mediatory processes can then experience nasal blockage and stuffiness.

House Dust Mite and Animals

Allergy to house-dust mite and its faeces is extremely common in children with asthma. The main factors involved in determining the number of house-dust mites found in house dust are temperature and humidity and these in turn can be affected by the number of individuals sharing a room within the home; the size of the room, insulation and airing. Der pl, a constituent of house dust mite faeces which causes the allergic reaction can be found mainly in bedding. House dust allergy is common in those with perennial rhinitis who present with a range of nasal symptoms throughout the year.

A further source of symptoms is brought about by allergy to animals and insects the basis of which is usually proteins in the skin (dander), hair, saliva and urine. Animal allergy can also be a source of perennial symptom presentation. Changes in housing conditions intended to make the indoor environment increasingly energy efficient have meant that there is less chance for air exchange and a greater chance of build-up of allergens. Central heating, air conditioning, wall-to-wall carpeting and increased insulation may all have an impact on indoor air quality and may have an effect on asthma prevalence and morbidity.

Pollen

Allergy to pollen from grasses, trees and weeds, is also a source of symptoms. Allergy to grass pollen is the most common in the U.K. and is usually confined to a period between May and August, peaking at about the middle of this period. The daily pollen count can vary greatly in this period. A process of sensitisation or nasal priming may come into operation in that increased nasal irritation or rhinitis over time

results in a lesser amount of pollen being needed to produce symptoms. Seasonal rhinitis or 'hay-fever' is a form of allergic rhinitis where symptoms are usually confined to the pollen season. Symptoms of rhinitis can sometimes be indistinguishable from those associated with the 'common cold', i.e., sneezing, runny nose, blocked nose, itchy/sore./watery eyes, aches and other pains. Children who are allergic to grass pollen may have attacks from late May to the end of July.

Food

Food may also produce an allergic reaction but not all reported reactions will be brought about by allergy. Many will comprise of non-allergic reactions brought about by other physiological mechanisms such as, for example, intolerance due to enzyme deficiency. Milk can bring about a true allergic response but a reaction to milk might reflect this systemic inability to break down and absorb milk.

Exercise, cold air and irritants

Many so-called 'allergies' involve only aspects of the true allergic response, as is the case in exposure to irritants and the effect of cold air on the already sensitive bronchi of the child with asthma. Some stimuli such as exercise and environmental irritants can act as triggers to the already damaged and sensitive airways of those with allergic disease. 'Exercise-induced asthma' can be brought about by a high level of physical activity or by breathing dry cold air (Reed & Townley, 1983). Irritants can range from changes in weather, temperature and cold air to triggers such as particulates from exhaust fumes, sulphur dioxide, carbon monoxide, nitrogen dioxide, ozone and cigarette smoke. Damage to airway epithelium by irritants can leave nerve endings exposed with secondary stimulation by inflammatory mediators resulting in smooth muscle contraction, mucous hypersecretion and associated airway swelling. Through these processes the site of the allergic inflammatory response becomes irritated and hyperresponsive to a variety of environmental stimuli.

No evidence exists for outdoor pollution as a primary factor in changing prevalence and morbidity of asthma (Weiss & Gergen, 1993). In one survey indices of prevalence, severity and diagnosis were found to be lower in Scotland (Strachan, Anderson, Limb, O'Neill, Wells, 1994). A relative lack of variation elsewhere in England and Wales led to the conclusion that the environmental factors responsible for childhood asthma were widespread throughout Britain. Climate and air pollution, though possibly important in causing short-term variations, were not considered important determinants of regional patterns of prevalence or severity. The 12-month prevalence of wheeze was similar in urban, mixed urban and rural, and rural categories of environment but frequent attacks of asthma tended to be about half as common in rural areas as in mixed or urban areas. It was noted that ozone tends to be higher in rural areas of the south. Such findings have therefore given no support for this agent being responsible for either the observed urban-rural or regional variations. A further report on the prevalence of asthma and wheeze in 12 and 13 year olds in the Highlands of Scotland (Austin, Russell, Adam, Mackintosh, Kelsy & Peck, 1994) also adds support to Strachan et al's findings. Employing exercise tests and monitoring ozone levels, these investigators found an asthma prevalence rate of 14%. Expecting a lower rate in this rural area, these investigators concluded that their findings did not support the proposal of increased asthma prevalance in areas of high pollution.

A number of factors which can influence the process of sensitisation and/or eliciting of symptoms, may co-operate to increase the risk for bronchial asthma. For example, exposure to multiple pollutants is reported to have important synergistic effects, whereby exposure to ozone, for example may potentiate the asthmatic response to sulphur dioxide (Koenig, Covert, Hanley, van Belle,. Pierson, 1990). Living in a home with confirmed dampness increases the risk for prolonged cough during upper respiratory tract infections, wheeze, asthma and allergy. Adding exposure to cigarette smoke synergistically increases the risk for bronchial asthma (Andrae, Axelsson, Bjorksten, Fredriksson & Kjellman, 1988). The relative risk for asthma is doubled by

maternal smoking (Weitzman et al, 1990). Exposure to environmental tobacco smoke, particularly maternal smoking, and lower socioeconomic status are risk factors which have been associated not only with transient wheezing in early childhood but also with persistent wheezing later in childhood (Morgan & Martinez, 1992; Martinez, Wright, Taussig et al, 1995).

1.3 Summary

Asthma is an inflammatory disease of the airways which is common in children and is frequently associated with bronchial hyperresponsiveness. Children with allergic or atopic disease inherit a predisposition to hyperresponsiveness arising from an increased ability to mount an antibody/mast cell mediated response to common environmental allergens. A range of environmental triggers can give rise to nasal symptoms and attacks of asthma in children and these include allergens, irritants, exercise, viral infection and psychological stress. A number of these factors together with season of birth may also determine the age when symptoms begin..

Despite methodological problems, studies have indicated that the prevalence and morbidity of asthma is increasing. The prevalence rate ratio for diagnosed asthma is greater for boys than girls but evidence indicates that this gap may be decreasing. Girls have shown a relatively greater increase in diagnosed asthma than boys but smaller ratio increases in eczema and in hay-fever. A gender crossover in asthma prevalence, results in increased prevalence in females compared to males by the age of 20. However, this age by gender interaction in morbidity has also been noted for other chronic illnesses, neurotic disorders and the utilisation of health services.

Some researchers have suggested that an increased allergen load in the environment may be responsible for the increasing prevalence in asthma. However, there is no clear evidence. Environmental factors, such as climate and air pollution, though possibly important in causing short-term variations are not important determinants of regional patterns of asthma prevalence or severity.

CHAPTER 2

UPPER RESPIRATORY INFECTION (URI) AND CHILDHOOD ASTHMA

Background to Chapter

While a number of allergens and irritants play an important role in asthma morbidity, both the research literature and clinical experience have indicated that the majority of significant episodes of asthma in children of all ages are brought about by ***symptomatic*** *viral infection. Viral infection has also been cited as a factor in the development of increased bronchial responsiveness to a number of environmental stimuli in children with wheezing illness.*

2.1 Upper Respiratory Infection (URI)

Colds and 'flu are both examples of common viral infections. The picornaviruses and coronaviruses are the two families of viruses responsible for the majority of colds (Larson, Reed & Tyrrell, 1980). Of the two, the rhinovirus members of the picornavirus family are responsible for up to 50% of colds (Gwaltney, 1985; Phillpotts & Tyrrell, 1985) and the coronaviruses up to 20% (Sperber & Hayden, 1988). The remaining 30% represent mainly influenza caused primarily by two types of viruses Flu A and B each with many subtypes and strains. 'Influenza-like' diseases can also be caused by many other respiratory viruses including adenovirus, parainfluenza and respiratory syncytial virus.

Human rhinovirus (HRV) is the predominant cause of the generally mild infection known as the 'common cold' (Gwaltney, Hendley, Simon & Jordan, 1966). Infection by at least 100 distinct serotypes of HRV can result in a cold (Hamparian, Colonno, Cooney, Dick, Gwaltney et al, 1987). The 'common cold' virus attacks the respiratory system causing a range of upper respiratory symptoms. This may include nasal problems, such as sneezing and runny or blocked nose, together with itchy/sore/watery eyes and sore throat as well as other bodily symptoms including headaches, fever and aches and pains. However, viruses may produce ***symptomless*** subclinical infections either acute or chronic. Infection, therefore, can range from ***viral colonisation*** through ***asymptomatic infection*** to full clinical illness with both ***infection and expression of symptoms***.

Respiratory infections are a leading cause of community morbidity in many countries (Pio, Leowski, ten Dam, 1985). There is, however, limited understanding of the role of immunological mechanisms in URIs and their relative importance in particular infections. Overcrowding (Kendall & Leeder, 1985) and cigarette smoking (Kark, Lebuish & Rannon, 1982; Colley & Reid, 1970; Rush, 1974) are recognised as risk factors for both upper and lower respiratory tract infections. Passive smoking is associated with increased risk of acute respiratory infection in young children (Fergusson, Horwood, Shannon, 1980). Air pollution has been linked with lower respiratory illness mortality and chronic respiratory illness in children (Leeder & Holland, 1978; Douglas & Waller, 1966) and may also influence susceptibility to upper respiratory illness (Lunn, Kowelden & Handyside, 1967). Those with vulnerable or weakened immune systems can also be more susceptible. In those with asthma, a possible relationship between psychological stress and URI (Busse, Kiecolt-Glazer, Coe, Martin, Weiss & Parker, 1995) has been suggested. This suggestion has been made because of increasing evidence elsewhere in the literature of the existence of such a relationship in both healthy adults and children (Cohen & Williamson, 1991; Cohen, Tyrrel & Smith, 1991; Cohen Tyrrel & Smith, 1993; Stone, Bovbjerg, Neale, Napoli, Valdimarsdottir, Cox, Hayden & Gwaltney, 1992; Meyer & Haggerty, 1962).

There may be gender differences in susceptibility to upper respiratory infection. Some reports suggest that males may be more susceptible to *lower* respiratory infection than females (Denny & Clyde, 1986) but, again, this risk equalises out in the 9 to 15 years age band. Others have suggested that, with the exception of respiratory syncytial virus infections in children (W.H.O., 1980), females may be more susceptible than males (Badger, Dingle, Feller et al, 1953; Gwaltney et al, 1966; Monto, Higgins, Ross, 1975). A recent paper investigated adult subjects (n=1700) who had previously participated in research at the Common Cold Unit in Salisbury (MacIntyre, 1993). This paper reported that clinicians and researchers at the Unit

were of the opinion that females were more susceptible to URI than males. In conclusion, therefore, there is little clear evidence for the role of gender or a possible gender by age interaction in susceptibility to URI .

2.2 URI and Asthma

Respiratory infection can be problematic in the sensitive airways of children with asthma who are already vulnerable through inflammation, exposure to irritants and toxins, previous viral infection and through asthmatic predisposition. In these children the likelihood of airways colonisation and infection of the lower airways is increased (Busse, 1991). Clinicians have long suspected a relationship between respiratory tract infections and asthma, particularly in children. Recurrent wheezing episodes can result from viral respiratory infections especially in children and several studies have confirmed the association between respiratory viral infections and the worsening of asthmatic symptoms (Roldaan & Mansural, 1982; Mills, 1981; Minor, Dick, Baker, Ouellette, Cohen, Reed, 1976; Minor, Dick, DeMeo, Ouellette, Cohen & Reed, 1974; McIntosh, Ellis & Hoffman, 1973; McIntosh, Ellis, Hoffman, Tillinghast, Eller, Fulginiti, 1973). In younger children , this relationship was found to be common with respiratory syncytial virus infection (McIntoch, Ellis, Hoffman, Lybass, Eller & Fullginiti, 1973).

These epidemiology studies, of two decades ago, also found that HRV was a common respiratory infection that precipitated wheezing in patients with asthma. However, it was found that patients needed to be ***symptomatic*** with a viral URI for asthma to increase (Minor, Dick, DeMeo, Ouellette, Cohen & Reed, 1974). A review of these early studies demonstrated the presence of HRV in association with 30% of childhood asthma exacerbations (Pattemore, Johnston & Bardin, 1992). With the application of advanced techniques, based on the polymerase chain reaction (PCR), in addition to standard virology, the presence of viral pathogens was demonstrated in 80% of asthma exacerbations in a community sample of 9 to 11 year olds. HRV was responsible for 50% of these episodes (Johnson, Sanderson, Pattemore, Smith,

Bardin, Bruce, Lambden, Tyrell & Holgate, 1992; Johnson Pattemore, Sanderson, Smith, Lampe, Josephs, Symington, O'Toole, Myint, Tyrrell & Holgate, 1995).

URI and bronchial hyperresponsiveness

The mechanisms by which colds may trigger wheezing are not clear and are the subject of active research. Suggestions have included increased production of virus-specific IgE (Welliver, Wong, Sun, Middleton, Vaughan & Ogra, 1981), increased mediator release (Huftel, Swenson, Borcherding, Dick, Hong, Kita, Gleich & Busse, 1992), airway damage and narrowing of the bronchi and 'late response' asthma resulting from inhaled antigen (Bardin, Johnston & Pattemore, 1992; Busse, 1991).

Busse (1995) reported evidence from clinical observation and from studies in patients experimentally infected with HRV. This evidence showed that a mechanism by which viral respiratory infections increase symptoms in asthma is an accentuation of the allergic reaction and resulting inflammation. The operation of such a mechanism together with the recruitment of cells to the airways can persist into the convalescent period. Busse suggests that this may be the means whereby lower respiratory morbidity can outlast the acute symptomatic effect of the cold on the upper airways, as commonly experienced by those with asthma (Fraenkel, D.J., Bardin, P.G., Sanderson, G., Lampe, F., Johnston, S.L., Holgate, S.T., 1995) Earlier studies have shown that epithelial damage can sometimes extend over a period of 4 to 6 weeks (Hers, 1966; Camner, Jarstrand & Philipson, 1973; Empey, Latimen, Jacobs, Gold & Nadel, 1976).

Increased bronchial responsiveness together with inflammatory processes are characteristic features of asthma. One step in confirming a diagnosis of asthma and in measuring BHR is to expose the child to chemical stimuli such as histamine and methacholine known to produce bronchoconstriction (Cockcroft & Berscheid, 1982; Chai et al, 1975). Histamine initiates a reflex arc which passes through the central nervous system via the vagus nerve while methacholine is a derivative of

acetylcholine released by vagal stimulation when bronchial receptors are stimulated. The resulting bronchospasm can be partially blocked by medication. Bronchial receptor sensitivity, which may occur in URI, therefore, may provide a partial explanation for increased airways responsiveness

However, the relationship between a heightened response to allergens and inflammatory processes during upper respiratory infection may not be a straightforward one. While studies have indicated that the presence of atopic disease appears to render subjects more vulnerable and place them at particular risk to develop severe exacerbations of asthma after a preceding bout of 'cold' and 'flu (Bardin, Johnston & Pattemore, 1992) others have indicated that this may occur independently of the development of BHR in the course of infection. It has been demonstrated that increases of histamine and antigen responsiveness persisted for at least 4 weeks in subjects with atopic rhinitis, infected with HRV, with 80% of subjects developing the 'late' asthmatic reaction ***independently*** of the development of BHR during the cold (Lemanske, Dick, Swenson, Vrtis & Busse, 1989).

Similarly, while bronchial hyperresponsiveness is a characteristic feature of asthma, the relationship between BHR, asthma and atopic status is a complex one. BHR has been demonstrated in many, but not all, subjects suffering from asthma (Juniper, Frith & Hargreave, 1981) and in subjects who have recurrent respiratory symptoms in the absence of diagnosed asthma (Woolcock, Peat, Salome et al, 1987). One-in three children who responded to bronchial challenge in population surveys have been found to be asymptomatic (Hopp, Bewtra, Nair, Watt & Townley, 1986; Salome, Peat, Britton & Woolcock, 1987; Pattemore, Asher, Harrison, Mitchell, Rea & Stewart, 1990; Sears, Jones, Holdaway et al, 1986). A number of studies have also shown no association between atopic skin test reactivity and BHR in asthmatic and non-asthmatic subjects (Welty, Weiss & Tager, 1984; Woolcock, Colman & Jones, 1978; Cockcroft, Ruffin & Frith, 1979; Bryant & Burns, 1976). Such findings have been supported by the evidence from other studies examining the relationship between

wheeze and BHR (Pattemore, Asher, Harrison, Mitchell, Rea & Stewart, 1990) and the variability of BHR over time (Josephs, Gregg, Mullee & Holgate, 1989).

In a series of ***community*** studies involving children with a range of respiratory problems, 11% of subjects with both atopy and wheeze, 64% with atopy, 69% with wheeze alone and 40% with asthma did not demonstrate BHR at all over a 12 month period (Clough, Williams & Holgate, 1992). Nevertheless, compared with non-atopy and cough in 7 and 8 year olds, atopy and wheeze were both independently associated with an increased prevalence and a greater degree of BHR. However, neither atopy nor wheeze could sufficiently explain the occurrence of significant episodes of asthma. These findings led Clough and colleagues to the conclusion that the incidence of URI and patterns of symptom presentation together with investigation of those children susceptible to infection should be the subject of future study into the etiology of episodes of asthma. This suggestion has received support from a number of other prominent researchers in the field of asthma who have made similar proposals (Busse, Kiecolt-Glazer, Coe, Martin, Weiss & Parker, 1995).

2.3 Summary

Respiratory infections are a leading cause of community morbidity. The evidence for possible gender differences or the role of age in susceptibility to upper respiratory tract infection is not clear.

Both clinical experience and research has shown that URI is also an important factor in asthma morbidity. Busse (1995) has proposed that a mechanism by which viral respiratory infections increase symptoms in asthma is through an accentuation of the allergic reaction to allergens, etc., with resulting airway inflammation.

Airway responsiveness and inflammatory processes together with recruitment of cells to the airways during HRV colds may also extend into the convalescent period and result in epithelium damage and asthma morbidity which can endure for a period of 6

weeks. However, airway responsiveness and inflammation may develop independently of each other in the course of upper respiratory infection. Evidence from a series of studies conducted on children in the community has also indicated that the presence of atopy and wheeze alone cannot account for the occurrence of episodes of asthma.

A number of investigators have suggested that further research should be directed towards the role of URI and patterns of symptom presentation. In addition, other factors involved in susceptibility to infection, particularly in children with asthma, need to be investigated. Research involving healthy children and adults, has already indicated that one such factor, psychological stress, may play a role in individual susceptibility to URI.

CHAPTER 3

THE SOCIAL AND PSYCHOLOGICAL IMPACT OF CHILDHOOD ASTHMA

Background to Chapter

While a number of physical factors, particularly upper respiratory infection, are important environmental triggers of asthma, social factors may also play an important role in the etiology of this disease. A number of reports suggest that the social burden of asthma, arising from factors such as restrictions in everyday childhood activities, disruption in peer and family relationships and the imposition of strict medical regimes, may leave children at increased risk for social, emotional and behavioural 'maladjustment' in comparison with healthy peers. Risk factors involved in decreased psychological 'adjustment' include a lack of coping resources, low socioeconomic status, disease severity, family dysfunctioning and increased levels of life events (Varni & Wallander, 1988; MacLean, Perrin, Gortmaker & Pierre, 1992).

A number of researchers have found a relationship between disease severity in asthma and measures of psychological adjustment. The latter includes measures of psychiatric functionioning, as reflected in Childhood Behaviour Checklist scores (CBCL; Achenbach & Edelbrock, 1983) and measures of self-image such as self-concept, perceived self-competence and self-esteem. However, a number of studies have failed to confirm a relationship between disease severity and measures of adjustment. The relationship between adjustment and disease severity can be a complex one. For example, children may report normal levels of psychological adjustment but engage in inappropriate coping behaviours. Such behaviours can result in the maintenance of illness through, for example, non-compliance with medication, or may result in other inappropriate responses to disease symptoms which can cause exacerbation of the illness.

This proposed relationship between disease severity and measures of psychological adjustment is consistent with a biopsychosocial model of disease (Lask & Fosson, 1989; Brown & Harris, 1979; Cronkite & Moos, 1984; Vandvik & Eckblad, 1991) (Figure 1). Such a model proposes that the etiology of disease is determined by the interaction between ***hereditary*** *and* ***environmental factors*** *of a physical, psychosocial*

and psychological nature ***(input variables)****. As a result of this multifactorial causality, patterns of symptom presentation can emerge which are dependent on the relative contribution of each of the variables to the illness process and also on their interaction with each other. This interaction of input variables results in outcomes in the short and long term such as* ***disease severity*** *and* ***psychosocial functioning (outcome variables)*** (Figure 1).

3.1 The Social Impact of Childhood Asthma

In their survey of 5472 children, Strachan, Anderson, Limb, O'Neill & Wells (1994) found a trend towards more 'diagnosed asthma' in the less privileged classes, a pattern which remained almost unaltered after adjustment for age, region and degree of urbanisation. With falling social status there was only a modest increase in the 12-month period prevalence of wheezing but a marked trend towards more severe, more frequent and more sleep disturbing episodes in the lower socioeconomic groups. These investigators concluded that social factors may affect the severity of the condition more than the prevalence of wheezing itself. They also suggested that a parental difference in perception of symptoms of asthma in different socioeconomic groups may also be a factor. The role of socioeconomic status has been considered in a number of reports and especially in relation to race where asthma prevalence, hospitalisation and mortality rates are consistently higher in blacks than whites and where in many cases there may be low levels of social support (Weiss, Gergen & Wagener, 1993). Increased levels of social support can moderate the effects of stress and encourage improved coping with illness.

A recent report by Lenney, Wells & O'Neill (1994) has drawn upon the findings of a national survey, 'The Lifestyle Study'. This qualitative study explored the day-to-day consequences of the disease for 773 children with asthma (aged 5-17 years) and their 248 parents. The paper highlighted factors contributing to the social burden of asthma both on the child and family. This arises through its effect on the daily activities of the child, including restrictions on school activities and attendance,

together with its effect on sibling and parental relationships. For example, the study found a prevalence rate of 80% of exercise-induced symptoms in this sample with 50% of children at some stage being unable to complete or participate in a sports lesson because of asthma. The study suggested that an average of 7-10 days per year were lost by absence from school due to asthma. However, there is a wide variation in statistics reflecting reported school absences. Anderson et al (1983) found that 6 school weeks of absence was reported by 12% of a sample of wheezy primary school children. Absences from school were related to night time disturbance. This factor affected approximately three quarters of children in the Lifestyle Study, with 41% of all children reporting having stayed home from school, work or college because they were too tired after waking with asthma the night before. 74% of children aged 5-11 years and 61% of 12-17 year olds said they felt sleepy in lessons or at work the next day. When asked without prompting which activities they would like to be able to do better, 'sleeping through the night without waking' was reported by 51% of children. About one quarter of children reported embarrassment at taking their inhaler or other medication to school. More strikingly, 71% reported that they did not like carrying their medication with them with 57% expressing frustration at having to use medication many times during the day. When questioned regarding attacks at school, work or college, 56% reported feeling embarrassed when this happened and 63% reported being frightened.

In relation to parents and siblings, 46% of parents believed that their other children felt that the sibling with asthma was treated better by the parents than they were themselves. On the other hand, however, two thirds of parents felt that the presence of a child with asthma in the family made the other children more kind and understanding. One in three parents felt their house work routine differed from that of other households. Approximately, one in four parents of 5 to11 year olds took at least one day off work in the previous 3 months because of their child's asthma. 62% of parents reported that their social activities were affected by their child's asthma

with 70% of parents reporting that they were "constantly aware" of their child's illness. Nocon (1991) referred to this as a "constant state of red alert".

3.2 The Psychological Impact of Childhood Asthma

Within psychological stress theory, the presence of long-term stress and continuing arousal at "red alert" level of may be accompanied by a chronic level of physiological activation (Cox, 1987). Such chronic psychological stress levels together with the social and personal burden associated with chronic illness in general can have an adverse effect on the lives of the children involved and their families. This arises, as already noted, from disruptions in everyday activities and family routines, restrictions in peer activities, the imposition of strict medical regimes and various other constraints in family and social interactions (Eiser, 1990; Nocon, 1991; Walsh & Ryan-Wenger, 1992; Graetz & Shute, 1995; Celano & Geller, 1993; Hobbs, Perrin & Ireys, 1985; Lenney, Wells & O'Neill, 1994).

Conditions of chronic or acute stress and maladaptive coping may result in a more indirect manner in more severe and longer-lasting illness. This can happen through a number of factors which contribute to disease progression and maintenance of illness, for example, non-compliance with medication, lack of sleep, diet, etc., psychological dependency on the illness or medication, behaviours related to secondary gain, inadequate goal seeking behaviour in striving towards good health and low levels of self-esteem. However, children may report normal or high levels of psychological adjustment but also engage in behaviours which result in the maintenance of their illness (Matus, 1981).

These secondary consequences have led to studies investigating the effects of chronic disease and the role of psychopathology not only in children with long term illness (Graham, Rutter, Yule & Pless, 1967; Rutter, Tizard & Whitmore, 1970; Pless & Roghmann, 1971; Cadman, Boyle, Szatmari & Offord, 1987) but also in parents and siblings (Drotar & Crawford, 1985; Dunn, 1988; Eiser, 1990; Beardsall & Dunn,

1992). The chronic diseases under study have included illnesses such as haemophilia (Bruhn, Hampton & Chandler, 1971) and juvenile arthritis (McAnarney, Pless, Satterwhite & Friedman, 1974). While these studies have produced some mixed results, it has generally been concluded that long-term illness in these children places them at increased risk for social, emotional and behavioural 'maladjustment' in comparison with healthy peers.

Identified risk factors involved in lower levels of psychological adjustment include a lack of coping resources, disease severity, family dysfunctioning, lower socioeconomic status and increased levels of life events (Varni & Wallander, 1988; MacLean, Perrin, Gortmaker & Pierre, 1992). Apart from disorders involving the central nervous system or physical disability (Eiser, 1990) increased risk of maladjustment has not been considered specific to particular illnesses (MacLean et al, 1992). Some researchers have therefore focused on more general illness parameters such as disease severity and its relationship to psychological adjustment (Stein & Jessop, 1982).

The measurement of psychological adjustment in such studies has been carried out using measures of psychiatric functioning such as the Childhood Behaviour Checklist (CBCL; Achenbach & Edelbrock, 1983) and measures of self-image. It should be considered that, when dealing with a sample of chronically-ill children, problems can arise in measuring aspects of self-image, such as self-esteem, self-concept and self-perceptions (Rosenberg, 1965; Piers & Harris, 1969; Harter, 1982, 1985). The processes through which self-perceptions for chronically-ill children are developed and maintained may be complex and, as such, may require further assessment procedures (Harter, 1986). The use of standardised measures of psychiatric functioning such as the CBCL can also be problematic particularly in relation to asthma and allergy. For example, responses to questions in the CBCL dealing with asthma and allergy symptoms can be regarded as behaviour problems when assessing psychiatric symptomatology.

Studies in Psychological Adjustment and Asthma

As a common chronic childhood illness, asthma has been studied by a number of authors (Noorish, Tooley & Godfrey, 1977; Steinhausen, 1983; Mrazek, Anderson & Strunk, 1985; Perrin, MacLean & Perrin, 1989; Kashani, Konig, Shepperd, Wilfley & Morris, 1988; Vazquez, Fontan-Bueso & Buceta, 1992). A number of reports have concluded that children with asthma are at increased risk for decreased psychological adjustment (Cadman et al, 1987; Gortmaker et al, 1990; Pless & Roghmann, 1971; Wallander, Varni, Babani, Banis & Wilcox, 1988) with one review finding an increased incidence of psychopathology or more negative emotions in children with asthma (Lehrer, Isenberg & Hochron, 1993). A high incidence of behavioural and school-related problems has also been reported together with social competence problems in boys and low self-esteem in girls (Hambley, Brazil, Furrow & Chua, 1989). Significantly lower measures of self-esteem (Seigel, Golden, Gough, Lashley & Sacker, 1990), and greater psychiatric disturbance (Graham, Rutter, Yule & Pless, 1967) has also been reported in *adolescents* with asthma compared with their healthy age-matched controls.

Maclean, Perrin and colleagues (1992), in a study of 81 children, aged 6 to 14 years, incorporated a measure of disease severity. They found that lower socioeconomic status and greater asthma severity, together with negative life change requiring some measure of readjustment on the part of the individual, were predictive of less optimal psychological adjustment. An earlier study by the same researchers (Perrin, MacLean & Perrin, 1989) suggested that the relationship between illness severity and levels of adjustment may not be a linear one. Employing the CBCL, they found that children with moderate asthma had more optimal psychological adjustment scores than those with either mild or severe disease. Other studies have found no relationship with disease severity. For example, in a study of 56 children, 7-16 years of age, no difference was found between asthma and controls on a measure of self-concept and no relationship was found between severity of asthma, as assessed by medication

usage, and psychiatric symptomatology (Kashani et al, 1988). Similarly no differences were found between 48 children with mild to moderate asthma and 41 healthy children on a measure of perceived self-competence (Vazquez, Fontan-Bueso & Buceta, 1992).

Some further methodological problems may arise in studies using measures of disease severity. A variety of such measures have been used with few being validated. These include maternal reports of days missed from school, medication use and frequency of asthma attacks. The disease is also characterisically variable in nature. Symptom presentation can be perennial or intermittent with children sometimes experiencing relatively long asymptomatic or illness-free periods. The diagnosis, treatment and management of asthma can also vary between medical practitioners (Burr, 1991; Usherwood & Barber, 1985; Bucknall, Robertson, Moran & Stevenson, 1988a,b).

3.3 Summary

Within a biopsychosocial model of multifactorial disease the stress-illness process in asthma is determined by the interaction of a number of hereditary and environmental factors resulting in outcomes of disease severity and psychosocial functioning. While producing some mixed results, the balance of reports are consistent with such a model and suggest that the added social and psychological burden imposed by chronic illness leaves children with asthma at increased risk for decreased psychological adjustment in comparison with their healthy peers. However, conditions of chronic and acute stress and maladaptive coping may result ***indirectly*** in more severe and longer lasting illness through a number of illness-related behaviours and low levels of self-esteem. However, children can report normal measures of self-esteem but also indulge in illness-related behaviours which result in disease progression and maintenance of illness. The more ***direct*** role played by chronic and acute stress on the course of asthma will be discussed in Chapter 5.

CHAPTER 4

PSYCHOLOGICAL STRESS AND CHILDHOOD ILLNESS

Background to Chapter

In 1995, the Division of Lung Disease of the National Heart, Lung and Blood Institute and the Fetzer Institute in America sponsored a Workshop on Stress and Asthma. The goal of this conference was to re-examine the role of psychological stress in asthma, both as an acute precipitant of airflow obstruction and also as an etiological component of the disease, topics which had received limited attention in the investigative community (Busse, Kiecolt-Glaser, Coe, Martin, Weiss & Parker, 1995). Other reports suggest that, even at a public health level, psychological stress is rarely considered a significant risk factor (Graham, 1988) This may be explained by the fact that stress arising from both major 'life events' and more minor everyday life events such as 'daily hassles' are common life experiences for an individual and are regarded as being outwith the domain of public health.

There is now growing evidence, however, that social and environmental stressors increase susceptibility to disease. Nevertheless, many remain sceptical (Kleinman, Eisenberg, Good, 1978; Engel, 1977). Methodological drawbacks in psychosocial research (Angell, 1985) have been cited as being partly responsible for this scepticism. These difficulties have derived from differences in the definition of what constitutes 'stress' . This has resulted in the emergence of two differing traditions in the stress-illness field of study. One supports a checklist-based measure of life events and the other an interview-based measurement.

The majority of studies on stress and illness have employed a checklist measure and are retrospective in nature. Issues surrounding the definition and measurement of stress will be discussed before examining these studies. Studies relating to the role of ***acute*** *and* ***chronic*** *stress in childhood asthma will be dealt with in Chapter 5.*

4.1 The Definition and Measurement of Psychological Stress

Psychosocial 'stressors' in the environment are not invested with negative tone or strength. The 'strength' of an event lies in the perception of the event by the

individual and this in turn is shaped by the nature of the event itself and the context surrounding it. Individual differences in emotional response to events, therefore, are not brought about by some inherent quality of the event but by (1) the initial emotional threshold triggered in the individual by the event together with (2) the strength of the emotional response elicited and (3) the individual's perception of this response. The subjective experience of stress through emotions such as anger, anxiety or fear may be brought about by a person's inability to cope with demands in his/her psychosocial environment. Studies have shown that the relationship between psychological stress and illness is mediated by the presence, duration and severity of a range of events of a physiological, sociological and psychological nature together with the individual's ability to cope with these events. Coping ability may be moderated by a number of factors. These include personality (Kobasa, 1979; Kobasa, Maddi & Puccetti, 1982; Garrity, Somes & Marx, 1977; Ranchor & Sanderman, 1991); social support and networks (Boyce, 1981; Berkman, 1984; Thoits, 1982); coping style (Pearlin, Menaghan, Lieberman & Mullan. 1981; Andrews, Tennant, Hewson et al, 1978) and controllability of life events (Stern, McCants & Pettine, 1982).

While a number of studies have investigated the role of psychological stress in physical illness in children, very few studies have examined this relationship in childhood asthma. The majority of studies which have found evidence of a relationship between psychological stress and physical illness in children are retrospective in nature and, therefore, lead only to the conclusion of a broad relationship between these variables. A number of commentators have suggested that if the goal is to determine the role of psychological stress in the onset and course of disease then such studies and the stress measures they employ are inadequate to examine temporal relationships. However, despite a period of systematic study over the last 25 years, methodological limitations are still evident in studies examining the role of psychological stress on the onset and course of illness. The principal difficulties centre round the definition and measurement of stress. During this period

research into psychological stress and its relationship to disease has developed within two traditions, one psychological and the other sociological. The psychological approach is based on a checklist/questionnaire type measurement of stress while the sociological adopts an interview-based measurement of stress.

Both traditions are based upon a measurement of stress in the form of life events, occurrences impacting on the life of the individual either through their positive and/or negative effect or through the extent to which they may be capable of bringing about some degree of life change for the individual. ***Acute life events*** are often perceived as having a fairly brief time course. The positive and/or negative impact of such events may extend over a short time period of a day or two or may endure for a period of approximately two weeks. An undesirable feature of events may be their role in giving rise to or exacerbating stress of a more ***chronic or long-term*** nature (Thoits, 1983). For example, a child may change school (***acute event***) and this may give rise to a prolonged period withing which the child experiences problems in peer relationships or may be a victim of bullying (***chronic or long-term experience***). Alternatively, individuals may be experiencing some ongoing discord in marital relationships (***long-term experience***) and a serious marital row occurs (exacerbating ***acute event***). The checklist approach records the occurrence of acute events. The interview based approach takes account of the presence of ***both*** acute life events and more chronic or long-term experiences. Such experiences are perceived as being relatively persistent and sometimes without a clear onset or termination as may be the case, for example, with marital discord.

Increased attention is now being given to the interaction between these forms of stress and evidence of their joint effect indicates that long-term stress may provide a mediating link between life events and adverse illness outcomes (Glickman, Tanaka & Chan, 1991; Brown & Harris, 1978; McGonagle & Kessler, 1990; Pearlin, Menaghan, Lieberman & Mullan, 1981). There is already clear evidence that both predisposing chronic stress (Rutter, 1985, 1991) (which may predispose the

individual to respond to an event with illness) and acute negative life events (acting as provoking factors which give rise to the onset or exacerbation of illness) contribute to psychiatric disorder. This is particularly so in the case of chronic stress which threatens the psychological security of the child (Goodyer, 1990; Sandberg et al, 1993).

The main features of both the checklist and interview-based measures are outlined below.

Checklist measures

This method of stress measurement was pioneered by the works of Holmes & Rahe (1967) with their Schedule of Recent Life Events. This instrument measures the stressfulness of an event by the extent to which it causes ***life change*** and requires readjustment of a person's normal routine. The assessment of stress is equated with the degree of life change judged to be brought about by events in domains of the individual's life over a particular period. This self-report questionnaire measures the number of recent major events such as death in the family, divorce, financial changes and change in employment status that have happened. An individual's total stress score is then based on the sums of the weights, expressed as 'Life Change Units', which are mean ratings of the relative degree of required readjustment. Individuals who experience more life change are proposed to experience more psychosocial stress. The individual's perception and ***subjective*** rating of life change is of central importance in this method. A number of similar checklist-based measures have arisen following on Holmes & Rahe's original measure (Appendix 1) and the majority of studies investigating the stress-illness dyad have employed such retrospective checklist instruments. In the measurement of stress in children, Coddington's paediatric modification (1972) of the Schedule of Recent Experience provides a score for each life change reflecting its relative magnitude as estimated by a combined group of paediatricians, teachers and mental health workers. The total life change

score for each child is computed as the sum of scores experienced during the period of study.

Another checklist or questionnaire method is the measurement of stress through the recording of daily minor stressors or ***'hassles'*** rather than major life events. These 'hassles' are stressful, annoying or unpleasant but more minor events which occur frequently. These are measured by a number of instruments including the Daily Hassles Scale (Kanner, Coyne, Schaefer & Lazarus (1981). The Daily Hassles Scale is a 117 item ***questionnaire*** recording items which have 'hassled' subjects within a specified period of time employing frequency and severity scores. The Daily Stress Inventory (Brantley & Jones, 1989) asks respondents to indicate those events which have occurred (event score) and rate each event for perceived stress (impact score). Impact ratings for the day are summated and an averaged score calculated (impact/event score). A number of studies have suggested that the frequency of daily hassles is a better predictor than major life events of stress and physical health (Kanner, Coyne, Schaefer & Lazarus, 1981; DeLongis, Coyne, Dakof, Folk man & Lazarus, 1982; Weinberger, Hiner & Tierney, 1987; Russell & Davey, 1993). However, the relationship can be circular since hassles may influence the stress response being measured which in turn influences the perception of events.

Interview-based measures

The Camberwell Family Interview devised by Brown and Rutter (Brown & Rutter, 1966; Rutter & Brown, 1966) is the forerunner of those interviews being used to assess both acute events and chronic experiences in childhood and adult life. 'Contextual' measurement is a key feature of investigator-based interview assessments of stress which purport to take into consideration the personal context or meaning of life events when making an ***objective*** rater assessment of stressful impact. This contextual based measurement is the basis of measurement of the Life Events and Difficulties Schedule (LEDS) employed by Brown & Harris (1978) in their studies on depression in women.

A life events interview for measuring stress in children and adolescents was devised by Goodyer & colleagues (Goodyer, Kolvin & Gatzanis, 1985). This involved mothers and not children as respondents and no measurement was made of chronic experiences. However, Goodyer concluded that parental account of the occurrence of stressful life events, their context and stressful impact, even if accurate, could not provide an adequate view of the child's inner perceptions of such events. Some work based on a modification of the LEDS interview has also been carried out with older adolescent girls (Monck & Dobbs, 1985) with a joint 'consensus' interview with mother and daughter carried out.

A further extenstion of such interview-based measures for children has been the Psychosocial Assessment of Childhood Experiences (PACE) of Sandberg, Rutter, Giles, Owen, Champion, Nicholls, Prior, McGuinness & Drinnan (1993). This is an interview-based instrument relying on the 'contextual' measurement of stress and has been devised for use separately with both parents and children. Acute positive and negative life events are recorded, together with coverage of a wide range of ***chronic experiences***, again both positive and negative. What constitutes a life event or chronic experience is determined and defined pre-interview. Events are reported separately and dated and rated for threatening impact by the child or parent being interviewed. They are also subsequently rated for objective contextual threatening impact.

Events and long-term experiences are also rated for 'independence' from (1) the illness being measured and (2) the behaviour of the child and family. For example, any events or experiences related to the illness under investigation, such as a stay in hospital related to the illness, would be excluded from analysis. Also, in order to identify whether the behaviour of the child and/or family brings about the occurrence of an event or experience, all reports are classified according to their relatedness to such behaviour. For example, if the child experienced a move of house, this would

probably be ***independent of any behaviour of the child*** but probably ***related to the behaviour of the family*** especially if the move was not imposed on the family by any authority and was related, for example, to the purchase of a new home. On the other hand, if the child was excluded from school because of bad behaviour, such an event would be ***related to the behaviour of the child.***

Ratings of 'independence' help to prevent problems of circularity in analysis. Adverse events and experiences of many kinds predispose children to long-term risk for psychiatric disorder and maladjustment. In many instances the child can be an active participant in shaping his or her environment and can increase the likelihood of their own exposure to adverse life events and difficulties (Goodyer, 1990). The classification of events and experiences in terms of their association particularly to the behaviour of the child helps to reduce the likelihood of problems of circularity where one may only succeed in proving that stress results in stress, especially in studies concerning the role of psychological stress in psychiatric or psychosomatic illness.

Reports of all admissible events from the parent and child interviews are combined in an investigative procedure which by a method of 'triangulation' tests for the actual occurrence, timing and 'contextual' or objectively rated impact of events reported by the child alone, the parent alone and by both child and parent. The presence of chronic stress is recorded by the interviewer alone and is subsequently rated for both contextual impact on child and family and for independence status.

Criticism of methods:

A number of criticisms have been made of these approaches, particularly in relation to checklist measures. These focus on:-

(1) the practice of summation of stress scores on the basis that this practice ignores both the nature of threat involved and its cognitive appraisal. For

example, the threat score derived from a number of relatively minor or low threat events may, after summation, be equivalent to the threat score for one or more highly negative or threatening events;

(2) failure to take account of the presence of chronic stress and its interaction with acute events;

(3) problems of investigating the temporal relationship between acute event and illness onset or exacerbation;

(4) failure to take account of the event in terms of its relatedness to the behaviour of the child and/or family which may lead to problems of circularity.

The psychological checklist approach is based on the proposal that the individual's ***perception*** of the impact of an event is crucial in the psychological processes which mediate in the relationship between event and any subsequent onset or exacerbation of illness. An important difference between the checklist method and interview-based sociological approach is that within the interview method the individual's perception of change is not regarded as important. A panel-based ***objective*** measurement of the impact of stress involved in an event is made and is derived from contextual details obtained at the interview from the parent and/or child. However, because the nature of the context surrounding an event is taken into account, proponents of the interview-based approach claim that this is thus an ***objective but personalised*** measure. As noted in the criticism under (1) above, the practice of summation of stress scores in the checklist method effectively negates any cognitive appraisal of threat involved. Therefore, any comparison in terms of the relative advantages and disadvantages of each method and centering on the 'subjective appraisal' of events is not useful because of the practice of summation of stress scores.

A more cogent and practical criticism of the interview-based measure might be that this method is time-consuming and expensive to use. Nevertheless, because of the retrospective nature of studies employing the checklist instrument and criticisms levelled at its method, it has been suggested that checklist approaches are inadequate

if the goal of research is an understanding of the role of psychological stress and adversity in disease. Other reports have also suggested that because of problems of recall and misclassification checklist approaches should not be used if the goal is to understand the role of stress in adverse health outcomes (Raphael, Cloitre & Dohrenwend, 1991).

4.2 Psychological Stress and Studies in Childhood Illness

A number of studies have already shown associations between adverse life experiences both acute and chronic and the onset or course of psychiatric disorders in adult life (Brown & Harris, 1978, 1989) and in childhood (Rutter, 1966, 1979; Vincent & Rosenstock, 1979; Eth & Pynoos, 1985; Garmezy & Rutter, 1983, 1985; Goodyer, 1990; Johnson, 1982). A number of methodological child and adolescent studies have also emerged employing several developments and innovations in the measurement of stress but broadly based on the checklist measurement of stress devised by Holmes & Rahe (1967) (Coddington, 1972 a,b; Monaghan, Robinson & Dodge, 1979; Johnson & McCutcheon, 1980; Berden, Althaus & Verhulst, 1990).

In the main, research has focused on the relationship between stress and psychiatric illness. The relationship between stress and physical illness has been less well researched. There are many adult studies indicating a role for negative life events in the onset and course of physical illness (Brown & Harris, 1989). The much smaller number of studies in children have involved checklist measures. Here findings point only to a broad relationship between life change and undesirable life events and the onset of illness or the exacerbation of an already present illness.

A number of these studies have shown that a serious physical illness in childhood is often preceded by the accumulation of stressful events. For example, emotional factors were found to play a role in triggering of type I (insulin dependent) diabetes. The incidence of stressful life events in the months preceding the onset of diabetic disease in children was two-fold higher than in control subjects (Robinson & Fuller,

1985). A higher incidence of parental loss and severe family disturbances has also been found in diabetic children compared to non-diabetic controls. (Stein & Charles, 1971; Leaverton, White, McCormick, Smith & Smeikholislam, 1980).

Heisel, Ream, Raitz, Rappaport & Coddington (1973) studied 100 children who had been admitted to hospital with a newly established diagnosis of physical illness; illnesses included rheumatoid arthritis, appendicitis and cardiovascular disorder. This group found an accumulation of major family life events, 2 to 3 times more than healthy controls, in the year preceding general paediatric hospitalisations. In one-third of cases the onset of illness was preceded by an event considered to require major re-adjustment to the external environment.

Other studies have shown that major psychosocial stress may constitute one of the precipitating factors in the onset of leukaemia. Greene & Miller (1958) studying the development of leukaemia in children and adolescents found a strong relationship between 'loss' events and the onset of disease. Of 33 children studied, 31 had experienced an event involving personal loss in the previous 2 years prior to onset of illness with half of the losses occurring in the 6 month period before diagnosis. Events included change of residence or school (57% of the leukaemic children were found to have moved within a two year period), the death of a parent and separation or threat of separation from grandparents.

This study was replicated by Jacobs & Charles (1980) who studied 25 children and adolescents and a comparison group of 25 children. They found that children with a newly established diagnosis of leukaemia had experienced parental separation, death of a close family member and change of residence, with major implications for re-adjustment, some three to four times as often as comparison children attending a general paediatric clinic. In the year prior to onset of disease, 72% of the children who developed cancer experienced a change of residence within the two year period prior to onset of illness. This was three times the rate in the comparison group.

A subsequent investigation of monozygotic twins discordant for leukaemia also supported the findings of an association between major psychosocial stress and the onset of leukaemia (Greene & Swisher, 1969).

It cannot, however, be ruled out that the physical and environmental aspects involved in a change of residence and possibly related to exposure to infection may be a major factor in the development of leukaemia rather than the psychological consequences associated with a move of house and change of physical environment.

Adverse life experiences have also been related to acute symptoms associated with an already established chronic illness. Bedell, Giordan, Amour, Tavormina & Bolt (1977) studied children at a summer camp for the chronically ill. These children included those with a variety of illnesses including diabetes, asthma, cleft palate and cystic fibrosis. Those children who had experienced several adverse life events over the past year suffered significantly more acute illness episodes relating to their illness, a difference which was almost four-fold compared with children with low life stress scores.

Not all the literature suggests positive relationships with a number of studies finding negative results. A generally high frequency of stressful life events has been consistently reported in families of children with juvenile chronic arthritis (Anderson, Bradley, Young et al, 1985). However, Vandvik, Hoyeraal &Fagertun (1989) investigating different disease course types in 106 families of children with juvenile arthritis using an interview assessment to record acute life events and chronic family difficulties found no difference between disease course types in these measures and no relationship to severity of disease. Similarly, no evidence of an increased prevalence of life events, measured by Paykel's life event scale, was found in a study examining anxiety and life events in childhood migraine (Cooper, Bawden, Camfield

& Camfield, 1987) while an increase in hypertension has been found in children after migration (Beaglehole, Eyles, Prior, 1979).

4.3 Summary

All of these studies investigating the relationship between psychological stress and physical illness in children have been carried out using a checklist measurement of stress with the exception of the study by Vandvik et al (1989) which employed a non-standardised interview measure. In addition, it cannot be excluded that the stress of the onset of an illness may focus attention on the recent past thus enabling the subject to recall events more clearly than healthy controls. Feelings of guilt related to the onset of disease may also be alleviated by associating the onset of the disease with a stressful life event. Such factors together with the retrospective nature of these studies tend only to the conclusion of a broad relationship between psychological stress and the onset and course of physical illness.

The interview method is based on a more objective rater-based 'contextual' assessment of the impact of acute life events and experiences. This rating of 'contextual' threat takes into account the personal and social context surrounding the reported event or experience. A number of modifications of the interview-based measure have been developed, some of these for use with children. The most recent of these has been the PACE. devised by Sandberg, Rutter et al (1993). The PACE has been developed for use with both child and main caregiver and records the presence of not only acute major life events of either a positive or negative impact but also long-term positive experiences and chronic negative stress. Another methodological advantage of this method is that it allows for the investigation of temporal aspects of the stress-illness process, an important feature if causality is the ultimate goal of research. Another important feature is the assessment and recording of the 'independence' of an event or experience from the behaviour of the child or family. This reduces problems related to circularity.

While this method incorporates a number of methodological advances, it is more expensive and time consuming. Because of this, the majority of studies investigating the stress-illness relationship have been based on a cheaper and less time-consuming checklist measurement of stress.

From a theoretical point of view, however, while the interview-based measure may offer some methodological advances, it still needs to be the subject of future empirical research to establish whether 'objective' panel-based ratings or 'subjective' ratings of the threat impact of events are the more predictive of illness. Both types of ratings are incorporated in the interview-based measure but only the objective panel-based ratings are employed in analyses.

CHAPTER 5

PSYCHOLOGICAL STRESS AND CHILDHOOD ASTHMA

Background to Chapter

Not only may the presence of childhood asthma constitute a source of chronic stress that can significantly affect the course of psychological development and psychosocial functioning of the child but it may also leave those exposed to the burden of illness-related stresses at increased risk in the relationship between psychological stress and illness.

Further, in the lower socioeconomic classes where there is a trend towards increased prevalence and severity of asthma, a lack of social support may result in reduced coping not only with illness but also with the 'normal' everyday stresses which can confront children and their families.

Such proposals would again be consistent with a biopsychosocial model of disease. This model proposes a role for a number of psychological variables in the etiology of illness. These include predisposing variables such as prior levels of chronic stress and provoking variables such as high threat acute life events together with a number of modifying variables, such as coping, which may modify the relationship between provoking variable and the onset or course of disease. It may also be the case that the burden of a chronic illness such as asthma may act as a predisposing risk factor which when combined with the otherwise normal levels of everyday stresses to which children are exposed may leave those with asthma at increased risk in any relationship between psychological stress and the exacerbation of illness.

However, while both patients and physicians may often report that psychological stress and emotional factors may exacerbate symptoms of asthma, there is in fact very little research data to support this assumption. Recently, a number of research proposals have been made which have been designed to examine the relationship of psychological stress to current concepts of asthma (Busse, Kiecolt-Glaser, Coe, Martin, Weiss & Parker, 1995)

5.1 The role of Acute and Chronic Stress in Childhood Asthma

Chronic stressful experiences and asthma

Adverse family circumstances have been proposed to play a role in the triggering of asthma in the early psycho-analytic literature (French & Alexander, 1941; Peshkin, 1930) and in more recent reports relating to the early onset of asthma (Gardner, Grank & Taber, 1984; Klinnert, Mrazek & Mrazek, 1994). Stress arising out of family relationship problems has also been proposed to play a role in bringing about children's asthma attacks (Purcell, Brady, Chai, Muser, Molk, Gordon, & Means (1969). Purcell et al studied 25 children with asthma during periods in which they lived with their families and during an experimental separation in which they had no contact with their families but were cared for in their own homes by a substitute parent. Investigators predicted improvement in asthma for some of the children (n=13) and no improvement for others (n=13). For those with a positive prediction, there was a statistically significant decrease in asthma symptoms during the period of family separation followed by an increase in symptoms upon the family's return. For those children with a predicted negative response, only one of four measurements suggested improvement during separation.

In a further study investigating family relationships and their relationship to asthma, Zlatich, Kenny, Sila & Huang (1982) divided children and adolescents with asthma into groups of responders (n=22) and non-responders (n=22) on the basis of response to medical management. They found that female non-responders reported their mothers' behaviour as more intrusive than did female responders, while male non-responders compared with responders perceived their mothers as granting a higher degree of autonomy. Among the girls, responders reported their mothers as granting a higher degree of autonomy. It was also found that mothers of non-responders experienced a significantly greater number of undesirable life events than mothers of responders. Female non-responders reported significantly more undesirable life events in the previous year than did female responders. Greater numbers and severity

of life events among these children with asthma therefore appeared to be associated with less favourable responses to medical treatment.

Mothering attitudes and negative parent-child interactions have also been associated with treatment failures or complications in a number of other asthma studies (Weiner, 1977; Rees, 1963; Pinkerton & Weaver 1970; Liebman, Minuchin & Baker, 1974; Hermanns, Florin, Dietrich, Rieger & Hahlweg, 1989; Hermanns, Florin, Dietrich, Lugt-Tappeser & Rieger, 1989; Schobinger, Florin, Zimmer, Lindemann. & Winter, 1992). A more recent study found that mothers of children with asthma made significantly more critical remarks to their children. Further, it was found that those mothers who showed a higher total amount of negative verbal behaviour in a problem discussion session had children with higher IgE levels (Schobinger, Florin, Reichbauer, Lindemann & Zimmer, 1993). There are also some indications in the literature that high IgE levels may be associated with disturbances in behaviour like distractability and inattentiveness (Marshall, 1989) together with reports suggesting a number of associations between childhood asthma and attention deficit disorder (Biederman, Milberger, Faraone, Guite et al, 1994).

Acute life events and asthma

The stress of having chronic illness in childhood has been studied but not the extent to which such children perceive the normal stressors of childhood. For example, investigators know little about the stress confronted by children with asthma other than the stresses of the illness or the extent to which their stressors are similar or different to other children of their own age. One study examined 84 children, 8-13 years old, with moderate to severe asthma attending a camp for children with asthma (Walsh & Ryan-Wenger, 1992). These children completed the Feel Bad Scale (Lewis, Siegel, Lewis, 1984) which defines sources of stress, daily occurences or hassles, from the perspective of children aged 8-12.years. The Scale is scored on a scale of frequency and severity, higher total scores on each scale indicating more frequent and severe stress than low scores. Investigators found that the children

experienced stressors similiar to those experienced by other children. However, these findings are inconclusive because of the limitations arising from the summing of stress scores. In addition, the effect of stress over time was not examined nor was there alternative verification of the actual occurrence of stressful events by a parent.

While it is not clear whether children with asthma may experience stressors similar to other children, the effect of such stressors on the course of childhood asthma has also not been investigated. In their review of stress and illness, Jemmott & Locke (1984) suggest that the evidence points to a modest association between major life events and respiratory illnesses such as asthma. According to the anxiety hypothesis, acute stress and/or anxiety may cause acute changes in asthma symptom severity (Erskine & Schonell, 1979). Goreczny, Brantley, Buss & Waters in 1988 found, however, that "to date, no study has satisfactorily measured the changes in asthma severity as they relate to acute changes in stress and anxiety. Thus, a temporal relation between stress/anxiety and asthma symptoms has never been demonstrated". This is still the situation today in studies of asthma in children.

In 1988 Goreczny and colleagues did go on to investigate daily minor stress and anxiety and their relation to daily fluctuations of symptoms, in ***adults.*** 12 adult asthma and 12 adult chronic obstructive pulmonary disease patients were examined over a three week period. Subjects recorded their daily anxiety level and the number and perceived impact of daily stressors or hassles. The latter were found to be associated with the severity of a range of subjectively recorded asthma symptoms but there was no relation to anxiety. Nathan, Brantley, Goreczny & Jones (1988) replicated this study and found that daily stressful events were associated with asthma symptoms, but not with more objective measures of respiratory functioning such as peak expiratory flow recordings. In a follow-up study Goreczny (1989) categorised subjects into stress responders and stress non-responders. Results indicated that not all asthmatic patients respond similarly to stressful events, with 15/39 subjects being classified as stress responders and 19/39 being classed as non-responders. The non-

responders showed no within-subject correlations between asthma symptoms and daily stressors. However, as previously noted, these studies only relate to adults with asthma. In addition problems of circularity and confounding may exist since current levels of anxiety can have an effect on the perception and severity of more minor daily events and hassles rather than on more clearly defined and severe major events.

5.2 Psychological Stress and Immunity in Asthma

In his review of the psychological contribution to childhood asthma, Matus (1981) proposed that psychological factors which act as precipitants or stimuli, such as stressful life events and situations, can affect the course of childhood asthma. Further, the emotional arousal caused by stress can lead in a more direct manner to bronchospasm and cause asthma-related symptoms such as airway obstruction, coughing and wheezing. While emotional arousal may result from stressful situations, it can also be triggered by perception of changes in respiration or, possibly, a combination of both of these factors. In a Fear Survey Schedule for Children administered to over three thousand children between 8 to 16 years (King, Ollier, Iacuone, Schuster, Bays, Gullone & Ollendick, 1988), apart from the fear of nuclear war, foremost of the fears was that of 'not being able to breathe'. It was presumed that this fear might be associated with distressing and life threatening situations such as suffocation or drowning and to diseases, such as asthma. From a clinical point of view the researchers regarded this as an intriguing finding as breathing difficulties were frequently assocated with anxiety and particularly panic disorder. This fear of 'not being able to breathe' may underly reports in the literature finding evidence of exacerbatory psychological influences triggered initially by perception of changes in respiration (Viney & Westbrook, 1985). Such emotional and physiological responses may result in a spiralling process of anxiety and respiratory disease (Lehrer, Isenberg & Hochron, 1993); Pine, Weese-Meyer, Silvestri, Davies et al, 1994; Carr, Lehrer, Hochron & Jackson, 1996; Bussing, Burket & Kelleher, 1996; Carr, Lehrer & Hochron, 1995).

The physiological pathways through which emotional factors may influence airway obstruction have been cited as hyperventilation, hypocapnea, vagal constriction, changes in adrenal medullary or cortical activity and endocrine functions (Reed & Townley, 1983; Creer, Harm & Marion, 1988). Stress is normally associated with the increased production of epinephrine, norepinephrine and of corticosteroids released by the sympathetic nervous system and with the release of acetylcholine by the parasympathetic system. Under normal circumstances such release would have no effect on airway muscle. In individuals with asthma, however, the parasympathetically mediated release of acetylcholine may cause bronchoconstriction (Nadel, 1984). Relaxation may also have the potential to exacerbate asthma through such parasympathetic activity. Similarly, sympathetically released corticosteroids and epinephrine associated with stressful situations may paradoxically play a protective role in asthma and may act to relieve symptoms. Epinephrine may also be an inhibitor of cholinergic transmission. An imbalance has been proposed between these excitatory and inhibitory systems of the ANS. Asthma has been associated with a deficiency of beta-adrenergic receptors and thus insufficient dilation resulting from epinephrine (adrenaline) which brings about bronchodilation. There is also evidence that individuals with asthma may have abnormal secretion of epinephrine and may fail to elevate their circulating catecholamines during bronchoconstriction (Weiner, 1987) but are otherwise able to secrete epinephrine normally. This, therefore, might suggest a defect in the initiation of epinephrine secretion in asthma.

At a recent 'Workshop on Stress and Asthma' a number of research recommendations were made by members of the asthma research community and investigators in the area of psychoneuroimmunology. These related to the effect of psychological stress on asthma (Busse, Kiecolt-Glaser, Coe, Martin, Weiss & Parker , 1995). It was proposed that stress may affect asthma either directly through CNS-neuroendocrine-immune interactions or, indirectly, through increased susceptibility to respiratory illnesses. Some of the evidence linking stress to the generation of inflammatory

signals was reviewed including studies which suggest that stressors can alter both cytokine producing cells and the production of cytokines.

Individual differences in ANS activity and reactivity may also interact with stressors to produce different patterns of immunologic and endocrinologic changes (Manuck, Cohen, Rabin, Muldoon & Bachen, 1991). It was suggested by Busse and colleagues that such stress-related changes may alter the response to pathogens and increase susceptibility to viral infection. A number of areas of investigation were proposed based on the following questions:

(1) Is there a particular type or subtype of asthma patient who is responsive to stress?

(2) What are the characteristics of stressors and the affective responses that play a role in triggering asthma?

(3) What role does stress play in influencing health practices such as compliance with medication?

(4) What is the prevalence of stress in patients with established asthma and its importance as a factor in the development and natural history of the disease?

(5) What role does stress play in the male predominance in asthma prevalence in childhood and the reverse female predominance in adults?

(6) What is the role of infection in mediating the effects of stress and asthma since infection can exacerbate asthma and mediate increases in airway responsiveness either directly or, indirectly, as a result of allergen exposure?

In the case of (6) above, as yet, there have been no studies in the literature which examine the relationship between psychological stress and URI in children with asthma. There is, however, growing evidence of a relationship between psychological stress and URI or the 'common cold' in healthy adults and children. These studies are examined in the next Chapter.

5.3 Summary

The stress arising from family relationship problems and mothering attitudes and its role in the stress-illness process has been the subject of some investigation. These asthma studies appear to indicate that the presence of such chronic adversity and life events may be related to measures of disease severity and compliance to medication. However, there is a lack of consistency across studies which have been based on non-standardised measures of family relationships and checklist measures of life events. In addition, the extent to which children perceive the normal stressors of childhood and the temporal relationship between such stress and symptoms of asthma has not been investigated. An association has been found between minor daily hassles or events and symptoms of asthma in adults, but again, results may be questionable because of problems related to circularity and summation of psychological stress scores. These studies point towards, at the most, a broad relationship between psychological stress and asthma in children. More consistent and standardised measure of chronic stress are needed together with more standardised measures of the other variables involved if more definite conclusions are to be reached.

To date, no studies have examined the relationship over time between the incidence of acute and chronic stress and the occurrence of episodes of asthma. However, accumulating evidence has indicated that the majority of episodes of asthma are associated with the incidence of upper respiratory tract infection. There is now growing evidence in the literature of a relationship between psychological stress and this important URI factor, in both healthy adults and children. A number of prominent researchers from the fields of asthma research and psychoneuroimmunology have recently combined to focus research effort on an investigation into the effect of psychological stress on asthma and the mediating role of infection in this relationship. To date, the relationship between URI and psychological stress *in children with asthma* has not been investigated.

CHAPTER 6

PSYCHOLOGICAL STRESS AND URI

Background to Chapter

Both clinical experience and the research literature have indicated that the majority of significant episodes of asthma in children of all ages are brought about by ***symptomatic*** *viral infection. Viral infection has also been cited as an important factor in the development of increased bronchial responsiveness to a number of environmental stimuli in children with wheezing illness. A relationship between psychological stress and URI in both adults and children has been found in a number of experimental and community studies. However, this relationship has not been examined in children with asthma. This is surprising for a number of reasons: (1) children are more prone to respiratory infection than adults; (2) children with asthma may be at even greater risk because of prior damage to airways and airways vulnerability; (3) viral infection is considered to play a prominent role in triggering episodes of childhood asthma and (4) the personal burden and added psychological stress associated with the chronic nature of the illness may leave children at increased risk in the relationship between psychological stress and illness. However, children with asthma may respond differently to psychological stress in terms of sympathetic nervous system activation and, in addition, reports have indicated that girls may have lower levels of activation compared to boys. Processes which mediate the relationship between stress and URI may therefore differ both between these children and relatively healthy children and between girls and boys with asthma.*

6.1 Psychoneuroimmunology of URI

A number of reviews have examined the relationship between social and psychological factors and infectious disease, particularly URI, and the possible mediating role of the immune system (Dorian & Garfinkel, 1987; Cohen & Williamson, 1991; Ader, 1981; Jemmot & Locke, 1984; Stein, Keller & Schleifer, 1985; Cohen, 1996). Stress may influence immunity either through direct anatomical links between the nervous and immune system or through the release of neurohormones of either the pituitary-adrenal axis or the sympathetic-adrenal medullary axis. These include the catecholamines epinephrine and norepinephrine

secreted by the adrenal medulla and cortisol secreted by the adrenal cortex ((Felten, Felten, Carlson, Olschowka & Livnat, 1985; Felten & Olschowka, 1987; Baum, Grunberg & Singer, 1982; Laudenslager, 1987; Cohen & Williamson, 1991; Miller & Wood, 1994; Cohen, 1996).

Studies on adults help to explain the relationship between stress and URI. Such studies are partly based on the effect of psychological stress such as life events on markers of immune function specifically known to alter susceptibility to URI (Cohen & Williamson, 1991; Jemmott & Locke, 1984). These include increased circulating catecholamines (McClelland, Floor, Davidson & Saron, 1980); impaired T-lymphocyte function (Kaplan, 1991; Bartrop, Luckhurst, Lazarus, Kiloah & Penny, 1977; Schleifer, Keller, Camerino, Thornton & Stein , 1983; Locke, Hurst, Heisel, Kraus & Williams, 1979); decreased natural killer cell activity (Kaplan, 1991; Irwin, Daniels, Risch, Bloom & Weiner, 1988; McClelland & Jemmott, 1980; Kiecolt-Glaser, Garner, Speicher, Penn, Holliday & Glaser, 1984; Locke, Hurst, Heisel, Kraus & Williams, 1979) and decreased salivary IgA (McClelland, Floor, Davidson & Saron, 1980; Stone, Cox, Valdimarsdottir, Jandorff, Neale, 1987; Jemmott, Borysenko, Borysenko, McClelland, Chapman, Meyer & Benson, 1983; Kugler, 1994). The anti-inflammatory and immunosuppressive effects of corticosteroids on immunity (Claman, 1972; Fauci, 1978) occur at levels comparable to those induced by stress (Bach, Duval, Dardenne, Salomon, Tursz & Fournier, 1975). It has also been demonstrated that positive events may have a beneficial effect on the immune system (Dillon, Minchoff & Baker, 1985; Lefcourt, 1989).

The above findings indicate that a number of psychosocial variables including psychological stress can influence immune responses but while providing some evidence to support a relationship between stress and URI, it is still unclear whether alterations in endocrine regulation and immune responsiveness brought about by stressors are of the ***type or magnitude*** that would influence susceptibility to infection (Jemmott & Locke, 1984; Laudenslager, 1987). In addition, many individuals appear

to show little or no immunologic reaction to such events suggesting that any modulating role for psychological stress on immune function must be subject to individual variability (Manuck, Cohen, Rabin, Muldoon & Bachen, 1991). Such variability has also been demonstrated in behaviourally evoked sympathetic nervous system activity. Suppression of lymphocyte function and changes in lymphocyte subpopulation have been correlated with elevations in the plasma concentrations of epinephrine and norepinephrine under the same stimulus stress conditions (Manuck et al, 1991).

In addition, early studies on the physiology of psychological stress indicate that there may also be gender differences in sympathetic adrenomedullary activity in situations of stress with both female adults and children showing a lower response in comparison with males (Johansson, 1972; Johansson & Post, 1972; Frankenhaeuser, 1975; Cox 1987). If there is a relationship between psychological stress and asthma in children then the processes which mediate this relationship may be subject to such gender differences. Kaplan (1991) has suggested that to map the mediating role of immunosuppression in the relationship between psychosocial variables and disease, it will be necessary to investigate temporal relationships in the stress-immunity-disease triad.

6.2 Community Studies in Psychological Stress and URI

Studies in psychoneuroimmunology have provided some weak evidence for the general hypothesis that psychological stress increases susceptibility to URI. Further evidence has been found in community studies for an association between stress and infectious disease reflected in illness behaviours such as (1) ***reported URI symptoms***, (2) the ***use of health services e.g. GP***, and (3) by ***verifed pathology***. Within this field of research, these illness behaviours have been considered sufficiently accurate indicators of underlying pathology. It has, however, been recognised that stress elicited psychological factors, such as alcohol consumption, smoking, etc., can indpendently influence such behaviours (Cohen & Williamson, 1991).

A number of community studies, both retrospective and prospective have looked at the relationship between naturally occurring stresses and symptomatic URI and upper respiratory symptom behaviour. These studies are particularly important since they have been conducted not only on adults but also on children. Looking firstly at those carried out on adults, a number of retrospective studies on adults have reported an association between the occurrence of negative life events and the incidence of ***subject reported URI***. However, these reports were not validated by medical (***GP verified***) or ***verified pathology (isolation of virus or increased antibody titers)*** of the presence of disease (Belfer, Shader, Mascio, Harmatz & Nahum, 1968; McClelland, Alexander & Marks, 1982; McClelland, Floor, Davidson & Saron, 1980; Sarason, Sarason, Potter & Antoni, 1985; Hinckle & Plummer, 1952). In another retrospective study, Jacobs, Spilken & Norman (1969) reported an association between 'personal failure and role crisis' events and physician diagnosed cases of URI.

There is also evidence showing an association between life changes and events and the incidence of URIs in adults, from both prospective studies employing ***verified pathology*** (Cluff, Canter & Imboden, 1966; Hinckle, 1974) and studies of ***subject-reported URI*** (Imboden, Canter & Cluff, 1961; Stone, Reed & Neale, 1987; Evans, Pitts & Smith, 1988; Evans & Edgerton, 1991; Spilken & Jacobs, 1971; Linville, 1987; Glaser et al, 1987; Parens, McConville & Kaplan, 1966). Results have shown that psychologically vulnerable individuals reported a three times higher incidence of influenza than a non-vulnerable group (Cluff, Canter & Imboden, 1966) and that such vulnerability was related to speed of recovery from URI (Imboden, Canter & Cluff, 1961). A higher number of life events in general (Spilken & Jacobs, 1971; Linville, 1987), events occasioning self-reported sadness (Hinckle, 1974), events occasioning feelings of personal failure (Jacobs, Spilken & Norman, 1969) and general life dissatisfaction (Hinckle & Plummer, 1952) were also related with a higher incidence of episodes of URI in subjects.

One investigation of 'hassles' and their relation to the occurrence of URI in adults has demonstrated an increase in these events in the 3-4 days prior to the onset of a reported URI episode (Stone Bruce & Neale, 1987; Evans, Pitts & Smith, 1988) together with a decrease of desirable events 4 days prior to onset (Stone Bruce & Neale, 1987; Evans & Edgerton, 1991). Following any relevant viral exposure, a typical mean incubation period is around 48 hours, and seldom exceeds 72 hours. (Smith, Tyrell, Coyle, Willman, 1987). Smith and colleagues concluded that this time lag could be related to the affective impact of events and their influence on immune system activity through reducing levels and/or activity of secretory IgA. A previous study found secretory IgA to be responsive to daily mood (Stone, Cox, Valdimarsdottir, Jandorff, Neale, 1987). Illness could then be regarded as a consequence of viral exposure occurring at a time of compromised immunocompetence induced by psychological stress.

While the above studies relate to adults, there is also increasing evidence in children that stress increases susceptibility to acute respiratory infections. This evidence has been obtained from a number of community studies involving children, both prospective (Graham, Douglas & Ryan, 1986; Meyer & Haggerty, 1962; Clover, Abell, Becker, Crawford & Ramsey, 1989) and retrospective (Boyce, Jensen, Cassel, Collier, Smith & Ramey, 1977). Some of these studies have focused on family lifestyle and functioning. For example, Boyce et al (1977) investigated 58 children, of 1 to 11 years of age. These researchers hypothesised that a high level of life change in the absence of strong family routines would be associated with more frequent or more severe illness, while the presence of strong routines would be protective. Each child was observed five days per week over a one year period for respiratory illness and underwent biweekly nasopharyngeal culture for viruses. Each illness was evaluated by a nurse practitioner or paediatrician. Scores for cumulative life change were calculated using Coddington's (1972) paediatric modification of the Schedule of Recent Experience developed by Holmes and Rahe (1967). A score for

cumulative life change was calculated at the end of the one year study period and was based on the sum of life change scores over the period.

During the one-year period of this study pathogens were isolated from 28% (87/314) respiratory illnesses. Results showed that an increase in disruptive life change was significantly associated with an increased average duration of illness. When subject scores were grouped into high, middle and low terciles based on scores for both life change and family routines, these joint scores were related to the average severity of illnesses with illnesses becoming more severe as the magnitude of life change and the strength of family routines jointly *increased.* The joint effect of life change and family routines on illness severity was in the *opposite* direction from that predicted by these investigators. It was initially predicted that high levels of life change in the absence of strong family routines i.e. low family routine score, would be associated with more frequent or more severe illness, while the presence of strong routines would be protective. Their subsequent analyses, however, compared those children with high or middle scores on both family routine and life change with those children with low scores in one or both of these variables. It was concluded that major life change in the setting of a highly ritualized family may predispose to greater illness severity and that strong family routine scores may actually reflect family rigidity or the harshness of family rules. It was concluded that children from such families may be more stressed than protected by such routines when a significant life change occurs while uncertain and changeable daily life may play a protective role in situations of crisis.

These findings may not necessarily imply the presence of negative family relationships. It may be that regularity in family life does not reflect family rigidity or harshness of rules, but still may leave children more vulnerable and at risk to the effects of life change when it occurs in comparison with those children already exposed to an uncertain daily routine. Life change was also recorded retrospectively over a one year period and not related to the course of illness in this study. This

checklist measure, based on a summation of stress scores, is intended to reflect some additive measure of disruptive life change over the period in question. In effect, it may be reflecting, to some extent, a measure of chronic stress rather than the accumulated negative effect of acute events over time. For example, this is particularly the case if a number of reported events are related to each other by virtue of arising out of some ongoing difficulty such as, for example, family or marital relationship problems. Rather than the hypothesised moderating or protective effect of strong family routines on disruptive life change, it may be that these two variables are more directly related to each other in some manner and this relationship could result in confounding. It is difficult to draw any specific conclusions on the evidence of this study.

The hypothesis that family dysfunctioning and stressful life events increased the risk of developing an influenza infection during an epidemic has also been studied (Clover, Abell, Becker, Crawford &Ramsey, (1989). Here families consisted of two adults and at least one child between the ages of 1 and 18 years. Subjects were asked to visit the clinic within 24 hours of the onset of any respiratory tract illness, regardless of its severity, for physical examination and throat swab specimen for viral culture. Each symptomatic patient was given a daily illness form to complete and return after recovery from the illness. Families were called weekly to monitor respiratory tract symptoms. Illness associated with infection was defined as influenza-like illness symptoms combined with isolation of an influenza virus from a throat swab or a fourfold or greater titer rise of antibodies. A serum sample was also obtained from each family member in advance of the 'flu season and again two weeks after the 'flu season. Life event change was measured by the Schedule of Recent Experience (Holmes & Rahe, 1967). It was hypothesised that individuals who perceived their families as being more dysfunctional in terms of family cohesion or bonding, rather than being balanced and moderately cohesive, were more likely to develop infection. In terms of a measure of family change or adaptability, it was also hypothesised that those individuals who perceived their families as being chaotic or,

in the other extreme, rigid, rather than being moderately adaptive were also more likely to develop infection.

Of the 246 participants who completed the study, 66/246 (26.8%) developed laboratory-confirmed infection. This consisted of, 46/130 (35.4%) children and 20/116 (17.2%) adults. Clover and colleagues concluded that life event change was not associated with infection. However, it was found that family dysfunctioning increases the risk of acquiring influenza B infection. Families that were enmeshed, chaotic, or rigid had increased frequencies of flu B infection compared with balanced families. Less cohesive or disengaged families manifested lower levels of infection than balanced families or enmeshed families spending much time together. Clover and colleagues concluded that family dysfunction may (1) lead to altered immune responses which increases susceptibility to infection and/or (2) increase risk of exposure because of physical proximity to influenza.

Again, this study must be interpreted cautiously. While 66/246 (26.8%) of subjects developed laboratory recorded infection, this report did not include detail of the number of infections recorded in adults and children within families. Further, of the 46 children and 20 adults with laboratory documented infection only 12 children and 6 adults had influenza-like illness associated with such infection. This may point to cross-infection within families which would be consistent with the finding that disengaged families, those who spend less time together, manifested lower levels of infection. It may be, therefore, that physical proximity has resulted in confounding in this study. Further, the combination of family characteristics and interpretation of findings seems somewhat arbitrary. The duration of this study has not been made clear nor the period over which life events were measured by the checklist instrument. In addition, many of the families did not return their illness records to the clinic or keep an illness record at home.

The most impressive data, however, come from two prospective community-based studies (Meyer & Haggerty, 1962; Graham, Douglas & Ryan, 1986) investigating the relationship between acute respiratory infection and psychological stress. 100 members of 16 lower middle-class families, each with two or more children, were followed prospectively over a one year period, and life events that were distressing to the family were recorded in diaries. Throat cultures screened for streptococcal infection were taken every three weeks and at times of infection, with antibody levels being recorded every 4 months.

Meyer & Haggerty found that a greater degree of chronic family-related stress (as judged by observers) was related to greater numbers of new infections, prolonged carriage of the bacterium without symptoms, higher streptococcal illness rates and elevated antibodies to a streptococcal-produced toxin. Events disrupting family life were 4 times more likely to precede than to follow new streptococcal and non-streptococcal infections especially among the children 2 years of age or older. Among family members, a greater degree of family-related stress occurred during the 2-week interval before a clinical acute respiratory tract illness or a documented streptococcal infection than occurred during the 2-week interval after such infection and clinical disease. Separate analyses indicated that a large group of control variables including sex, family history of respiratory infections, family size, and allergic history were unrelated to infectious outcomes.

Finally, a six month prospective study investigated the relationship between psychological stress and acute respiratory infection in 235 adults and children aged 14-57 years, from 94 families (Graham, Douglas & Ryan, 1986). All families in this study included at least two children under 12 years of age. Respiratory data were collected using respiratory symptom diaries for six months and participants were asked to record the daily presence of runny nose, sneezing, blocked nose, sore throat, hoarse cough, fever, chills, headache and muscle ache. An episode was considered to have commenced if a minimum of two symptoms was present for at least 24 hours or

if a minimum of one symptom was present for 48 hours. Episodes were, by definition, separated by at least three days clear of any respiratory symptomatology. Symptom diary cards were replaced monthly and checked weekly during a home visit be a research nurse. Pre-study measures of stress included: life events in the two-year pre-study period; a measure of daily hassles or more minor events together with psychological symptoms or strain in the one month period prior to the study. Intra-study stress measures were based on data collected with the Life Events Inventory, the Daily Hassles Scale and the General Health Questionnaire.

Episodes were designated 'swabbed' or 'unswabbed' and were further differentiated into classifications of 'definite' 'uncertain' and 'doubtful'. In an attempt to reduce the effect of confounding, where stressed individuals may record higher psychosomatic symptomatology or have a lower threshold level of symptom recognition, the researchers examined the more objective subgroups of respiratory data, that is, swabbed respiratory episodes together with 'definite' episodes confirmed by the visiting nurse. 405/524 (77.3%) of episodes were swabbed of which 62/405 (15.3%) produced positive cultures. 91 people experienced at least one respiratory episode that was not swabbed and 17 persons who experienced at least one respiratory episode were not swabbed at all. Subjects in the incompletely swabbed group were demographically similiar to the whole population while individuals in the unswabbed group experienced less pre-study stress.

Results showed that pre-study measures were less strongly related to measures of respiratory illness than the same stress measures collected during the study. Graham et al considered that pre-study stress scores more reflected a measure of chronic stress. It was found that an intrastudy high stress group had significantly more episodes and symptomatic days of upper respiratory illness than a low stress group . High and low stress groups were defined by splitting the data collected on the Life Events Inventory, the Daily Hassles Scale and the General Health Questionnaire into groups based on above and below median scores. The high and low groups were

almost identical with respect to age, sex, occupational status, smoking, passive smoking, exposure to air pollution, family size, and susceptibility to acute respiratory infection in childhood. However, significantly more episodes of upper respiratory illness were experienced in the high stress group. In all of the multivariate analyses performed, female sex and age also emerged as important correlates of respiratory illness.

Graham et al, together with a number of other investigators, have suggested that future prospective studies of the etiology of acute respiratory infection should include more sophisticated measures of stress to take account of the temporal relationship between an event and the onset of a URI episode. Meyer & Haggerty's pioneering study investigating the temporal relationship between life events and experiences and the onset and course of illness employed *non-standardised* measures of chronic stress and *self-report* measures of life events in diaries. There is therefore the possibility of reporting bias in that subjects 'co-operated' in some respects, possibly by exaggerating reports of life events in the period just prior to infection. Symptom diary keeping can also have some disadvantages. Subjects may forget to complete diaries or they may be poorly completed. Reports indicate that when asthma symptoms or medication use are objectively measured, these measures can correlate poorly with diary completion Archer & Simpson, 1985; Lister, Burdis-Jones, Palmer & Cochrane, 1989).

Previously, community studies have also suffered from methodological drawbacks, in particular, the inadequate screening of symptomatic subjects for viral pathogens. Improvements in viral detection, particularly through the use of polymerase chain reaction (PCR) techniques, have substantially increased success rates in finding responsible agents. After the application of PCR, in addition to conventional methods, the presence of a range of viral pathogens was detected in 80% of asthma exacerbations in a sample of 9 to 11 year old children (Johnson, Pattemore, Sanderson et al, 1995). These high rates of viral detection with modern molecular techniques contrast extremely favourably with verification rates in past studies using more

conventional microbiological techniques e.g., 28% in the study by Boyce et al (1977) and 15% in the study by Graham et al (1986). These newer methods are clearly going to be more effective in investigating the temportal relationship between viral infection and psychological stress.

6.3 Experimental Studies in Psychological Stress and URI

Studies directly assessing the relation between stress and URI in community samples provide some additional evidence that social stressors increase risk for verified upper respiratory disease in both adults and children. However, because previous community studies have experienced drawbacks in the inadequate screening of symptomatic subjeccts for viral pathogens, a number of researchers have investigated the risk of psychological stress for susceptibility to URI through experimental viral challenge studies. Community studies also cannot control for the possible effects of stressful events on exposure or susceptibility to infection as opposed to effects on host resistance in that stress-elicited behaviours may make an individual more susceptible to URI. Examination of the effects of experimentally-induced colds has served to overcome concerns about the differentiation between clinical and subclinical infections where persons can be biologically infected without manifesting symptoms. These studies carried out in adults have produced mixed results but some later studies more clearly support the hypothesis of a relationship between stress and URI.

For example, Locke & Heisel (1977) failed to find a relationship with antibody titers after 'flu vaccination while other studies have found a relationship between distress and lymphocyte response to the 'flu virus (Bovbjerg, Manne & Gross, 1990; Petry, Weems & Livingstone, 1991). Introverts were found to be more susceptible to infection from cold producting viruses but not influenza viruses (Broadbent, Broadbent, Philipotts & Wallace, 1984). Some studies have produced only small correlations between stress, personality traits and virus shedding (Totman, Kiff, Reed & Craig, 1980; Smith, Tyrrell, Coyle, Higgins & Willman, 1990). Reviews of such studies have concluded that they provide only weak support for a relation between

stress and susceptibility to URIs (Cohen & Williamson, 1991; Cohen, 1996). A number of methodological flaws include insufficient sample sizes, the possibility of stress-elicited changes in health practices and lack of controls for important predictors of susceptibility such as gender, age and pre-existing antibodies to the infectious agent (Jackson, Dowling, Anderson, Riff, Saporta, Turck, 1960).

Many of these deficiencies in earlier studies.were addressed in a study by Cohen, Tyrrell & Smith (1991). At the Common Cold Research Unit in Salisbury, Cohen and colleagues examined the relation between psychological stress and the frequency of documented clinical colds among 394 healthy adult subjects who were exposed to one of five respiratory viruses. The identification of an episode of 'infection' involved the isolation of virus or the demonstration of an increase in antibody titer, or both. Standard research criteria for diagnosis of ***clinical*** infectious disease require both biologic evidence of infection ***and*** manifestation of related symptomatology (Beare & Reed, 1977). Infection' reflected viral replication and was documented by viral isolation, specific antibody responses, or both, with the severity of illness being rated by both volunteers and clinicians. Their Psychological Stress Index score was based on the combined score of three separate measures of stress: (1) the number of major stressful life events judged by the subject as having had a negative impact on his or her psychological state in the past year; (2) a measure of perceived stress expressing the degree to which the subjects perceived that current demands exceeded his or her ability to cope, and, (3) an index of current negative affect over the previous week. The score for the number of stressful life events during the previous year was measured by the List of Recent Experiences (Henderson, Byrne, Duncan-Jones, 1981), a checklist measure.

Cohen et al's results indicated a relationship between Psychological Stress Index scores and both viral infection and the rate of development of 'clinical colds', defined as verified infection together with 'cold' symptoms. They concluded that psychological stress was associated in a dose-response manner with an increased risk

of acute infectious respiratory illness but that this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection, i.e. clinical colds in those with infection. A number of potential stress-illness mediators could not explain the association between stress and illness and, in addition, controls for personality variables (self-esteem, personal control and introversion-extraversion) had little effect on the relation between stress and colds and did not alter their findings.

In a further paper, however, Cohen, Tyrrell & Smith (1993) examined the relation between each of the three ***separate*** stress scales and risk for clinical colds in those with infection. In this second paper, negative life events were found to be related to clinical illness and the increased risk was primarily mediated by increased symptoms among infected persons i.e. increased susceptibility to the development of cold symptoms in those with higher levels of negative life events. Perceived stress and negative affect were also related to clinical illness, but their associations with increased risk were primarily atrributable to increased infection.

Cohen and colleagues concluded that the negative life events instrument was measuring something different than the perceived stress and negative affect scales and that the constructs these measures tap may have different consequences for the pathogenesis of infectious illness. It was suggested that the independent relations these scales have with illness and the fact that they appear to be mediated by different processes challenges previous assumptions of psychological stress theory that individual ***perceptions*** of stress and negative affect mediate the relationship between events and illness outcomes and are necessary for stressful life events to influence disease risk (Lazarus & Folkman, 1984). Having controlled for their effect, it was proposed that perceived stress, negative affect, or health practices, were not mediators and that stressful life events may alter other cognitions or behaviours that make infected persons more likely to develop clinical illness. These investigators concluded that the self-report life event measure should be replaced in the future by

an interview measure of life events such as the LEDS (Life Events and Difficulties Schedule) incorporating an objectively judged severity of threat and the separate measurement of both events and ongoing difficulties or chronic stress.

In effect, it could be that the measure of life events over the year in this study may reflect to some degree a measure of chronic stress while the other stress scales tend to reflect a measure of more currently perceived stress and mood. Looking at Cohen et al's results, it could be concluded that more current measures of perceived stress and negative affect may have consequences for infection while the presence of chronic stress may be an additional risk factor for the subsequent development of symptoms in those infected. In their 1993 paper, Cohen et al suggested that actively and effortfully coping with stressful events may modulate the sympathetic nervous system and thus consequently suppress immune response (Manuck, Harvey, Lechleiter & Neal, 1978). Differences in infection could therefore be attributable to stress elicited changes in immune processes such as those involving secretory IgA or possibly NK cells which destory viral-infected cells. The ability of mucosal tissues to block the virus from entering the system or the functioning of nasal epithelium may also play a role. Since measures of life events in this study may reflect a measure of chronic stress, it may be that more prolonged psychological stress is associated with sympathetic nervous system activation.

Following Cohen et al's studies, another group of researchers examined the development of symptoms among infected persons (Stone, Bovbjerg, Neale, Napoli, Valdimarsdottir, Cox, Hayden & Gwaltney, 1992). Life events were measured using a checklist method, The Life Experiences Survey (Sarason, Johnson & Siegel, 1978). Subjects were 17 University of Virginia undergraduates and exclusion criteria included a history of atopy, sinusitis, asthma and chronic rhinitis. The mean age of the subjects was 20.2 years with 11 of 17 subjects being female. This group of researchers believed that if prechallenge stress had an important effect on rhinovirus colds, it was more likely to influence the development of illness rather than the

acquisition of infection. Previous studies of rhinovirus infection show that about one-third of persons with confirmed viral infection do not show evidence of cold symptoms (Gwaltney, 1989) and the factors that determine which infected individuals will develop colds are not known.

Using a rhinovirus inoculation protocol, Stone and colleagues explored the possible role of recent life events, current mood, and perceived stress in the development of symptoms in individuals known to be infected. They found that although all 17 subjects had confirmed rhinovirus infection, only 12 subjects developed clinical colds, as indicated by self-reported symptoms and by objective indices. They found that those with a higher level of prior life events were more likely to develop ***clinical*** colds. Measures of perceived stress and negative affect or current mood were unrelated to illness. The average number of reported major life events for the previous year was significantly higher for those who developed colds than for those who did not ($p<0.05$). However, when positive and negative life events were analysed separately, a significant difference was found between the groups only in the number of positive events. Although a threefold higher incidence of negative events was found in the cold group, this difference did not reach significance. Measures of affect and perceived stress before the inoculation were not different for those who did and did not develop colds.

These findings confirmed those of Cohen et al's 1993 study. Three points were suggested by which psychological factors could impinge on infectious symptomatology. These were the reporting of symptoms, nasal inflammatory responses to mediators and the production of inflammatory factors. Since symptom reporting was objectively corroborated in this study, they concluded that psychological and biological processes interact during the course of human rhinovirus infection. It was suggested that the proposed mediating mechanism in this relationship was the release of cytokines, previously asssociated with challenging life

events, such as divorce (O'Leary, 1990) and possibly related to the development of symptoms (Gwaltney, 1989).

The number of subjects involved in this latter study was small. In addition, the authors concluded that the evidence indicated that the development of cold symptomatology in experimentally-infected individuals with rhinovirus infection was related to prior levels of life events. However, this referred to the combined level of both positive and negative life events and when negative life events were examined separately, no significant difference was found in this measure between subjects who developed colds and those who did not. What may be concluded from this study is that possibly some general measure of 'life change' may be related to the development of colds in infected subjects. Again, however, this checklist measure of psychological stress could possibly be reflecting some broad measure of chronic stress and it may be that it is this measure which is related to the development of clinical colds.

6.4 Summary

A number of studies have attempted to link psychological stress to URI. These include studies investigating (1) the relationship between stress and neuro-endocrine and immune functions in adults; (2) retrospective and prospective community studies in adults and children and (3) experimental viral inoculation studies in adults. The evidence from earlier studies investigating stress-elicited endocrine and immune changes in response to stress is inconclusive since changes found in these studies may not be sufficient to result in increased susceptibility to upper respiratory tract infection. In addition, the functional balance between the two branches of the autonomic nervous system may regulate the tone of an individual's behaviour and this mechanism may underly individual variability in behaviourally-evoked sympathetic nervous system activation and subsequent immune responses in situations of stress. Differences in sympathetic nervouse system activation may also be gender-related.

Retrospective and prospective community studies in adults have shown an association between life changes, the incidence and reporting of URIs and the speed of recovery from infection. An increase in negative events and a decrease in desirable events has been found in the period prior to respiratory infection. A greater degree of family-related stress has been found in the period immediately preceding a clinical acute respiratory tract illness or a documented streptococcal infection compared to the period immediately following such infections. Community studies involving children have found that stress, mainly related to family lifestyle and functioning, increases susceptibility to URI. Stress measures have also been related to increased risk of infection and the duration and severity of illness.

These studies, however, have drawbacks. Various stress measures have been employed based on checklist or daily hassles instruments and self-report diary measures of life events. In addition, the community studies have often suffered from inadequate viral detection methods. Recent advances in these methods have greatly increased success rates in finding responsible agents in URI episodes. This problem together with a lack of control over stress elicited behaviours has been overcome in experimental viral challenge studies investigating the risk of psychological stress for susceptibility to both clinical and subclinical URI. Consequently, the results of such studies may be attributed to stress-induced influences on immunity and not to stress-induced increases in exposure to URI pathogens. Findings have shown that negative life events may be related to the production of cold symptoms in virally infected individuals. This is a particularly important finding in relation to those with asthma. According to Busse (1995), upper respiratory infection in such individuals must be ***symptomatic*** before changes in immune processes possibly resulting in inflammatory reactions may be brought about. The development of symptomatic upper respiratory infection rather than merely viral infection may therefore be central to the processes which determine and map out the sequelae to URI in children with asthma. It is not clear from the literature what may drive the production of symptoms among persons who are infected.

Commenting on the role of psychoneuroimmunological processes, Cohen and colleagues (1993) suggested a role for sympathetic nervous system activation and changes in immune function. They proposed that, in the first instance, symptoms may appear when a threshold number of cells are virally infected. Alternatively, different processes may be involved where infection may be attributable to viral replication and clinical colds to an inflammatory immune response to infection which may result in the release of a number of chemical mediators and the production of symptoms. They also found that the effect of life events on the production of symptoms in infected individuals was independent of measures of perceived stress and negative mood. It was therefore suggested that some more objective quality of life events or possibly some measure of chronic stress ***unrelated to*** cognitive process or the perception and appraisal of threat may play a role in the stress URI relationship. Such a proposal is contrary to a psychological conception of stress which regards cognitive appraisal and the perception of stress ***central to*** the whole psychological stress process. Cohen and colleagues suggested that future studies should perhaps employ a sociologically-based interview measure of life events incorporating a contextual but more objective rater-based measurement of stress together with a separate measurement of chronic stress. This suggestion is in concordance with that of a number of other researchers who have recommended that an interview method of stress measurement may be generally more appropriate than a checklist-type measure when examining the relationship between psychological stress and illness.

In summary, therefore, the results from viral inoculation studies and other research literature suggest that there may be a relationship between levels of stress reflected by the incidence of stressful life events over a prolonged period, individual differences in sympathetic nervous system activation in response to such stress, the subsequent effect on immune responses and the development of symptoms in virally infected subjects. In those with asthma, this may result in bronchial inflammatory processes and contribute to a process of asthma morbidity and bronchial responsiveness within

which the development of URI-related upper respiratory tract symptoms must play a role.

Not only may URI result in significant episodes of asthma morbidity but recent studies have shown that the majority of such episodes have been attributed to infection of the upper and/or lower respiratory tract. A recent study on a community sample of 9-11 year olds with cough and/or wheeze (Johnson, Pattemore, Sanderson et al, 1995), employing advanced viral detection techniques, showed that viruses were detected in 80% of episodes of respiratory morbidity and in 85% of these episodes both upper and lower respiratory tract symptoms were accompanied by reduced peak flow. The most common virus implicated in most cases was the common cold. In addition, the sequelae to such infection can extend over a period of weeks. Busse (1995) has also reported evidence that rhinovirus ***symptomatic*** respiratory infections can lead to the development of late allergic reactions to inhaled allergens thus supporting the possibility that respiratory infection may promote bronchial inflammation and may be a factor for increased wheezing with respiratory infection. However, it has also been demonstrated that the development of the 'late' asthmatic reaction can occur independently of the development of BHR during the cold (Lemanske, Dick, Swenson, Vrtis & Busse, 1989). It is clear, therefore, that the initial development of symptoms in those virally infected can have important consequences in terms of increased respiratory morbidity not only within peak episodes of infection but also between such episodes.

There is now growing evidence in the literature of a relationship between URI and psychological stress in relatively healthy children, there are no such studies investigating this relationship in children with asthma. The absence of such a study was the stimulus to the present study which examines the relationship between psychological stress and upper respiratory symptoms and infection in children with asthma.

CHAPTER 7

SUMMARY AND CURRENT STUDY

7.1 Summary

A number of points have arisen from the discussion over previous Chapters and these can be summarised as follows:-

(1) Asthma is the most common chronic disease of childhood. It is also the most common cause of school absence in childhood. Studies show that both prevalence and morbidity are increasing. This increasing prevalence is not fully explained. A number of explanations have been put forward, the most prominent being an increased allergen load in the environment. Macroenvironmental factors such as climate and air pollution, though possibly important in causing short-term variations, are not considered major determinants of prevalence or severity. The prevalence rate ratio for diagnosis of asthma is greater for boys than girls and this increased susceptibility in boys to wheezing respiratory illness has been attributed to the smaller relative size of airways which corrects by puberty. However, the boy/girl gap in diagnosed asthma does not level out until the mid-teens and by 20 years of age the incidence of asthma is greater in females. There is also some evidence that the boy/girl gap in diagnosed asthma may be decreasing.

(2) Childhood asthma imposes personal, psychological and financial costs on families. A recent report examining evidence from a national survey has sugggested that social factors may affect the severity of asthma more than the prevalence of wheezing. Socioeconomic status has been related to patterns of morbidity in asthma. The personal and psychological impact of a chronic illness such as asthma may also leave children and their families more vulnerable to everyday stresses and at increased risk in the stress-illness relationship. Studies examining psychological adjustment in children with asthma have produced some mixed results.

(3) Clinical experience has noted, and recent research confirmed, that the majority of episodes of asthma in children are brought about by ***symptomatic*** URI due mainly to the 'common cold' virus, rhinovirus. Previous community studies have been

hampered by the failure of viral detection methods to detect virus but the application of molecular techniques has confirmed clinical suspicions and shown that the majority of asthma exacerbations are related to viral infections. Studies have also shown that associated epithelium damage in some infections may extend for a period of up to 6 weeks after viral respiratory infection. This damage may result in increased susceptibility to the effects of other environmental factors such as aero-allergens, irritants and further infection. Evidence from studies suggests that atopy may place individuals at particular risk to develop severe exacerbations of asthma after a preceding bout of 'cold' or flu'.

(4) Younger children are more susceptible to infection than older children. The evidence on gender differences is not clear and the effect of age on such differences has not been investigated. Boys may be more susceptible to lower respiratory infection than girls but findings suggest that this risk may level out in the 9-15 years age band. Gender susceptibility after this period has not been recorded. A similar pattern of change has been found in other chronic illnesses and psychiatric disorders but with girls presenting with increased morbidity compared to boys after this age.

(5) On the whole, a number of studies in adults and children have found some evidence of a relationship between psychological stress and illness. In the case of URI, studies in adults have found an increase of negative minor events or hassles and a decrease of desirable events in the period immediately prior to infection. A greater degree of family-related stress has also been found in the 2-weeks before compared to the 2 weeks after a clinical acute respiratory tract illness or a documented streptococcal infection in both children and adults. The findings of other studies suggest that stress related to family lifestyle and functioning may increase susceptibility to URI and may also have an effect on the duration and severity of illness. Stress related to family functioning has already been implicated in studies of disease severity in children with asthma where the nature of the mother-child relationship may play a role.

(6) This evidence indicating a broad relationship between stress and URI has been further strengthened by findings from experimental viral inoculation studies in the field of psychoneuroimmunology. These studies show that psychological stress, in the form of events over a prolonged period, but possibly reflecting a more chronic measure of stress, increase susceptibility to ***symptomatic*** infection. Early viral inoculation studies showed only weak support for the relation between psychological stress and susceptibility to URI. However, later studies have provided stronger evidence for an association between psychological stress in the form of life events and the subsequent development of *symptomatic* illness in those infected. Cohen and colleagues (1993) suggested that stress in the form of life event measures may have an independent effect on disease course separate from measures of perceived stress and negative mood. This proposal is not consistent with a psychological model of stress within which the perception and appraisal of stress is central. A number of researchers have proposed that a life event interview method, incorporating a contextual and objective panel-based measure may be a more appropriate measure of psychological stress for future studies. Cohen (1996) has concluded that, overall, the evidence for a stress-URI relationship is impressive.

(7) A number of investigators in the fields of asthma research and psychoneuroimmunology have recommended research into the role of upper respiratory tract infection in mediating the effects of stress and asthma. These researchers have suggested that limited attention has been directed towards the role of psychological stress in asthma and its pathogenesis. It has been proposed that further research is needed into the nature of stressors and their role in matters related to compliance with medication, gender differences in symptom presentation and whether particular subtypes of patient were particularly responsive to such stress.

Such specificity in response may arise because of interindividual variability in sympathetic nervous system activation and immune response in situations of stress.

The physiological pathways through which emotional factors may influence airway obstruction potentially include hyperventilation, hypocapnea, vagal constriction, changes in adrenal medullary or cortical activity and endocrine functions. In those with asthma, the parasympathetically mediated release of acetylcholine may cause bronchoconstriction. It has been suggested that there may also be a defect in the initiation of epinephrine secretion which mediates bronchodilation in asthma. In addition, to interindividual variability, there may also be gender differences in response. Females, both adults and children, have shown lower levels of sympathetic nervous system activation in situations of stress. Thus, if a relationship does exist between psychological stress and URI or asthma, this relationship may be different for boys and girls.

(8) The main reason for a lack of focus on psychological factors has been attributed to methodological shortcomings in research into psychological stress and illness. These shortcomings include the retrospective nature of the majority of studies, the use of checklist measures, problems related to circularity and the lack of focus both on the measurement of chronic stress and on the temporal aspects of the stress-illness relationship.

The checklist measurement of stress adopted by the psychological tradition is essentially based on a subject-based or self-reported measure of the perception of stressful impact of events. This has been criticised as being too 'mechanistic'and methodologically inadequate when the ultimate goal of research is to establish causal relationships in the stress-illness process. In contrast, the interview tradition has its basis in a 'contextual' or objective panel-based measurement of stress which incorporates a measurement of chronic stress, the dating of events and provides information relating to the relationship between events and experiences and the behaviour of the individual. Contextual measures have been described as being both 'objective and personal' in that they incorporate an ***objective panel-based*** measure of impact assessed on the basis of the ***subject-reported*** context surrounding an event.

7.2 Summary of Aims

A number of features of the present study were chosen to overcome the methodological shortcomings of previous studies investigating the relationship between psychological stress and illness, in general, and more particularly in this relationship in those with asthma.

The present study employed an interview investigator-based contextual measure of the stressful negative and positive impact of both life events and long-term experiences (PACE). This measure was employed on children with asthma and enabled a prospective measure of chronic stress and also allowed the investigation of temporal aspects of the relationship between psychological stress and URI in these children.

When possible, the occurrence of URI was verified using standard laboratory tests and also more advanced microbiological tests. Visits to the GP were also noted as were any paediatrician-recorded episodes of asthma coinciding in time with the URI.

The overall aim of the present study was to investigate the incidence of both URI and upper respiratory tract symptoms in children with moderate to severe asthma and to investigate the relationship between these measures, psychological stress and psychological adjustment. A number of variables and their interrelationships were therefore measured. These included: (1) the incidence of URI or the 'common cold'; (2) upper respiratory symptom levels; (3) psychological adjustment as measured in levels of self-perceptions and anxiety in the children; (4) prior levels of positive long-term experiences and chronic stress particularly those experiences of a high threat nature and (5) the occurrence of positive and negative acute life events in the course of the study period, particularly those events of a high threat nature.

7.3 Hypotheses

The null hypotheses underlying these aims are -

1. There is no relationship between the occurrence of both URI and upper respiratory tract symptoms and levels of psychological adjustment.

2. There is no relationship between upper respiratory morbidity and prior levels of long-term experiences both positive and negative.

3. There is no temporal relationship between URI and high threat acute life event nor a moderating role for prior long-term experiences.

4. There is no difference between boys and girls in the relationship between psychological stress and URI.

PART TWO

METHODOLOGY

CHAPTER 8

SUBJECTS, MEASURES AND PROCEDURES

8.1 Subjects

The children were selected from a group of children with asthma attending the specialist Asthma Clinic at the Royal Hospital for Sick Children, Glasgow. All were receiving prophylactic inhaled therapy, either Sodium Chromoglycate or more frequently inhaled steroids, together with bronchodilator therapy either regular or intermittent. The parents of 114 children at the Clinic selected at random were initially approached by the paediatrician-in-charge and given a brief explanation of the study. If the child and family expressed an interest one of two interviewers met with them for a fuller explanation and discussion of the study. Of the 114 approached, 18 parents and 2 children declined to take part. 94 subjects were enlisted to the study. A further 7 subjects withdrew at an early stage (3 because of family commitments, 3 because of the personal nature of the information sought and 1 because the child did not wish to participate). Of the 87 subjects who took part in the main study, 9 subjects were omitted from the current study for a number of reasons (lateness in submission of asthma diaries; poor dating of data; pressing domestic matters; lost diaries and illness in the family). The remaining 78 child-parent pairs submitted sufficient respiratory symptom data for the one year period under study. Table 2 presents the composition of the study sample in terms of age, sex, atopic status, British Thoracic Society (BTS) rating and social class of parents by occupation as reflected by the Registrar General ratings (Office of Population Censuses and Surveys, 1980). Of the 16 subject pairs not included in the present or main study, 12 subject pairs were of Social Class V or VI or were unemployed, 3 subject-pairs were of Social Class III & IV and 1 subject-pair was of Social Class II. The lower social class groups were therefore slightly underrepresented in this study.

8.2 Measures and Procedures

Respiratory symptoms

Asthma Diary:(Upper Respiratory/Nasal Symptoms)

The children and main caregivers kept a record of the daily occurrence and severity of a range of upper respiratory symptoms in an asthma diary which was also used for the

recording of daily peak flow readings (Appendix 2). The respiratory symptom checklist has been employed elsewhere in the literature to alert for the presence of a 'cold' or URI (Clough, Williams & Holgate, 1992; Clough & Holgate, 1994). The checklist included the following symptoms: runny nose; sneezing; blocked or stuffy nose; itchy/sore or watery eyes; sore throat; hoarse voice; fever/shivery; headaches or face aches; aches or pains elsewhere.

Subjects were requested to make daily recordings of the presence and severity of these upper respiratory symptoms in their asthma diaries. The diaries, covering a 13 week period, were issued and returned at each quarterly visit of the subject to the paediatrician at the cliinic. Recording of upper respiratory symptoms continued over a 52-week period. Regular contact was maintained with subject pairs between clinic visits through the use of a 24-hour answerphone. The project office also made frequent enquiries regarding the general health of the children, progress with completion of diaries and the presence of respiratory infection. Parents regularly used the service to arrange or change appointments with the paediatrician, to seek advice relating to medication and health problems and to request new diaries. They were instructed to contact the office when the presence of symptoms on the symptom checklist alerted them to the possibility that a URI was present. Parents were asked to rate the presence of symptoms on a severity scale of 1 to 3 where 1 = mild, 2 = moderate and 3 = severe. If the child's score was 4 or more in any one day ***or*** if it was felt that a 'cold' or bad bout of chestiness was coming on, then the parent was asked to contact the Project Office. Arrangements were then made, when possible, to visit the child's home for the purpose of taking a throat swab, usually within 24 hours of the parental report. Parents were encouraged to record the occurrence of a suspected cold in the diary even if, for whatever reason, they could not contact the Project Office.

Asthma Diary (Lower Respiratory Symptoms - Asthma Episodes):

Data regarding the occurrence and severity of episodes of asthma for the sample of children was extracted from medical files. The occurrence and severity of asthma

episodes were assessed independently by the attending paediatrician and a statistician. Various sources of data were employed to determine whether an episode of asthma had occurred. These sources included reported morning and evening age-adjusted Peak Expiratory Flow (PEF) measurements from the asthma diaries, calculated diurnal PEF variation, medication usage, hospital admission, visits to the GP, asthma symptom problems such as wheezing, school attendance and sleep patterns. Data relating to atopic status and British Thoracic Society medication ratings (Table 2) was retrieved from medical files.

URI/Throat Swabs:

The presence of a URI was investigated by means of throat swabs taken from children. Specimens were subjected to routine viral analysis (Department of Microbiology, Yorkhill Hospital for Sick Children, Glasgow) and to more advanced PCR [polymerase chain reaction] techniques (Central Public Health Laboratory, Virus Reference Division, London) in order to isolate and identify a range of viruses associated with upper respiratory tract infection.

Within 24 hours of receiving a call from a parent regarding the possible incidence of a URI, the author visited the child's home and obtained a throat swab from the child. This was immediately placed in viral transport fluid and taken to the Department of Microbiology in Yorkhill Hospital for analysis. Routine laboratory tests were carried out for the detection of respiratory syncitial virus [RSV], Influenza A, Influenza B and parainfluenza through viral culture and isolation. More advanced PCR testing to detect the presence of Picornavirus RNA and further specific testing for URI were carried out on those specimens where virus had not been detected by the routine laboratory methods. While throat swabs are less efficient than naso-pharyngeal swabs in the process of detection of viruses, it was felt that this method would prove less intrusive and uncomfortable for the children.

Psychological stress measures

PACE (Psychosocial Assessment of Childhood Experiences)

Details regarding the incidence, timing and reported impact on the child of psychological stress in the form of discrete life events and longer term experiences was gathered using the PACE [Sandberg, Rutter, Giles, Owen, Champion, Nicholls, Prior, McGuinness and Drinnan, 1993]. PACE originated from the Camberwell Family Interview [Brown & Rutter, 1966; Rutter & Brown, 1966] and from the Bedford College Life Events and Difficulties Schedule [Brown & Harris, 1978].

A summary of the key features of PACE are included in Appendix 3. The PACE semi-structured investigator-based interview schedule has parallel versions for children (Appendix 4) and for their parents (Appendix 5) and allows measurement of both positive and negative acute life events (e.g. move of home, change of school or winning a prize) reported by both child and parent.

PACE also measures both positive and negative longer term experiences [e.g. the presence of continuing marital discord, chronic illness or participation in an absorbing interest or hobby] in both child and parent. The criteria by which a shorter term experience can be defined as an acute life event or one of a longer term and possibly more chronic nature to be defined as a long term experience are predetermined in coding manuals and dictionaries which accompany the PACE Child and Parent Interview Schedules (Appendix 6 & 7).

The interview schedule also allows assessment and coverage of a broad range of family and family-related experiences which may, for example, act as vulnerability factors, such as lack of social support or the absence of a confiding relationship (Brown & Harris, 1978). Some such factors are developmentally important and may involve a psychiatric risk for children e.g., admission to hospital at an early age; a history of parental psychiatric disorder or the presence of abnormal psychosocial

situations (Quinton & Rutter, 1976; Rutter & Quinton, 1984; Rutter, 1985; van Goor-Lambo, Orley, Poutska & Rutter, 1990).

The reliability of PACE was examined by Glen, Simpson, Drinnan, McGuinness & Sandberg, 1993. In this study, 15 children and parents were interviewed on two occasions ten days apart for the main test-retest and inter-rater reliability study. 63% of child reported life events and 72% parent reported events at second interview had been reported at first interview. Inter-rater reliability tests yielded high agreement between categories of contextual ratings for the same events ranging from 0.88 to 0.95 for child reported events and 0.87 to 0.92 for parent reported life events.

Interview Schedule:

For the present study, each parent-child pair were interviewed separately and by different interviewers but, whenever possible, at the same time. Where it was preferred, both parents were interviewed together. The minimum time taken to complete a parent interview was about one and a half to two hours, while the child interview could be completed in approximately one hour. Interviews were conducted in the child's home. The first or baseline interview recorded all LEs and LTEs which occurred or were in existence over the previous 12 month period. Two follow-up interviews were carried out at 9 month intervals to record any further LEs or LTEs which had arisen in the intervening periods. The life event data employed in this one year study was derived from the baseline and lst follow-up interviews.

Long-Term Experiences:

The details of long-term experiences of duration more than one month (at the time of interview) and of both a positive and/or negative nature, were independently recorded by the interviewer at the time of interview. All of these were classified into types and dated and rated for positive or negative impact. Subjective ratings of the impact of experiences were not made by either the child or parent. Instead, all ratings independently assigned by the interviewers were reviewed in a contextual panel rating

procedure for the degree of positive and/or negative impact impinging on the child. This rating procedure was carried out separately by each interviewer on the basis of separate child (Appendix 8) and parent (Appendix 9) interviews and reports . A very threatening long term experience or chronic adversity was rated 2 or 3 on negative impact while mild threat and absence of threat was rated 1 and 0. A rating was also made for the extent to which the event or experience in question was 'related to' or 'was independent of' the behaviour of the child and family. For example, if the child was a member of the local badminton club, this would be rated as being ***related to the behaviour of the child*** and ***probably related to the behaviour of the family***, especially if the child's parents were providing financial support to enable the child to participate in this hobby. Continuing marital discord would be rated as being ***related to the behaviour of the family*** but ***independent of the behaviour of the child.***

Life Events:

Each event reported at interview and defined as a life event by the interviewer was ***subjectively rated*** by the child (Appendix 10) and/or parent (Appendix 11) on a four point scale using a post-box system in terms of their own perceptions of its impact. For the children, this system incorporated colour-coded post-boxes (based on intensity of colour) to give the child a visual cue to help him/her rate the degree of both positive (pleasant) and negative (unpleasant) aspects of each event. These aspects were rated for the immediate (same day = **ST**) and long-term (10 days later = **LT**) effects. Events could be reported by the child alone, by the parent alone or by both child and parent. When a parallel set of ratings of 'reported impact' was obtained for the same event from the parent, again with respect to the impact on the child, this enabled a comparison to be made between adult and child perspectives of the same event.

Appendices 10 and 11 show that an 'objective' or ***contextual panel-based rating*** of the impact of stress was also subsequently assigned to the positive and negative aspects of each event. This rating was in addition to the reported ratings of the impact

of the event on the child obtained from the child himself/herself and from the child's parent at the time of interview. 'Contextual threat' refers to the level of threat caused or implied by the life event to an average child of the same age, sex and biographical characteristics as those of the child in question. A 'high threat life event' was considered to be one which was contextually rated as 2 or 3 on the scale of unpleasantness while a rating of 1 reflected mild threat and 0 the absence of threat or unpleasantness. Events could be rated with either a wholly positive or a wholly negative impact or could have aspects of both.

'Best Estimate' Life Events and Experiences

A panel of two or three raters, including the author, for each subject subsequently discussed, for each subject, ***all*** material ***contextually*** rated on the basis of both child and parent reports i.e. reports of the occurrence of all life events and long-term experiences. If, for example, the same life event had been reported by both child and parent and subsequently contextually rated for impact, these separately rated reports would be combined for further discussion. This final rating procedure was necessary since the child might have provided valuable information about an event or its context of which the parent was not aware and thus did not report. The opposite might also have been the case, where the parent offered information about an event which the child may have not mentioned or possibly not wished to mention. Similarly, where both interviewers had reported the presence of the same long-term experience, both reports were combined and discussed in order that the full contextual detail surrounding the experience could be assessed. From these discussions, a final set of contextual ratings emerged for all acute life events (Appendix 12) and long term experiences (Appendix 13) reported and deemed to be valid by the panel. Included in this final set of reports were those remaining events and experiences which had already been contextually-rated and had been reported either (1) by the child only or (2) by the parent only. The contextual ratings of positive and negative impact of these latter events and experiences often remained unchanged after discussion but, sometimes, on the basis of further information which emerged from general

discussion, previously allocated contextual ratings were changed. All final ratings reflected in effect a 'best estimate' in the panel's view of all of those events and experiences that had occurred, together with their degree of impact both positive and/or negative on the child and family.

Psychological questionnaires

Self-Esteem Questionnaire (Harter):

Self-esteem and perceived self-competence in a number of important domains in the child's life was measured using the Self-Esteem Questionnaire (Appendix 14). This contains six separate subscales: Scholastic Competence; Social Acceptance; Athletic Competence; Physical Appearance; Behavioural Conduct and Global Self-Worth. These scales are designed to tap into children's perceptions of their perceived self-competence or self-adequacy in specific domains of their lives together with a direct more global judgement about self-worth. Harter standardised her questionnaire on school children living in Colorado, USA (Harter, 1995). Harter found Cronbach alpha reliability values for the subscales ranged from 0.71 for the Behaviour subscale to 0.86 for the Athletic subscale. Harter (1985) did not provide an independent assessment of self-esteem so that the construct validity of the questionnaire is not known. 24 items or questions are categorised under 6 subscales (4 items per subscale). Individual subscale scores are derived from averaging the score of each of the four subscale-related items. Each of the 4 items are scored 1 to 4, with 1 and 2 indicating a low score or negative response while 3 and 4 indicate a high score. On this basis, therefore, a score of >2.5 for a subscale is considered to reflect a measure of high perceived self-competence or self-esteem on that particular subscale.

On completion of both the baseline and 2nd follow-up interviews, the Harter Questionnaire was administered to the children, with full instructions from the interviewer and assistance given when required. For the purposes of clarity and understanding, minor amendments were made to the wording in the Questionnaire similar to those changes made to the instrument in the Hoare et al study (1993). The

Questionnaire took approximately 15 minutes to complete and all questionnaires were subsequently examined for correct completion and data entered. The Questionnaires were also passed to the Computing Department in the University of Glasgow for data entering. For the purposes of accuracy, all data was coded and entered twice.

State/Trait Anxiety Inventory for Children (Spielberger)

Anxiety in the children was measured using the State-Trait Anxiety Inventory for Children developed by Spielberger, Lushene, Montuori & Platzek,1973 (Appendix 15). The STAIC consists of separate self-report scales for measuring two distinct anxiety concepts, state and trait anxiety. Each scale consists of 20 items designed to asses individual differences in anxiety proneness with higher scores reflecting increased anxiety proneness. Detailed evidence of test-retest reliability, internal consistency and construct validity is presented in the manual for the STAIC (Spielberger et al, 1973). No Scottish normative data is available for this questionnaire. 20 items in this Questionnaire investigated how the child felt 'right now' or 'at this very moment'. These scores provided a measure of 'state' anxiety. A further 20 items investigated how the child 'usually' felt and these scores provided a measure of 'trait' anxiety. Each item in the 'How I Feel' Anxiety Questionnaire was scored on a scale of 1 to 3 with higher scores reflecting a higher level of anxiety. A score above 1 SD above the mean on either scale represents a measure of high anxiety.

The Questionnaire was administered to the children at the 1st follow-up interview and took approximately 10 minutes to complete. All Questionnaires were checked for correct completion and all data coded and entered twice.

Ethics

The study was approved by the Ethics Committee of the Royal Hospital for Sick Children, Glasgow. Informed written consent was obtained from parents and children after a full explanation of the study (Appendix 16).

PART THREE

RESULTS

CHAPTER 9

UPPER RESPIRATORY SYMPTOMS AND URI

Results relating to illness measures are presented under two main headings in this chapter: upper respiratory symptoms and upper respiratory infections (URI).

Upper respiratory symptom presentation is considered firstly in terms of the mean upper respiratory symptom measures per subject over the period of the study. Measures of upper respiratory or nasal morbidity over a given period based on a 'mean' symptom statistic are influenced by two factors: (1) the proportion of days on which symptoms are reported and (2) the number of symptoms reported on such days. A mean statistic conceals the separate contribution of these factors. Clough,Williams & Holgate (1991) defined factor **(1)** as symptom 'chronicity' and **(2)** as symptom 'severity'. For example, if over a 365 day study period, a child reported symptoms on a total of 73 days of that period, then **symptom chronicity (1)** would be calculated as **73/365 x 100 i.e. 20% of days** on which symptoms were reported. Similarly, if over those 73 days the child reported a total of 146 symptoms, then **symptom severity (2)** would be calculated as **146/73 i.e. 2 symptoms per day** on symptomatic days. For the present data, symptom presentation was similarly investigated in terms of overall mean symptom presentation and both chronicity and severity of symptoms in order to determine whether differences between children in symptom presentation were attributed mainly to one or other or both of these factors.

The influence of a number of factors which may have an effect on symptom presentation, such as day in the week, age, gender and social class, were also examined. Since younger children can be more prone to upper respiratory morbidity than older children, the children were divided into three age bands: < 9 years (n=27); 9 to 11 years (n=30); > 11 years (n=21). They were also classified into three social class groupings based on a combination of Registrar General's Social Classes: I & II (n=24); III & IV (n=32) and V & VI together with the unemployed (n=22).

Levels of symptom presentation were also examined by classification of subjects into three symptom groups based on a tercile division of the ranked mean symptom

scores. This allowed examination of differences in various psychological and psychosocial measures between subjects with 'low', 'mid' and 'high' levels of symptom presentation. The relationship between upper respiratory morbidity and psychological factors such as psychological 'adjustment' in the form of measures of self-perceptions and anxiety, prior levels of chronic stress and the incidence of acute stressful life events are reported in later chapters.

9.1 Upper Respiratory Symptoms

The asthmatic children studied reported a mean of ***0.66 symptoms*** per day (median 0.45; SD 0.62; range 0.01 - 2.82) over ***all days*** in the one-year study period. However, focusing only on those days on which symptoms occurred, it was found that, on average, children reported symptoms on ***36.9% of all days*** with on average ***1.7 symptoms*** reported on each symptom day. Further details of symptom chronicity and severity are shown in Tables 3 and 4 respectively.

Figure 2 shows the average total number of symptoms reported over individual days in the week by subjects. This indicates that symptom reporting was at its highest level at the start of the week and fell to its lowest level on Saturday before rising again on Sunday. In order to investigate the possibility that symptoms recorded varied with the day of the week, an Analysis of Variance: (ANOVA: Repeated Measures) was performed on the total number of symptoms reported by subjects over each weekday ($F=4.22$; $df=6,462$; $p \leq 0.001$). Individual multivariate tests indicated a significant linear trend with symptoms decreasing linearly over days in the week from Sunday through to Saturday when symptom reporting appeared to be at its lowest ($t=2.92$; $p \leq 0.01$). Post hoc Tukey tests were applied to the data to compare means (Table 5). This showed a difference only approaching significance between the number of symptoms reported on Saturday and Sunday. A significant difference was found in symptom reporting between Saturday and Monday ($p \leq 0.01$) and Saturday and Tuesday ($p \leq 0.01$) but not between Saturday and the remaining days in the week. No other significant differences were found except for a difference

between mean symptom reporting on Monday and Friday ($p \leq 0.05$). These results indicate the start of an upturn in symptom reporting on Sunday from its lowest level on Saturday. This increase reaches significance on Monday and Tuesday. This is then followed by a downturn in reporting which continues until Sunday again when an upturn in symptom reporting approaches significance. A significant difference between the average symptoms reported on Monday and Friday also indicates that for these asthmatic children, symptom reporting at the start of the school week (Monday) is significantly higher than that at the end of the school week (Friday).

Respiratory symptom level groups

The mean symptom scores for all subjects were ranked and divided into three equal groups of subjects (n=26) (Figure 3). These consisted of subjects with 'low' (girls n=14 boys n=12), 'mid' (girls n=12; boys n=14) and 'high' levels of symptoms (girls n=11; boys n=15). Demographic data relating to the three groups is shown in Table 6.

Mean symptom presentation over groups is shown in Table 7. This shows that children with high symptoms reported 7 times the level of symptoms compared to those with low symptoms and 3 times those with mid symptom levels. It was not clear how such differences between symptom levels arose. For example, the children may have been reporting a similar number of daily symptoms but the number of days on which such symptoms were being reported may have been different. The reverse may have been the case. Groups may have been reporting symptoms on a similar number of days but the number of symptoms being reported on such days may have been different. Symptom chronicity and severity over groups are detailed in Table 8.

Differences over groups of subjects in terms of not only mean symptom levels but also in symptom chronicity and symptom severity are illustrated in Figure 4. In order to investigate differences in patterns of symptom presentation over groups, as reflected in the chronicity and severity of symptom presentation, an ANOVA was

conducted firstly on symptom chronicity (Table 9). This showed that the proportion of days on which symptoms were reported again differed significantly between all three groups (Low/Mid: $t = 4.27$, $p \leq 0.01$; Mid/High: $t = 7.88$, $p \leq 0.001$; Low/High: $t = 11.92$, $p \leq 0.001$).

A separate analysis on symptom severity (Table 10) indicated a significant difference in the number of symptoms reported on symptomatic days, but only between those with low and high symptom levels (Low/High: $t = 3.03$, $p \leq 0.01$). Age, gender and social class factors had no effect on either chronicity or severity of symptoms.

Differences in symptom presentation over groups therefore, in the main, could be accounted for by a significantly increasing proportion of days on which symptoms occurred. In those with 'high' symptom levels, however, the number of symptoms reported on such days also became significantly higher. In ranking these children with asthma in terms of increasing levels of mean symptom presentation, therefore, the number of days on which symptoms were reported preceded an increase in the severity of symptom reporting.

9.2 URIs

In order to identify periods of upper respiratory illness, particularly 'colds' or upper respiratory infections, upper respiratory symptom presentation was examined in four stages:-

(1) The occurrence of acute increases or peaks in the general level of symptom presentation were identified and recorded.

(2) The temporal relationship between such acute respiratory episodes was then analysed in order to highlight and identify the occurrence of distinct periods of illness comprising one or more acute upper respiratory symptom episodes.

(3) All such illnesses identified through an analysis of symptom presentation were then compared with subject reports of the occurrence of illness. All

illnesses were classified according to the subject-reported reason for such illness i.e., 'hay fever', 'chest infection', 'cold', 'flu', etc., and whether the illness was associated with a visit to the GP or, in the case of 'cold', whether a throat swab was taken

(4) All illnesses, particularly 'colds', were further examined in terms of whether the illness coincided in time with an independently determined paediatrician-recorded episode of asthma.

The results of this four stage analysis are outlined below.

(1) The occurrence of acute upper respiratory symptom episodes (REs)

When symptom data for subjects was plotted graphically some differences in the general background level of upper respiratory symptoms present, and the number, duration and severity of apparent episodes of upper respiratory symptom morbidity imposed upon this background level of symptoms were evident. These episodes of upper respiratory morbidity could occur in an isolated manner or more often, in a cluster, pointing to the occurrence of an upper respiratory or nasal illness of a more prolonged nature. In order to identify the occurrence of periods of illness, individual episodes of increased upper respiratory morbidity were identified in the first instance.

Those episodes which extended over more than 1 day were identified and their occurrence recorded. An individual RE was defined in such a way that it had to be of ***at least 2 days duration*** and separated from other such episodes by at least 2 days on which the level of upper respiratory symptoms was below an episode tolerance level, calculated as 1 standard deviation above the mean symptom score for the subject. Figure 5 shows a diagrammatic example of an acute upper respiratory symptom episode. Individual episode tolerance levels are incorporated in subject graphs and show in Figures 6, 7 and 8.

A total of 604 REs (n=78) were identified (mean 7.7; median 7.4; SD 3.5; range 1 to 20) (Table 11). A total of 262 REs (mean 7.1; median 7.2; SD 2.6; range 1 to 13) were recorded for girls (n=37) and 342 for boys (n=41) (mean 8.3; median 7.8; SD 4.1; range 1 to 20). Just less than half of the children , 37/78 (47.4%), reported above median levels of episodes i.e. >7 and about one quarter, 20/78 (25.6%), experienced 10 or more episodes.

The proportion of children in the different symptom groups who reported above median levels of episodes i.e. at least 8 episodes, was compared. A binary dependent variable was defined based on such proportions i.e. <8 or ≥8 and Logistic regression was used to model the effect of symptom level group on the proportion of children having 8 or more REs, after correcting for age, gender and social class factors (Table 12). The proportion of children reporting at least 8 REs did not differ between the three symptom level groups after correcting for such factors.

While no significantly increased risk of high levels of REs was found between symptom groups in the previous analysis, Table 11 shows that for those with low symptom levels the majority of all symptom days occurred within REs while for high symptom presenters the opposite was the case. For these children, the majority of symptom days occurred between REs and constituted a background level of symptom presentation.

ANOVA conducted on a number of symptom measures confirmed these findings (Table 13). The ***proportion of symptomatic days*** spent within, and thus between, episodes significantly differed between all groups (Low/Mid: $t = 8.88$, $p \leq 0.001$; Mid/High: $t = 2.98$, $p \leq 0.01$; Low/High: $t = 11.57$, $p \leq 0.001$). Not only did groups differ in the balance of symptomatic days spent within and between episodes, they also differed significantly both in ***mean symptoms*** reported ***within respiratory episodes*** (Low/Mid: $t = 4.16$, $p \leq 0.001$; Mid/High: $t = 5.53$, $p \leq 0.001$; Low/High: $t = 9.50$, $p \leq 0.001$) and mean symptoms in the periods ***between***

respiratory episodes (Low/Mid: $t = 2.73$, $p \leq 0.01$; Mid/High: $t = 3.77$, $p \leq 0.001$; Low/High: $t = 6.38$, $p \leq 0.001$).

For the sample as a whole, on the average, almost half of all symptomatic days (48.8%), were spent in these more acute episodes of upper respiratory morbidity (median=41.0%, range 3.8% to 100%).

(2) Identification of periods of illness

Subject reports of an illness or the incidence of a 'cold' or 'infection' were sometimes associated with the occurrence of a single RE but were more often associated with a number of such episodes occurring sometimes over a period of weeks. Such a pattern is consistent with reports that the sequelae to URI can extend for up to 6 weeks in duration in children with asthma (Bardin, Johnston, Pattemore, 1992).

In order to identifiy the occurrence of more prolonged periods of upper respiratory or nasal illness and so that the number of such illnesses should not be inflated, a group or cluster of episodes was defined in such a way that it consisted of at least two REs occurring **within** a six week period of each other. A number of periods of illness were thus identified. In some instances, therefore, illnesses could be of one acute upper respiratory symptom episode in duration or, more often, of two or more such episodes temporally related to each other. Periods of illness, as defined, were therefore separated from other such periods by at least a 6 week period of relative health within which no acute episodes of upper respiratory morbidity occurred.

A total of 228 upper respiratory or nasal illness periods were identified (mean 2.9; median 2.9; SD 0.9; range 1 to 5) (Table 14). The proportion of children in different symptom groups with above median levels i.e. >2 , of recorded illness periods was compared after controlling for age, gender and social class (Table 15). Logistic regression analysis again showed no significant difference between groups after controlling for these variables.

An ANOVA investigating the effect of different symptom groups, gender and age on the mean number of REs in each illness found a significant main effect of gender only (Table 16). 3.4 mean REs per episode of illness (median 2.4; SD 3.1; range 1 to 20) were recorded for boys and 2.4 mean REs per illness for girls (median 2.2; SD 1.03; range 1 to 5.5).

Results show that while there was no significant gender differences in the total number of upper respiratory or nasal illnesses identified, there was a significant difference in the mean number of REs comprising such illnesses which were greater for boys than girls. Further, since no difference was found between boys and girls in the mean symptom levels within REs, it may be concluded that the relative duration of periods of illness, in terms of episodes of acute respiratory episodes within periods of illness, was greater for boys.

(3) Upper respiratory infections or 'colds'

'Symptom-based' upper respiratory or nasal illnesses were classified according to the subject-reported reason for the illness, where one was provided. All but 4 subject reports of illness, including those associated with a 'cold', 'flu' or 'infection', coincided with one of the 228 periods of illness previously identified by examination of acute upper respiratory symptom episodes. Table 17 shows the classification of all 232 illnesses, including the 4 illnesses not identified through a symptom-based analysis. They were also classified according to whether an illness report was also associated with a recorded visit to the GP/hospital. In the case of reported URI illnesses or 'colds', these episodes were further classified according to whether or not the 'cold' was subsequently reported to the Project Office and swabbed.

Of all 232 upper respiratory or nasal illnesses, a total of 154 illnesses were reported as a 'cold' or 'flu' (mean 2.0; median 2.0 'colds'; SD 1.2; range 0 to 5). Using binary dependent variables based on median illness levels, logistic regression analysis

correcting for age, gender and social class was used to investigate the proportion of children over symptom groups reporting at least 3 colds (Table 18). While the analysis showed that the ***overall*** group effect only approached significance, individual comparisons between groups indicated an increased risk of reporting at least 3 'colds' in the mid symptom group compared to those with low symptoms. An effect of gender was also found with 9/41 (22%) boys and, almost double, 16/37 (43.2%) girls reporting at least 2 URI. There was therefore an increased risk of girls reporting at least 3 URI compared to boys. An effect of Age was also found with a higher proportion of 9 to 11 year olds (43.3%) reporting more than 2 URI compared to both younger children (25.9%) and children over 11 years of age (23.8%).

Of all reported URI, over half, 85/154 (55.2%) were swabbed and submitted for microbiological tests. The mid symptom level group had the lowest rate of URI which were swabbed (40%) in comparison to the other two groups (low = 52.6%; high = 73.2%). Of the 85 swabbed URI, 58 (68.2%) were associated with a visit to the GP when antibiotics were prescribed. Of the reported URI not swabbed 36/69 (52.2%) were associated with a visit to the GP. In total, therefore, 94/154 (61%) of all upper respiratory or nasal illnesses reported as a URI involved a visit to the GP.

Table 19 highlights the proportion of swabbed URI with a subsequent positive microbiological test result. While 85 samples were submitted for microbiological tests, 7 were misplaced by the laboratory in the course of testing. Of the remaining 78 samples, cold or 'flu virus was isolated from almost half, 37/78 (47.4%). Biologically verified colds therefore accounted for 37/154 (24%) of all recorded URI. Positive results from swabs were attributed to a number of viral antigens (Table 20), the majority of these being HRV. The proportion of positive results for swabbed URI were similar for children reporting low levels of symptoms (40%) and mid level symptoms (38.1%) while an increased proportion was found in the high symptom group (56.8%).

(4) Reported URI and asthma severity

A number of illnesses coincided in time with episodes of asthma morbidity i.e. wheezing episodes and/or a reduction in peak expiratory flow (PEF) values. Reports of the occurrence of episodes of asthma in subjects over the study period were taken from children's medical records. Details are included in Table 21. The occurrence of an episode of asthma was judged by a paediatrician and statistician and was determined by factors such as PEF measures, reported medication usage, reported symptom presentation, hospital and GP visits.

A total of 209 episodes of asthma were recorded for the group over the study period (mean = 2.7; SD 2.3; median 2.3; range 0 to 12). An analysis of the distribution of asthma episodes showed that 64/78 (82.1%) children experienced at least 1 episode; 47/78 (73.4%) experienced >1 episode; 37/78 (47.4%) children experienced >2 episodes; 23/78 (29.5%) children experienced >3 episodes and 13/78 (16.7%) children experienced >4 episodes. Girls experienced a mean of 3.5 asthma episodes and boys a mean of 2.0 asthma episodes.

The mean levels of asthma episodes in the children also appeared to be consistent with British Thoracic Society (BTS) medication ratings 2/3, 4 and 5(a/b) which reflects a range of treatment ranging from low dose prophylactic medication therapy (2) to oral steroid treatment (5b). Since only 1 child had a BTS rating of 2 this was combined with the group who had a BTS rating of 3. The mean number of asthma episodes in children with BTS rating 2/3 was 1.8 (median 1.7; girls 1.9, boys 1.7). Those with a mid-rating of 4 had a mean of 2.3 asthma episodes (median 2.2; girls 3.3, boys 1.5) and those with a higher rating of 5(a/b) a mean of 4.4 asthma episodes (median 3.8; girls 6.0, boys 2.9). The mean number of asthma episodes experienced over the different upper respiratory symptom level groups was: low 2.6 (median = 1.8; girls 3.6, boys 1.4); mid 2.3 (median = 2.1; girls 2.6, boys 2.1); high group 3.1 (median = 2.8; girls 4.2, boys 2.3).

Episodes of asthma often appeared to be temporally related to an illness in that they could either immediately precede, coincide with or follow an illness. The majority of asthma episodes coincided in time with an illness in that the asthma episode commenced while the illness period was still ongoing. An analysis of the coincidence between the occurrence of an asthma episode and the incidence of an illness was carried out. Approximately 4/5 of all asthma episodes, 165/209 (78.9%), coincided in time with a period of illness (low group: 69.1%; mid group: 80.3% and high group: 86.3%). Nearly 2/3 of asthma episodes, 135/209 (64.6%), coincided with a reported URI and 13/209 (6.2%) with reports of 'hospital admissions/GP visits' where antibiotics were prescribed. In total, therefore, 70.8% of all episodes of asthma coincided in time with URI and reported 'chest infections'. The remaining asthma episodes either preceded or followed such illnesses.

An examination of the proportion of respiratory illnesses coinciding with an episode of asthma was also carried out (Table 22). This showed that approximately one half of all reported URI and 'chest infections' coincided in time with an episode of asthma morbidity. About 1 in 5 of 'Other Illnesses' coincided with an asthma episode in comparison to approximately 3 in 5 URI. As would be expected, URI associated with a visit to the GP appeared to have a higher percentage of coinciding asthma episodes than those not associated with such a visit. In total, approximately 3 in 5 reported URI were associated with a visit to the doctor. Of such URI with a reported GP visit, 68/94 (72.3%) coincided with an episode of asthma. Of those not associated with a visit to the doctor, a lower proportion, 28/60 (46.7%) were associated with an asthma episode.

Table 23 gives details of the proportion of 78 swabbed infections coinciding with an asthma episode. In conclusion, therefore, cold or 'flu virus was isolated from almost half of all swabbed and microbiologically tested URI: **37**/78 (47.4%). Of all remaining URI, a further **90**/154 (58.4%) of URI were associated with a paediatrician/statistician rated episode of asthma and/or visit to the GP. The

remaining 27/154 (17.5%) constituted subject-reported URI not associated with an asthma episode or a visit to the GP (Table 24).

Illness behaviours, such as reported URI, use of health services and verifed pathology are all acceptable criteria in the research literature examining the relationship between psychological stress and upper respiratory infection (Cohen & Williamson, 1991).

CHAPTER 10

SELF-ESTEEM QUESTIONNAIRE (HARTER), UPPER RESPIRATORY SYMPTOMS AND URI

The Self-Esteem Questionnaire (Appendix 14) contains six separate subscales: Scholastic Competence; Social Acceptance; Athletic Competence; Physical Appearance; Behavioural Conduct and Global Self-Worth with 24 items or questions categorised under the subscales (4 items per subscale).

Individual subscale scores are derived from averaging the score of each of the four subscale-related items. Each of the 4 items are scored 1 to 4, with 1 and 2 indicating a low score or negative response while 3 and 4 indicate a high score. A score of >2.5 for a subscale, therefore, reflects a measure of high perceived self-competence or self-esteem on that particular subscale.

A number of analyses were conducted. Scores for the children with asthma were compared with scores from a normative sample of healthy school-children living in the Lothian region of Scotland (Hoare, Elton, Greer & Kerley, 1993). The relationship between Harter subscale scores and illness measures was also investigated. Illness measures included both upper respiratory symptom measures and upper respiratory infections.

10.1 Self-Esteem Subscale Scores - Comparison with a Normative Sample

Results indicated that, similar to scores in the Normative sample (Hoare et al, 1993), children in the asthma sample scored >2.5 on all subscales (Table 25). The children with asthma, therefore, reported normal levels of psychological 'adjustment' in comparison with other Scottish schoolchildren of a similar age.

Table 25 shows that the Asthma sample reported significantly higher scores than the Normative sample on most subscales. In addition, a number of trends were found to be consistent across both samples. Girls tended to score lower than boys on Athletic Competence while boys scored lower than girls on the Behaviour Subscale.

MANOVA investigating the effect of age and social class factors was conducted on the six subscales as dependent variables. Separate analysis was carried out for boys (Table 26) and girls (Table 27). These analyses showed that there was no effect of age or social class on the Harter subscale scores for boys. However, an effect of age x social class was found on the Scholastic, Social and Globabl Self-worth subscales for girls. In the case of the latter subscale, an independent effect of Social Class was also found. Those in lower social class groups (RG V and VI) particularly older children reported lower self-perception scores on these subscales.

10.2 Subscale Scores and Upper Respiratory Symptoms

A number of weak negative correlations (Spearman: 2-tailed) were found between mean upper respiratory symptom levels and the Harter subscale scores (**Scholastic - r=-0.2729, p=0.016**; Social - r=-0.1706, p=0.135; Athletic - r=-0.1655, p=0.148; **Appearance - r=-0.2355, p=0.038**; **Behaviour - r=-0.2986, p=0.008**; Global - r=-0.2030, p=0.075).

When boys' and girls' scores were examined separately, no significant correlations were found in the girls' scores. A number of significant negative correlations, however, were found between mean symptom levels in boys and subscale scores (**Scholastic - r=-0.3063, p=0.051**; **Social - r=-0.3688, p=0.018**; Athletic - r=-0.2343, p=0.140; **Appearance - r=-0.3093, p=0.049**; **Behaviour - r=-0.3592, p=0.021**; **Global - r=-0.4261, p=0.005**).

Further investigation showed that these significant negative correlations were related to the **number of days** on which symptoms were present in boys rather than to the number of symptoms being reported. Overall, the higher the number of days on which symptoms were reported, especially when occurring between illnesses in 'background' symptoms, the lower the level of self-perceptions over subscales for boys (Scholastic - r=-0.1979, p=0.215; **Social - r=-0.4145, p=0.007**; **Athletic - r=-**

0.3348, p=0.032; Appearance - r=-0.3559, p=0.022; Behaviour - r=-0.3253, p=0.036; Global - r=-0.4485, p=0.003).

10.3 Subscale Scores and Symptom Groups

Scores across Harter subscales by symptom group and gender are shown in Table 28. Scores tended to decline across groups, particularly for boys. This relationship is illustrated in Figure 9.

MANOVA investigating the effects of symtom levels on the 6 subscales as dependent variables was conducted separately for boys and girls. The resuls of these separate analyses are shown in Table 29 and show that there was no effect of symptom group level on the individual subscale scores for girls, although the Behaviour subscale approached significance. In the boys' analysis, however, a significant effect of symptom group was found on the Behaviour subscale and this lay between those with low and high symptom levels ($t=2.82$, $p \leq 0.01$). A more marked effect was found on the Global Self-worth subscale where significant differences lay between those with low and mid symptom levels ($t=2.25$, $p=\leq 0.05$) and between those with low and high symptom levels ($t=3.65$, $p \leq 0.001$). Results indicate that boys reporting higher upper respiratory symptom levels perceive themselves as less well-behaved and have a lower overall estimation of their own sense of global self-worth.

10.4 Subscale Scores and URI

No significant correlations (Spearman: 2-tailed) were found between individual subscale scores and the total number of 'URI for each subject (Scholastic - r=-0.1180, p=0.303; Social - r=0.0905, p=0.431; Athletic - r=-0.0577, p=0.616; Appearance - r=0.0304, p=0.792; Behaviour - r=0.0413, p=0.720; Global - r=-0.0193, p=0.867). When scores for girls and boys were examined separately, no significant correlations were found. Levels of reported 'colds', therefore, are not related to psychological 'adjustment' in the children as measured by Harter scores.

From the overall analysis of the Harter Questionnaire data, it appears that children with asthma have normal levels of psychological 'adjustment' in comparison with their healthy peers. In the Scholastic, Social and Global Self-worth subscales lower scores were found in older girls with lower social class groupings. No similar relationship between subscale scores and age and social class was found for boys. In boys, upper respiratory or nasal symptom morbidity was negatively correlated to subscale scores which reflect perceived self-competence and self-esteem in important domains of the child's life. The proportion of days on which symptoms were present in boys was negatively correlated with scores over all Harter subscales with the exception of the Scholastic subscale. Results indicate that within such a relationship between symptom days and self-perceptions, the higher the level of respiratory well-being ***between*** discrete episodes of upper repiratory or nasal morbidity, the higher the level of self-perceptions. Conversely, the lower the level of upper respiratory wellbeing between significant episodes of respiratory morbidity, possibly indicating towards a more perennial pattern of symptom morbidity, the lower the levels of perceived self-competence and self-esteem. In addition, the overall level of upper respiratory morbidity present in boys appears to be related to behavioural conduct scores. Those who report high levels of upper respiratory or nasal symptom morbidity perceive themselves as less well-behaved than those with a low level of respiratory symptom presentation. Perhaps, more importantly, measures reflecting an overall global sense of self-worth in boys appear to be negatively related to symptom levels.

It is not clear from these results, however, whether high symptom levels give rise to low levels of globabl self-worth in boys or whether the reverse may be the case. Alternatively, both of these factors may be related through a third factor.

CHAPTER 11

STATE/TRAIT ANXIETY IN CHILDREN 'HOW I FEEL' QUESTIONNAIRE (SPIELBERGER), UPPER RESPIRATORY SYMPTOMS AND URI

11.1 State/Trait Anxiety in Children

The Spielberger State-Trait Anxiety Inventory for children consists of two scales each with 20 items. 20 items investigate how the child feeels 'right now' or 'at this very moment'. These scores provided a measure of 'state' anxiety. A further 20 items investigate how the child 'usually' feels and these scores provide a measure of 'trait' anxiety. Each item in the 'How I Feel' Anxiety Questionnaire is scored on a scale of 1 to 3 with higher scores reflecting a higher level of anxiety. A score of above 1 SD above the mean for a subject represents a high score for that particular measure of anxiety.

Two children did not complete Spielberger questionnaires. Table 30 shows scores on both measures by gender and symptom group. Overall, scores tend to reflect a low level of reported anxiety (mean 27.6; SD 4.0) for state anxiety i.e. 'how I feel now", and a higher level of trait anxiety i.e. 'how I usually feel' (mean 32.0; SD 8.4). Only 6 children recorded a 'high' state anxiety score (>31.6) while 15 children recorded a 'high' trait anxiety score (>40). No significant gender differences were found between state ($t=0.89$, $p=0.38$)) or trait ($t=0.31$, $p=0.76$) measures of anxiety.

The effect of age and social class variables on both measures of anxiety was also investigated. A weak correlation (Pearson - 2-tailed) was found between state and trait anxiety measures ($r=0.3488$, $p=0.002$). This relationship was found in both girls ($r=0.3280$, $p=0.044$) and boys ($r=0.3799$, $p=0.019$). The role of age and social class factors, therefore, was examined using MANOVA with both measures of anxiety as dependent variables (Table 31). Results of multivariate analysis indicated a significant effect of age (Wilks: $F=5.49$, $df=4,132$, $p\leq0.001$) but not of social class (Wilks: $F=1.52$, $df=4,132$ p=NS) or of the age by social class interaction (Wilks: $F=1.92$, $df=8,132$, p=NS). However, while the latter age by social class interaction only approached significance in the multivariate tests ($p=0.06$), individual univariate F-tests (Table 31) did show a significant effect of this interaction. This was found on the trait measure of anxiety and only for children in combined Registrar General's

social classes III and IV. In this group ***younger*** children reported higher levels of anxiety related to how they usually felt compared to older children who reported lower scores in this measure of anxiety.

These results, however, are not quite as impressive as those found in the age analysis. A significant effect of age was found in ***both*** multivariate and univariate F-tests but only for the state measure of anxiety, i.e. 'how I feel now'. Older secondary-aged schoolchildren reported significantly higher anxiety scores in terms of how they currently felt (mean=1.54) compared to both younger children of 9 to 11 years (mean=1.30: t=3.30, $p \leq 0.01$) and those less than 9 years (mean=1.34; t=4.49, $p \leq 0.001$).

11.2 State/Trait Anxiety and Upper Respiratory Symptoms

The relationship between 'state' anxiety measures and mean respiratory symptoms was examined. No significant correlation was found between the mean upper respiratory symptom levels and the state anxiety measure (Spearman - 2-tailed: r=0.1583, p=0.172) nor these symptom levels and the trait anxiety measure (r=0.0812, p=0.486). Similarly, no significant correlations were found when reported symptoms for boys and girls were examined separately.

11.3 State/Trait Anxiety and Symptom Groups

Table 30 shows the mean scores over symptom groups and gender for both state and trait measures. MANOVA was conducted on both state and trait anxiety measures as dependent variables to investigate the role of symptom groupings. No significant effect of symptom groups was found on state anxiety measures (F=0.72, df=2,73, p=NS) or on trait anxiety measures (F=0.97, df=2,73, p=NS).

11.4 State/Trait Anxiety and URI

No significant correlation was found between mean state anxiety measures and the total number of URI (Spearman: r=-0.0552; p=0.636)) nor between trait anxiety

measures and the number of URI ($r=0.0873$; $p=0.453$). Similar results were obtained when scores for boys and girls were examined separately. Non-significant results were also found when the analysis included ***all*** reported upper respiratory or nasal illnesses.

In conclusion, therefore, no significant relationship was found between illness measures and state or trait anxiety measures in children. Older children, however, reported significantly higher state anxiety measures. These children were significantly more at unease with themselves in terms of how they presently felt but this was not apparently a function of illness or related to the frequency of symptoms. However, a lack of normative data represents a drawback in this analysis of state/trait anxiety and illness measures and results would have to be viewed in this light.

CHAPTER 12

PACE MEASURES (LTEs), UPPER RESPIRATORY SYMPTOMS AND URI

Chronic adversities or, in the case of positive experiences, self-enhancing circumstances, were judged to be present and rated for impact by the investigator on the basis of contextual information derived from the parent and child interviews. A rating of either positive or negative impact of the experience **on the child** was necessary for a long term experience (LTE) to be recorded in the first instance. Evidence in the literature, however, has suggested that it is particularly the negative impact of chronic experiences which gives rise to risk in the stress-illness relationship. The main focus of research interest has therefore been on those experiences judged to have a ***high*** negative impact on the child. However, in the present analysis, the total positive and negative experiences recorded for the children was firstly examined before investigating more fully the incidence of high threat negative LTEs and their relationship to symptom measures and URI.

12.1 Long-Term Experiences (LTEs)

A total of 444 positive and negative LTEs of at least one month duration at the start of the study were recorded for the 78 children. Of these experiences, 128 were of a predominantly positive nature (mean: 1.6; median: 1.6; range 0 to 4 experiences) and 316 of a predominantly negative nature (mean: 4.1; median: 4.1; range 0 to 11). Of the 316 negative experiences, 166 had ***high*** negative impact on the child ((mean: 2.1; median: 1.6; range: 0 to 10). Table 32 shows the distribution of positive, negative and high negative impact experiences over gender, age, social class and symptom groups. Table 33 shows the mean number of experiences over these groups.

Positive LTEs

The majority of the 128 positive experiences recorded for the sample consisted in the main of experiences involving the child in an activity such as a hobby or membership of a club. The proportion of children over symptom groups reporting above sample median levels of positive LTEs i.e. at least 2 positive experiences, was compared. A binary dependent variable was defined based on such proportions (≥ 2 or <2 positive experiences) and Logistic regression used to model the effect of symptom groups on

the proportion of children having 2 or more positive experiences, after correcting for age, gender and social class variables (Table 34).

The proportion of children reporting at least 2 positive experiences did not differ over the three symptom groups. There was also no significant effect of age or gender. However, a significantly increased likelihood of higher levels of positive LTEs was found in combined RG classes I & II compared to those in clases III & IV and those in RG groups V & VI. At least 2 positive LTEs were recorded for 88% of subjects in groups I & II while 48.6% of subjects in groups III & IV and 22.2% of subjects in groups V & VI had >1 positive LTE.

Negative LTEs

Of the 316 long-term experiences of any negative impact (either low impact = 1 or high negative impact = 2 or 3), the most common type of experience was illness, either in the immediate family or in the child, or in close relatives and confidants. Table 35 shows a breakdown of the different types of LTEs of all negative impact. An inverse relationship was found between the recorded number of positive and negative LTEs (Spearman: -0.3327; p=0.003). This relationship was significant for boys (r=-0.3951; p=0.012) but not girls (r=-0.2536; p=0.124).

Again, Logistic regression was used to model the effect of symptom groups on the proportion of children with more than 4 negative experiences after correcting for age, gender and social class (Table 36). The overall effect of symptom groups on the proportion of children with more than 4 recorded negative LTEs only approached significance in this analysis. Individual tests, however, indicated an increased risk of higher levels of negative experiences in children with high symptom levels compared to those with moderate symptoms. The comparison between low and high symptom presenters only approached significance. An examination of the number of LTEs across symptom levels showed that 38.5% of children in the low group, 30.8%, in the mid group and 61.5% of children in the high group had >4 negative LTEs. These

results point to an increased risk of high levels of negative experiences in those children with high levels of upper respiratory morbidity.

An effect of social class was also found. Children in higher groups (RG I & II), were more likely to have a lower number of negative experiences in comparison with children in the lower groups (V & VI). 24% of children in groups I & II had >4 negative LTEs recorded while 45.7% of children in Group III & IV and 66.7% of children in combined groups V & VI had at least 5 negative experiences. Age and gender factors were not significant.

High negative impact LTEs (HNI LTEs)

Evidence has suggested that the risk associated with life event stress arises from the negative impact aspects of such stress. Accordingly, those experiences of a high threat nature (negative impact on child = 2 or 3) were the main focus of analysis of the relationship between long-term experiences and symptom measures, symptom groups and recorded URI. All negative experiences were rated as having either low impact (1) or high negative impact (2 or 3) on the child and, where applicable, also on the family. Table 37 shows the classification of all negative LTEs for the whole sample on the basis of the level of rated threat impacting on the child and/or the family. Slightly more than half of all negative LTEs had high negative impact (HNI) on the child and more than half of these HNI LTEs also had high negative impact on the family. The remainder had either low or no negative impact on the family. A total of 166/316 (52.5%) of all negative LTEs had high negative impact on the child.

Table 38 lists the HNI LTEs by type for the whole sample. Such experiences were ongoing for ***at least*** a one month period prior to the start of the study. The mean duration of high threat experiences was just over 3 years (mean 40.9 months; median: 28.5 months). When the relationship between HNI LTEs and positive LTEs were examined, an inverse relationship was found between these experiences (Spearman:

r=-0.2819; p=0.012) and this relationship was again significant in boys (r=-0.3693; p=0.019) but not in girls (r=-0.1728; p=0.299).

HNI LTEs were further examined in terms of 'independence' and were classified according to whether they were independent of or related to the behaviour of the child. Of all 166 HNI LTEs, 36/166 (21.7%) were related to illness in the child or family. A further 112/166 (67.5%) were independent of the behaviour of the child and 18/166 (10.8%) HNI LTEs were related to the behaviour of the child. A full breakdown of HNI LTEs in terms of relatedness to the behaviour of both child and/or family is shown in Table 39. While just over 1 in 10 high negative experiences were related to the behaviour of the child, just over one half, 90/166 (54.2%), of all HNI LTEs were related to the behaviour of the family.

12.2 HNI LTEs and Upper Respiratory Symptoms

An examination of the relationship between high threat negative LTEs and respiratory symptom levels showed a weak correlation between mean upper respiratory symptom measures and HNI LTEs (Spearman: r=0.2693, p=0.017). When examined separately neither the relationship in boys (Spearman: r=0.2720, p=0.09) nor girls (Spearman: r=0.2832, p=0.085) was found to be significant. In order to investigate the possible protective effect of positive experiences in the relationship between mean symptom measures and HNI LTEs, a partial correlation analysis was also conducted on mean symptoms and the number of HNI LTEs but controlling for the number of recorded positive LTEs. A significant weak correlation was found (r=0.2998; p=0.008). This relationship was significant for boys (r=0.3718; p=0.02) but not girls (r=0.1703; p=0.314).

Since a significant correlation was also found in boys between mean symptom measures and Harter subscales, the relationship between HNI LTEs and Harter subscale scores was examined. A significant relationship was found only on the Behaviour subscale (r=-0.3214, p=0.004). When the relationship between mean

symptom measures and Harter subscale scores was re-examined but controlling for HNI LTEs, this relationship for all six subscales was no longer significant which tends to indicate some interrelationship between symptom measures, HNI LTEs and subscale scores, particularly so on the Behaviour subscale.

12.3 HNI LTEs and Symptom Groups

Logistic regression analysis was conducted on median HNI LTE levels (> 1 HNI LTE and less) (Table 40). No significant effects of age, gender or social class were found. A significant effect of symptom groups was found with high symptom presenters more likely to have higher levels of HNI LTEs recorded than all other children. Examination of the proportion of children with higher than median levels of HNI LTEs showed that 38.5% in each of the low and mid symptom groups had above median levels of HNI LTEs while twice this proportion, 76.9% of children in the high group, had >1 HNI LTE.

12.4 HNI LTEs and URI

No significant correlation was found between the number of high threat experiences and the total number of 'colds' (Spearman: r=-0.1737; p=0.128). A partial correlation controlling for positive experiences was also non-significant (r=-0.1166; p=0.313). Similar results were found when all reported upper respiratory or nasal illnesses were examined.

When considered together the results of analyses indicate that family functioning and social class are related to levels of chronic negative stress. In the case of high negative long-term stress, more than half of such experiences were related to the behaviour of the family. Results also indicate that these interrelationships may be stronger in boys because of the inverse relationship found in these children between positive and high negative experiences.

Chronic adversity of a high negative nature, in turn, appears to predispose children to high symptom levels, irrespective of age, gender or social class of the child. However, in the relationship between symptom levels and self-esteem measures, gender difference are found. Symptom measures have been found to be related to Harter subscale scores for boys, particularly on the Global and Behaviour subscales. Boys with high levels of upper respiratory symptoms perceive themselves as less well behaved and have a lower sense of global self-worth in comparison with those reporting low levels of symptoms. Interestingly, prior levels of high negative long-term experiences were also found to be related to Harter subscale scores but, again, only on the Behaviour subscale.

Prior levels of high threat long-term experiences, of average duration about three years, were therefore found to be related both to current symptom measures and to intra-study measures on the Behaviour subscale and these latter measures, in turn, are related to symptom measures in boys. There would appear to be some intercorrelations between HNI LTEs, subscale scores, and symptom measures, again, particularly so for boys. Considering the ***prior*** long-term nature of HNI LTEs, it may be that the previous relationship found between the Behaviour subscale scores and current symptom measures has arisen, particularly in boys, because of the prior relationship between this subscale and HNI LTEs. When controlling for prior levels of high negative experiences, the relationship between Harter subscales and symptom measures is no longer significant. Further, since results show the children have normal levels of self-esteem in comparison with healthy peers, this finding does not support a possible causal relationship between disease severity and psychological adjustment. Therefore, for boys, and particularly in the case of the Behaviour subscale scores, levels of self-esteem may moderate symptom levels, with high long-term stress playing a predisposing role in this relationship. Boys who perceive themselves as less well-behaved may be indulging in behaviours which give rise to increased symptom levels, particularly so within a context of high chronic stress.

CHAPTER 13

PACE MEASURES (LEs) AND URI

In order to investigate the temporal relationship between acute life events and the occurrence of URI or the 'cold', events were examined firstly for 'contextually' rated positive or negative impact and were classified according to whether they were predominantly positive or negative in nature. In the case of negative events, these were classified according to whether they were of low negative impact (threat impact rating = 1) or high negative impact (threat impact rating = 2 or 3). High negative impact events (HNI LEs) were further considered in terms of the temporal nature of the threat involved i.e. ***short-term threat*** (duration of threat - one to two days) and ***long-term threat*** (duration of threat - one week to ten days). Previous research has indicated that the risk arising from the relationship between acute life events and the onset of illness or the exacerbation of an already present illness is associated with life events of a high ***long-term threat*** nature. This research, however, was carried out on adults.

High threat life events were therefore the main focus of analysis in investigation of the temporal relationship between the occurrence of an event and the incidence of a 'cold'. However, the role of high threat long-term experiences and positive experiences in this relationship was also considered.

13.1 Life Events (LEs)

A total of 772 events both positive and negative were recorded over the period of the study (mean 9.9; median 9.4; SD 3.6; range 4 to 22 events). Of all recorded events, 347 (44.9%) were rated predominantly positive in impact (mean 4.4; median 4.2; SD 2.3; range 1 to 12) and 425 predominantly negative (mean 5.4; median 5.2; SD 2.7; range 1 to 16). Of all negative events, 374/425 (88%) were of high negative impact (mean 4.8; median 4.7; SD 2.4; range 1 to 13). Table 41 shows a breakdown of all negative LEs by type and impact. HNI LEs were rated with high negative impact in the short term (ST: duration of threat - one to two days) and/or long term (LT: duration of threat - one week to ten days). Of the 374 HNI LEs, 259 (mean 3.3) were of high short-term threat impact and 115 (mean 1.5) were of high long-term impact.

Although of high long-term impact, these latter events could also have high ST threat impact. Table 42 shows the distribution of events in the children classifed by gender, age, social class and symptom groups. Table 43 shows the mean number of events recorded under each of these categories for both boys and girls.

The majority of positive events were related in the main to leisure activities in which the children were involved and to 'good' events such as receiving presents or winning prizes. No significant correlation was found between positive LEs and positive LTEs suggesting that there was no significant tendency for positive events to arise from ongoing positive experiences of a more long-term nature. However, further analysis showed that the majority of positive LEs were related to the behaviour of the child or the family (Table 44).

The opposite was the case for negative events. Just over one-half of all negative LEs were unrelated to the behaviour of the child or the family. Approximately 1 in 5 LEs were related to the behaviour of the family and 1 in 10 to the behaviour of the child (Table 44). Again, no significant correlation was found between all negative LTEs and negative LEs suggesting that within the period of the study, there was no tendency for negative events to arise from ongoing negative experiences.

In terms of the individual types of negative events, those involving illness, accident and death had the largest number of events recorded (28%). Problems more directly involving relationships such as those related to family or marriage relationships, work, behaviour and work at school, sexual relationships, friendships and leisure activities in which the children were involved, constituted a further 172/425 (40.5%) of all events. Events related to witnessing or experiencing an unpleasant or frightening incident, sexual harassment or abuse, law contact, burglary or theft, and receiving or breaking unexpected news accounted for 79/425 (18.6%) of events. Of the remainder, events involving moving home and living conditions together with those involving pets constituted a further 8.9% of all events.

13.2 High Negative Impact LEs (HNI LEs)

Negative LEs were rated as either low in negative impact (threat impact = 1) or high in negative impact (threat impact = 2 or 3). Table 41 shows a breakdown of these 374 HNI LEs by type. The proportion of high threat events involving illness (27.3%), those related to relationships at home school, work, marriage and friendships together with sexual relationships (42.5%) and those involving a number of frightening or unexpected events and activities (16.8%) were similar to those recorded for **all** negative events. Table 42 also shows a similar distribution of HNI LEs to that found for *all* negative LEs. Just over one half of LEs were unrelated to the behaviour of the child or the family which is consistent with the finding of no significant correlation between LTEs and LEs. High threat events occurring in the period of the study did not tend to arise out of ongoing chronic adversity of a high negative nature.

Of these HNI LEs, the majority 69.3% were rated as short-term in impact (ST) HNI LEs (mean 3.3; median 3.1; SD 1.8; range 0 to 9) and the remainder 30.7% were rated as long-term (LT) HNI LEs (mean 1.5; median 1.00; SD 1.7; range 0 to 8). Table 43 shows that of those high threat events involving relationships in some form, those concerned with school and leisure were more likely to be of ***short-term*** high negative impact in nature. High negative events involving a number of frightening or unexpected events and activities involving pets also tended to be short-term in nature. Over half of such events were not related to the behaviour of the child or family (Table 44). However, events arising from relationships related to family, marriage, friendships and sexual relationships tended to give rise to events of a ***long-term threat*** nature compared to those arising from school or leisure related activities/relationships. A reduced rate of such high threat long-term LEs were related to the behaviour of the child. However, an increased rate of such events, almost 2 in 5, were related to the behaviour of the family.

In order to investigate measures of ***current*** psychological stress and since events of a high threat nature have been shown to play a role in the temporal relationship between psychological stress and illness, a Logistic regression analysis was conducted to compare children over symptom groups with increased numbers (>4)of **all** recorded HNI LEs, whether of a LT or ST threat nature (Table 45). Findings indicated no significant differences in the reporting of such events over children reporting different levels of upper respiratory symptoms. However, an effect of age was found with an increased risk of children 9 to 11 years of age reporting a higher number of such events compared to younger children of less than 9 years of age. Results also indicate an effect of gender approaching significance thus indicating towards an increased risk in girls of reporting higher levels of such events compared to boys. Further Logistic analysis was conducted ***separately*** on LT HNI events (Table 46) and ST HNI events (Table 47) and compared children over symptom groups with increased levels of such events. This showed a significantly increased risk of girls reporting increased numbers of events of a high ***long-term*** threat nature (girls: mean 1.9; median 1.5; SD 2.0; range 0 to 8) compared to boys (boys: mean 1.1; median 0.8; SD 1.3; range 0 to 5).

Also, high symptom presenters were significantly more likely to report increased levels of such long-term events compared to children reporting mid symptom levels. The significant effect of age found in the overall event analysis was therefore not specifically related to the ***temporal*** nature of the threat involved. Children of 9 to 11 years were at increased risk of reporting HNI events, either in the short-term or the long-term, with girls at significantly increased risk of reporting increased levels of LT HNI LEs.

In conclusion, results appear to indicate that both child and family appear to bring about the majority of positive LEs while only about 1 in 3 of ***all*** negative LEs are related to the behaviour of the child or family. These negative LEs are related mainly to illness or events involving relationships in some form and also events involving

frightening or unexpected incidents. ***High threat*** negative life events are similarly distributed in terms of both type and relatedness to the behaviour of the child or family. Events related to school and leisure activities tend to be short-term in nature as do events involving unexpected or frightening incidents or activities. However, high threat events related to family, marriage, friendships and sexual relationships tend to be **long-term** in nature. An increased proportion of these high threat LEs of a long-term nature were related to the behaviour of the family while a reduced proportion were related to the behaviour of the child. Investigation showed that upper primary-aged schoolchildren, 9 to 11 years of age, are at increased risk of reporting increased numbers of events of high negative impact compared to younger children of less than 9 years. Girls compared to boys appear to be at increased risk of reporting events of a high threat nature, significantly so in the case of more severe events with high long-term threat impact.

Since previous analyses also indicate an increased risk of a high number of reported URI in girls compared to boys and in 9 to 11 year olds compared to all other children, these results suggest a possible relationship between recorded upper respiratory viral infection and the occurrence of high threat life events, particularly in girls and in children 9 to 11 years of age. The results of the investigation of the temporal relationship between psychological stress and the occurrence of URI are presented in the following final analyses.

13.3 HNI LEs and URI

In this study, URI are separated from other such infections by an illness-free period of at least 6 weeks in duration. Investigation of a temporal relationship between high threat negative impact LEs and the incidence of URI was conducted in two separate analyses:

(1) In a **URI-centred analysis**, it was expected that the risk associated with the occurrence of at least one high threat event in the 6-week period ***preceding the start***

of all URI would be similar to that in the 6-week period ***following the start of all URI.***

(2) Similarly, in **an event-centred analysis**, it was expected that the risk associated with the occurrence of a URI in the 6-week period ***following all high threat events*** would be similar to that in the 6-week period ***preceding all high threat events.***

Events were excluded from analyses if insufficient data was available to determine if a URI had occurred within a 6-week period, for example, if an event occurred towards the end of the study period.

URI-centred analysis

Table 48 details the total number of ***URI*** preceded or followed by a HNI event within a 6-week period. This shows that 40% of all URI were preceded by a high threat event within a 6-week period. A similar proportion (36%) were followed by a high threat event within the same period. However, for girls, a higher proportion of URI appear to be temporally related to HNI events than is the case for boys. Almost 50% of all URI in girls were ***preceded*** by a high threat event with 41% followed by such an event.

A URI was considered to be ***temporally related*** to an event if an event occurred in the 6-week period ***either preceding or following*** the start of infection. The proportion of URI thus temporally related to a high threat event was compared to the proportion of URI not temporally related. A binary dependent variable was defined based on such proportions and Logistic regression was used to model the effect of period i.e. '6-weeks before URI'/'6-weeks after URI', on the proportion of URI temporally related to a HNI event, after correcting for age, gender and social class factors. Three separate analyses were carried out based on (1) all HNI events (Table 49); (2) LT HNI events (Table 50) and (3) ST HNI events (Table 51). Results showed that the proportion of

URI temporally related to an event differed for those URI with an event in the 6-week period preceding URI compared to the 6-week period following infection. A significantly increased risk of an event occurring in the 6-week period ***preceding*** the start of a URI was found but only for analysis (2) i.e. for events of a ***high long-term threat*** nature.

A significant effect of gender was also found in analysis (2) indicating a significantly increased risk in girls of a LT HNI event being ***temporally related*** to a URI. There was also some indication that for those with high levels of prior chronic stress (HNI LTEs), there was an increased risk of a high long-term threat event being temporally related to a URI. However, this effect only approached significance. While there is clearly an effect of 'period' in analysis (2) with the finding of an increased risk of a LT HNI event in the 6 week period preceding the commencement of a URI, it cannot be concluded that the significant effect of other factors also relate to this particular period. The binary dependent variable in the Logistic regression analysis was based on whether or not a high threat event occurred in ***either*** period.

In order to examine whether the significant effect of other factors such as age and gender were indeed related to the period '6-weeks before URI' rather than to the period '6-weeks after URI', ***separate*** Logistic regression analysis was conducted separately for the 'before' (Table 52, 53, 54) and 'after' (Table 55, 56, 57) periods for all HNI events, LT HNI events and ST HNI events. The results in Table 52 and 53 show that the significant effects of age and gender previously found relate to the 6-week period ***preceding*** the occurrence of a URI. Girls were significantly more likely to report an increased number of high threat events, particularly high threat events of a **long-term** nature, in the 6-week period prior to the occurrence of a URI. Children, 9 to 11 years old, were also significantly more likely to report high threat events in this period. No significant effects of age, gender or other factors were found in the '6-weeks after URI' period (Table 55, 56, 57).

In conclusion, therefore, a URI-centred analysis indicates that there is an increased risk, in girls, of a high long-term threat event occurring in the 6-week period preceding an infection compared to the 6-week period following infection, with girls of upper primary school age appearing particularly at risk.

Event-centred analysis

While a URI centred analysis investigated those ***URI*** which were preceded or followed by ***at least one HNI event***, an event-centred analysis examined ***all HNI events*** which were preceded or followed by a ***URI*** in a 6-week period. Before presenting the results of this event-centred analysis a number of factors which play a role in this analysis are discussed.

While all URI reported by subjects were capable of being preceded and/or followed by a HNI event within a 6-week period, not all events on the other hand were free to play a possible temporal role in the relationship between high threat event and URI. In many instances a HNI event occurred in the course of an existing URI. Assuming the existence of a temporal relationship between high threat event and URI, with a possible mediating role played by the immune system, such an event occurring in the course of an ongoing URI could be capable of exacerbating or extending the duration of a URI. Alternatively, it may have no further effect at all on the ongoing URI. This would be synonymous with a refractory period in illness when the course of the disease is resistent to both treatment or further adverse effects. Certainly in this study, however, the occurrence of an event in the course of an existing URI could not give rise to another such infection within a 6-week period. This is because, by definition, the current URI would still be considered as ongoing. Therefore in the analysis investigating the percentage of events preceded or followed by a URI within a 6-week period, not all events occurring within the course of this study were free to play a causal role in a possible HNI event/URI relationship. The following results should be considered in this light.

Table 58 shows the total number of all HNI LEs followed or preceded within a 6-week period by a URI. Again results indicate, overall, towards an increased percentage of events in girls being ***temporally related*** to the occurrence of URI in that they were ***either preceded or followed*** by such illness within a 6-week period. The data relating to boys tends to indicate towards a pattern of an increased number of URI preceding events compared to following events. For girls, the opposite is the case. However, on further examination figures show that similar proportions of all HNI for boys (0.231) and girls (0.237) were preceded by URI. Thus it is in the proportion of such events *followed* by URI in boys (0.215) and girls (0.353) that a difference again appears to arise. This is consistent with the pattern of results found in the URI-centred analysis. For girls an increased number of HNI events were followed by a URI.

In this event-centred analyses, the proportion of high threat events with a URI occurring within a 6-week period of the occurrence of the event (***either preceding or following HNI event***) was compared to the proportion of events not thus temporally related to a URI. A binary dependent variable was defined based on these proportions and Logistic regression was used to model the effect of period i.e. '6-weeks before HNI event'/'6-weeks after HNI event', on the proportion of events temporally related to a URI, after correcting for age, gender and social class factors. Three separate analyses were carried out based on (1) all HNI events (Table 59); (2) LT HNI events (Table 60) and (3) ST HNI events (Table 61). The proportion of HNI events with a URI occurring within a 6-week period differed for the period ***following*** the event compared to the period preceding such an event. A significantly increased risk of a URI occurring was found in analysis (2) for the 6-week period following the occurrence of a ***high long-term threat event*** only but not for the period following a short-term high threat event or a high threat event of any impact. There was no significant effect of other factors including age in this LT HNI analysis and the effect of gender only approached significance.

In order to examine the effect of age, gender, social class and LTE levels on individual 'periods', ***separate*** Logistic regression analysis was conducted for the '6-weeks after HNI event' (Table 62, 63, 64) and '6-weeks before HNI event' (Table 65, 66, 67) periods for all HNI events, LT HNI events and ST HNI events. The results in Table 62 show a significantly increased risk of any HNI event being followed by a URI in children 9 to 11 years compared to younger children. This effect is also significant in the LT HNI analysis (Table 63) but in addition, older children, over 11 years, also show an increased risk in comparison to children less than 9 years. A significant gender effect was again found but only for any HNI events followed by a URI (Table 62). In the same analysis, an effect of levels of positive LTEs was found to approach significance where those with low levels of positive experiences were more likely to have an increased number of HNI events followed by a URI. In the ST HNI event analysis, there was no significant effects (Table 64). However, the gender effect approached significance.

No significant overall effects were found in the analyses which examined HNI events ***preceded by*** a URI. Interestingly, however, in Table 65 the effect of positive LTEs approached significance but in this instance those with ***higher*** levels of positive experiences were more likely to report any HNI LE ***preceded by*** a URI. This is the reverse of the effect found in Table 62 which examined any HNI events followed by a URI where those with low levels of positive LTEs were more likely to have any HNI LE followed by a URI. The same was the case in the LT HNI life event analysis. Those children less than 9 years were more likely to have a LT HNI life event preceded by a URI compared to those 9 to 11 years of age, whereas these latter children were more likely to have a LT HNI event followed by a URI compared to the younger children.

In conclusion, therefore, results indicate that a temporal relationship exists between high threat events of ***long-term*** impact and the occurrence of a URI within a 6-week period, but only in girls with asthma. The high threat impact of such events is

considered to endure for a period of approximately 2 weeks. Age may play a role in this relationship in that older children particularly of an upper primary school age i.e. 9-11 years, may be at increased risk. Levels of high chronic adversity and positive long-term experiences, such as belonging to a club or having a hobby, may possibly play some role in this relationship but the evidence for this is relatively weak.

PART FOUR

DISCUSSION AND CONCLUSION

CHAPTER 14

DISCUSSION

This study examined the occurrence of upper respiratory symptoms and infections in children with asthma and investigated their relationship to measures of upper respiratory morbidity and a number of psychological factors including measures of self-perceptions, anxiety, prior measures of high threat adversity and long-term experiences of a more positive nature.

Previous studies in children with respiratory problems such as those conducted by Clough & colleagues (1991, 1992, 1994) have tended to focus on objective measures of lower respiratory tract illness such as wheezing episodes, peak expiratory flow values and the occurrence of infection of the respiratory tract. No study has yet examined, in detail, patterns of upper respiratory symptom presentation in children with asthma. In the present study, upper respiratory symptoms were regarded as a non-specific upper respiratory system response to the combined input of a range of environmental factors such as allergens, irritants, upper respiratory infection, etc. Symptom presentation was examined both in terms of symptom occurrence within and also between periods of illness, such as infection of the respiratory tract, in a background level of symptoms.

This discussion, firstly, focuses on an investigation of patterns of upper respiratory symptom presentation and their relationship to both PACE measures of long-term experiences and psychological 'adjustment'. A discussion of the results relating to upper respiratory infection , PACE measures of acute life events of a high threat nature, the temporal relationship between these two factors and the role of both positive experiences and high threat negative experiences of a long-term nature will follow

14.1 Upper Respiratory Symptoms

Data collection in this study was based on diary completion. Some reports, however, have shown that diary completion is not an entirely reliable method of data collection since subjects are not efficient in symptom reporting or in the perception of their

symptoms (Archer, 1985; Lister, Burdis-Jones, Palmer & Cochrane, 1989). Children in the present study were required to record the perceived severity of a range of upper respiratory or 'cold' symptoms in a daily diary over the study period. This procedure was incorporated in order to help alert the child and/or main caregiver of the presence of a 'cold'. However, the symptom measures actually employed in data analyses did not include this measure of ***perceived*** symptom severity. Symptom severity in analyses was based on the ***number*** of symptoms reported by each subject on those days on which symptoms were reported. The number of days on which such symptoms were experienced was also of interest in analyses.

In the main, the investigation of symptom reporting was based on a comparison of symptom presentation over different symptom groups which were created by a tercile division of ranked mean symptom scores. Scores over these symptom groups appeared to differ first in the number of days on which symptoms were present and thereafter both in this respect and in the number of symptoms reported on such days. There was no difference over groups in terms of the number of children who tested positive in atopic skin tests. It would be expected, therefore, that all groups would be similar in terms of upper respiratory symptom presentation arising from the presence of atopy.

Results showed that those with high symptoms had twice the level of high threat long-term stress recorded compared to those with low symptoms. One might think, therefore, that 'complainer syndrome' may have played a role in symptom reporting for this group, especially within a context of increased chronic adversity. However, cursory examination showed that while groups reported differing levels of such experiences, the actual proportions of such experiences for each group found to be 'related to the behaviour of the child' and/or 'related to the behaviour of the family' did not differ. In other words, children with high symptom levels, were not at increased risk of bringing about their own chronic adversity compared to those reporting low symptoms. Similarly, while children with high symptoms reported an increased

number of 'colds' for the purpose of being swabbed, a higher *percentage* of such swabbed 'colds' obtained positive results, compared to those for other groups, where one might have expected a similar proportion or indeed, a smaller proportion, if symptom reporting had been exaggerated in this high group.

There is no reason, therefore, to conclude that 'complainer syndrome' was more prevalent in one symptom group compared to another. Symptom reports were further corroborated by the fact that independently recorded episodes of asthma in the children also tended to increase over different symptom levels. Asthma episode level, in turn, was found to be consistent with standardised British Thoracic Society scores allocated to the children on the basis of prescribed medication.

In this study, the children reported symptoms on just over one third of days over a one year period and, on such days, an average of 1.7 upper respiratory or nasal symptoms were reported. These included symptoms such as blocked nose, runny nose, sore throat, etc. Surprisingly, no effect of age, gender or social class was found either for the number of days on which upper respiratory symptoms were reported or for the number of symptoms reported on such days. For example, previous studies have reported a tendency towards increased severity of asthma in lower socioeconomic groups (Strachan, Anderson, Limb, O'Neill & Wells, 1994).

It was also unexpected to find a noticeable upturn in upper respiratory symptom presentation on a Sunday when such a change might have been expected at the start of the school week, on a Monday. Symptom morbidity related to upper respiratory infection is generally more frequent during periods of school attendance. As an explanation for this, clinicians suspect that a number of environmental factors such as increased exposure to other children and their viruses on return after school holidays, poor ventilation in the classroom, central heating systems, etc., may account for increased respiratory morbidity in such periods. Similarly, clinicians would no doubt attribute a significant increase in the level of upper respiratory symptom presentation

on Mondays to such factors. However, in this study, increased symptom reporting on Sunday compared to Saturday (when reporting was at its lowest level) was almost significant at the 0.05 level whereas increased reporting between Monday and Saturday was significant at this level. Sunday, and not Monday, therefore, may signal the upturn in symptom presentation which occurred at the beginning of the week. This increase in symptom presentation on Sunday may arise from some artefact of symptom diary completion. However, it may point to a role for other psychosocial factors. For example, the effects of "rainy days and Mondays" in industry have been well documented. The worst of such effects have been reflected in statistics such as an increased number of suicides on a Monday compared to other days or to an excess of cardiac deaths on such days (Rabkin, Mathewson & Tate, 1980). It could be concluded that increased symptom reporting at the beginning of the week may be related not only to the fact that children ***do*** return to school on Monday but that they ***will*** be returning to school on Monday. Further, while not the subject of the present study, a perusal of the commencement of independently recorded episodes of asthma showed that an increased number of such episodes clearly occurred on a Sunday compared to other days in the week.

14.2 Upper Respiratory Symptoms and PACE Measures (LTEs)

With the presence of increased levels of high threat chronic stress in those with high symptom levels, the null hypothesis in the present study which predicted no relationship between these variables has to be rejected. The majority of these long-term high negative experiences were related to illness in the family and to family and social relationships of a negative nature. Setting aside those experiences, related to illness in the child or family, approximately 7 in 10 of all other high threat long-term experiences were related to the behaviour of the family with only one tenth of this proportion also being related to the behaviour of the child. In this study, a mean of 2.1 long-term experiences with high negative impact on the child were recorded over a *one-year period*. This is consistent with results presented in the PACE reliability study (Sandberg, Rutter, Giles, Owen, Champion, Nicholls, Prior, McGuinness &

Drinnan, 1993) which reported a mean of 2.7 such experiences over an *18 month period* for healthy controls and a mean of 4.8 for psychiatric cases, in this London study. Clearly, however, the family play an important role in bringing about the majority of these high negative experiences.

A number of reports in the literature on chronically-ill children have summarised factors contributing to the increased social, personal and financial burden associated with the presence of such illness (Lenney, Wells & O'Neill,1994). On the whole, however, this sample of children with asthma appear to be experiencing a 'normal' level of chronic stress when compared with *London* controls. However, comparing the mean of 3.2 high negative experiences in the high symptom group to the control mean of 2.7, for a longer 18-month period, this represents a high level of chronic adversity impacting on the lives of children reporting high symptom levels. Results in the present study indicate that the relationship between ***current*** upper respiratory symptom levels and ***prior*** long-term high threat stress (mean duration 40.9 months) may be a causal one. The average duration of such experiences leads to the conclusion that, in theory, one might be able to predict future upper respiratory symptom morbidity levels from a current measure of chronic adversity in the children's social and family background, with the majority of these adverse experiences reflecting the presence of illness in the family together with negative family and social relationships.

Increased levels of chronic high threat stress appear to predispose children to high symptom levels, irrespective of age, gender or social class of the child. Boys may be at slightly increased in this relationship. Positive long-term experiences may possibly play some protective role in this relationship, but the evidence for this is relatively weak. In addition,whether it may be the psychological effect of such positive experiences or their physical effect on children which may play a mediating role and have a beneficial effect on asthma would have to be the subject of further investigation.

Results also show that overall levels of long-term stress, not necessarily of high threat impact, and long-term positive experiences are both negatively related to social class. This may explain why some reports, although somewhat controversial, have found a relationship between the prevalence and severity of asthma and social class. Levels of chronic stress may be related to asthma severity, in much the same manner as upper respiratory symptom levels, but studies have not controlled for or measured this stress variable and the possible moderating or protective role of positive experiences.

Certainly, however, one must be cautious in generalising too much since 'asthma severity' does not necessarily equate with 'upper respiratory symptom levels'. However, it should be borne in mind that children with high symptom levels reported a higher number of asthma episodes (mean 3.1), had significantly higher levels of background symptoms and higher mean symptoms in respiratory episodes that comprise illnesses and also reflect peak occurrences in symptom morbidity. They also reported a longer duration of illnesses in terms of such episodes. Further, 77% of those with high symptoms had a high British Thoracic Society medication rating of 4 or 5, while 58% of children with mid symptoms and 50% of children with low symptoms had the same rating. Overall, therefore, there does appear to be some general increase in asthma morbidity over different symptom groups.

The relationship between upper respiratory symptom levels and prior levels of chronic stress found in this study is also consistent with the findings of studies examining the relationship between psychological stress and upper respiratory infection (Cohen, Tyrrel & Smith, 1991; Cohen, Tyrrel & Smith, 1993; Stone, Bovbjerg, Neale,Napoli, Valdimarsdottir, Cox, Hayden & Gwaltney, 1992). Upper respiratory symptom levels in the present study reflect symptom levels both within and between such infections which have been shown to be an important cause of asthma morbidity in children. Cohen et al and Stone et al suggested that the level of prior psychological stress present is related to the production of symptoms in those

infected. The mechanism by which this occurs is not clear. It has been suggested that either viral replication or inflammatory processes might be possible mediating mechanisms between prior stress levels and symptom production in the event of infection. In this study an increased level of virus isolation appeared to occur in high symptom presenters, those with an exceptionally high level of prior stress, compared to children with lower symptom levels. While these children with high symptom levels had an increased number of swabbed illnesses, one would have expected a similar *percentage* of such swabs to be returned positive over different symptom groups. This finding may add some support to Cohen et al's (1993) proposal that viral replication may play a role in symptom production. Increased levels of *chronic* adversity in the children may act to compromise the immune system leaving these children more vulnerable to increased symptom levels. However, in terms of the results in the present study, this vulnerability may relate not only to the development of symptoms in those virally infected but also to the development of symptoms on exposure to other evironmental factors such as allergens and irritants, etc., both within and between such episodes of infection.

These findings are somewhat consistent with a biopsychosocial model of stress, where the individual and combined effects of a number of environmental factors result in outcomes such as increased disease severity and decreased levels of psychosocial functioning. The combined effects of a range of environmental factors on symptom morbidity and prevalence in children with asthma, including the role of psychological stress and socioeconomic status in these processes, should be the subject of future study. A recent survey has found a trend towards more 'diagnosed asthma' and increased severity of illness in the less privileged or lower socioeconomic groups (Strachan, Anderson, Limb, O'Neill & Wells, 1994). The level of chronic adversity present may be a predisposing risk factor in disease prevalence and severity in these groups and the coping ability or level of 'psychosocial functioning' of the child with asthma may play a moderating role. This coping ability can be moderated

by a number of variables including the psychological 'adjustment' of the child as reflected in measures such as self-esteem. A discussion of these results follows.

14.3 Upper Respiratory Symptoms and Psychological 'Adjustment'

An investigation of measures of self esteem in the children found significant but weak correlations between Harter subscale scores and upper respiratory symptom levels, particularly so in the case of the Behaviour subscale. When the scores for boys and girls were examined separately only the correlations for boys remained significant. This was so for all subscales except, surprisingly, the Athletic subscale. The Global Self-worth subscale showed the highest correlation with symptom levels. Further investigation showed that scores over the different symptom groups did not significantly differ for girls, although the Behaviour subscale approached significance. However, for boys, a significant difference was found between low and high symptom presenters on both the Behaviour and Global subscales. Boys with higher symptom levels perceived themselves as less well-behaved and with a lower sense of global self-worth compared to those with low symptom levels.

Overall, this relationship between self-esteem and symptom levels is consistent with reports in the literature relating psychological adjustment to measures of disease severity (MacLean, Perin, Gortmaker & Pierre, 1992). Nevertheless, this is surprising in that a comparison with scores of children from a normative sample showed that the children with asthma reported normal levels of psychological 'adjustment'. This finding is *inconsistent* with the same literature which proposes that children with chronic illness such as asthma are at increased risk for decreased psychological adjustment and have lower levels of psychological adjustment in comparison with their healthy peers (Cadman et al, 1987; Gortmaker et al, 1990; Pless & Roghmann, 1971; Wallander, Varni, Babani, Banis & Wilcox, 1988; Seigel, Golden, Gough, Lashley & Sacker, 1990; Graham, Rutter, Yule & Pless, 1967). The normative scores were obtained from 3,886 schoolchildren living in a different area of Scotland

(Lothian region) from the asthma sample (Strathclyde region) and the present study also lacked a control group. Results would have to be interpreted in this light.

The question therefore arises why the children with asthma should report normal levels of self-esteem in comparison with healthy peers while, at the same time, report a relationship between symptom levels and self-esteem scores, particularly in boys. One would expect the children to have lower levels of adjustment compared to healthy peers if symptom levels were negatively related to self-esteem. Because of such inconsistencies, it was considered that measures of self-esteem may be related to symptom levels through some other factor. This was the case. Results showed that both high negative impact long-term experiences and self-esteem were related to symptom levels in boys and, when investigated, a correlation was found between these high threat experiences and self-esteem measures, but only on the Behaviour subscale. However, when controlling for the presence of high threat experiences, the correlation between self-esteem and symptom measures was no longer significant. These findings may partly explain why a number of studies have found mixed results when examining psychological adjustment in children with asthma. While these studies may control for factors such as social class, they have not controlled for the presence of chronic adversity or, indeed, for long-term positive experiences such as participation in a sport or hobby. While a relationship has been found between such experiences and social class in the present study, not everyone with low social class will have higher levels of negative experiences and/or lower levels of positive experiences. To complicate matters, results show that this inverse relationship is more like to occur in boys than girls.

It would appear that boys are more vulnerable to the presence of chronic stress of a long-term nature than girls. Again, it is not clear why this should be so. The triad of symptom measures, high threat long-term experiences and self-esteem in boys appear to be interrelated through self-perception scores on the Behaviour subscale of Harter's questionnaire. Considering the ***prior*** nature of high threat long-term experiences, it

may be that the relationship between current measures on the Behaviour subscale and symptom measures arises because of the relationship found between this subscale and the presence of prior adversity. This is confirmed by the lack of significance between symptom measures and subscale scores when controlling for such adversity. Therefore, long-term stress may predispose all children to high symptom levels with self-esteem levels, however, playing some moderating role in this relationship, especially in the case of the Behaviour subscale, and particularly so for boys. This proposal is consistent with the findings both of overall normal levels of self-esteem in the children with asthma and the particularly high level of chronic adversity to which these children are exposed, as has been shown in the previous comparison with London controls.

How then might boys who perceive themselves as less well-behaved report increased symptom levels in comparison with others who report lower symptom levels? These children may be indulging in behaviours which give rise to increased symptom levels, particularly so within a context of high chronic stress. In the Hoare et al (1993) normative study, the Behaviour subscale was the only subscale on which boys scored consistently lower than girls over school years. In the Secondary school years, however, scores on the Behaviour subscale for boys and girls can be seen to level out. Possibly one of the mechanisms which underpins these relationships in children with asthma, particularly within an environment of relatively high chronic stress, is non-compliance with medication or other behaviours which result in the maintenance of illness. Matus (1981) has suggested that children may appear apparently well-adjusted but present with a number of compliance problems which effect the management of illness and which may be ***stress-related***. Increased upper respiratory symptom levels, therefore, may be mediated by the effect of long-term psychological stress on the immune system or by other behaviours such as non-compliance with medication. This is particularly so in the case of boys. However, it should be noted that differences over symptom groups on Behaviour subscale scores for girls approached significance.

Boys with high symptom levels also significantly differed from those with low symptoms on scores on the Global Self-worth scale. In her original standardisation study, Harter (1985) found that physical attractiveness was the subscale most strongly associated with global self-worth. In younger children, the social acceptance, athletic competence and physical appearance subscales clustered together, perhaps implying that athletic prowess or physical atractiveness may lead to increased acceptance and popularity among peers. These subscale intercorrelations are not evident when children are older. The clear negative relationship found in this study between upper respiratory morbidity and global self-worth in boys may possibly be related to the fact that boys place increased importance on athletic prowess, an activity which may be restricted by asthma morbidity. If this was the case, however, one would have expected scores on the Athletic subscale to play a more significant role in analyses. This was not the case. It may be, therefore, that these scores are more related to negative perceptions regarding general behaviour rather than to perceived athletic competence and self-esteem.

In conclusion, therefore, low scores on the Harter Behaviour subscale and reduced perceptions of global self-worth, particularly within a context of high chronic stress, which may predispose children to high symptom levels, may help to identify those children at increased risk for higher levels of upper respiratory morbidity. This relationship may possibly be mediated by behaviours such as non-compliance with medication or by the immunosuppressive effects of long-term psychological stress on the immune system. There may also be gender differences in this relationship. These relationships appear to be stronger in boys than girls. However, results show that prior high threat stress influences general upper respiratory symptom morbidity irrespective of age, gender or social class. As previously mentioned, this symptom morbidity reflects the occurrence of symptoms both within and between more prolonged period of upper respiratory illnesses. The discussion which follows show

that girls are at increased risk of reporting higher levels of upper respiratory infections compared to boys.

14.4 URIs

On the average, about half of all days on which symptoms were reported occurred in periods of increased respiratory morbidity. This study employed a similar method to that used by Clough & Holgate (1994) to identify these significant episodes of respiratory morbidity. The number of upper respiratory episodes recorded were consistent with the findings of Mertsola, Ziegler, Ruuskanen, Vanto, Kolvikko & Halonen (1991). Mertsola and colleagues identified respiratory episodes, albeit in younger children, with measures based partly on upper respiratory symptom morbidity. A mean of 7.7 respiratory episodes were recorded for the children with asthma in this study over a one year period while Mertsola & colleagues recorded a mean of 2.1 episodes per 3 month period in their younger 1 - 6 year old subjects with severe symptoms. The majority of reports of illnesses coincided with at least one such respiratory episode or, more accurately, a cluster of such episodes. Since studies have shown that respiratory problems following respiratory tract infection in children with asthma can often extend for a period of up to 6 weeks (Hers, 1966; Camner, Jarstrand & Philipson, 1973; Empey, Latimen, Jacobs, Gold & Nadel, 1976), the occurrence of a number of 'episode-free' periods of at least 6 weeks duration were therefore used as markers to separate and identifiy the occurrence of more prolonged illness periods. The illnesses thus identified coincided with all subject reports of illness in the diary, except for a further 4 reported 'colds'.

In relation to the validity of these reports, a number of researchers consider that definite 'cold' episode reporting is not correlated with Neuroticism (Evans et al, 1988), often taken as a measure of 'complainer syndrome', whereas the reporting of aches and pains and general body symptoms is so correlated. This would suggest that subjects in this study were probably reporting what they considered to be acute episodes of upper respiratory tract infection or 'colds'/'flu. While child and main

caregiver may be confidently reporting what they consider to be acute episodes of upper respiratory infection or 'cold'/'flu, research criteria has demanded that the identification of an episode of infection should involve the isolation of the etiologic agent or an increase in antibody titer or both. However, since research has already established that the majority of exacerbations of asthma are brought about by upper respiratory infection, careful evaluation in terms of clinical symptoms may more clearly suffice in studies examining the relationship between psychological stress and the occurrence of infection in children with asthma.

About one-half (47.4%) of all reported upper respiratory tract infections in this study were swabbed with one-half of these showing a positive result. There was therefore an overall low verification rate (24% of all reported URI) for the microbiological detection of viral infection. While a higher percentage of positive results have been found in other studies, it should be noted that in this study not all viral agents capable of giving rise to an episode of 'cold' or 'flu were tested for. Throat swabs are not a particularly efficient method of viral detection. They can also be an uncomfortable and intrusive method for detection of virus and this may have deterred some children from informing the Project Office that a cold was ongoing. A naso-pharyngeal swab would have been more efficient but, at the same time, as with other methods, it is more intrusive and thus would probably have been less acceptable to the children. The use of throat swabs was, therefore, the least intrusive method available and throughout the study both children and parents were encouraged to record the occurrence of a cold whether or not they were able to contact the office.

Results from microbiological tests also indicated that the majority of infections were attributable to humanrhinovirus which appears to be consistent with other reports of the predominance of this virus in the etiology of URI (Gwaltney et al, 1966; Johnson, Sanderson et al, 1992; Johnson, Pattemore et al, 1995). Results showed that just over 70% of all paediatrician-recorded episodes of asthma coincided in time with a reported upper respiratory infection and/or a lower respiratory 'chest infection'.

Bearing in mind that results in the present study indicate that 9 to 11 year old children may be at increased risk of reporting such infection, this figure is consistent with other reports in the literature which have already confirmed that 80% of asthma exacerbations, in a community sample of *9 to 11 year olds*, were associated with upper respiratory infection with HRV being responsible for 50% of these episodes (Johnson, Sanderson, Pattemore, Smith, Bardin, Bruce, Lambden, Tyrell & Holgate, 1992; Johnson Pattemore, Sanderson, Smith, Lampe, Josephs, Symington, O'Toole, Myint, Tyrrell & Holgate, 1995). The majority of reports which were not corroborated by the identification of virus, were found to be associated with a visit to the GP when antibiotics were prescribed or were temporally associated with a paediatrician recorded episode of asthma or both. Only about 1 in 5 of all reported URI were not associated with a recorded asthma episode or GP visit.

When a comparison was made over symptom groups, this showed that high symptom presenters reported a similar number of colds to mid symptom presenters. However, a methodological flaw is present in such an analysis. A symptom group comparison may not accurately reflect the relative incidence of URI morbidity over different symptom levels. For the high symptom group, with more perennial symptom levels, there may be an upper or 'ceiling' limit both to the number of symptoms a child may report in any one day and to the number of upper respiratory infection reported over a given period in comparison with other children. For example, if a child reports on average 4 or 5 symptoms per day over the period of the study, the threshold for increased symptom reporting in the event of infection is effectively reduced compared to those children who have a relatively low level of background symptom presentation. The occurrence of an infection is not going to bring about a radical change in symptom reporting in such children. Further, it may be that the Respiratory Episode criterion level was not as efficient in identifying such episodes at a higher level of symptom presentation compared to a lower level where the difference between distinct episodes of repiratory morbidity and background symptoms was more clearly defined. In addition, the occurrence of a more perennial pattern of

symptom morbidity, both within and between episodes of illness, will impose a constraint on the number of infections which can be reported *over a given period,* in comparison with other symptom groups. Under such circumstances, the siimilar number of 'colds' found in those with high symptom levels (mean 2.2) compared to those with mid symptom levels (mean2.3) may not accurately reflect the relative incidence of colds in these groups .

14.5 URIs and PACE Measures (LEs and LTEs)

For reasons already outlined above, an analysis investigating the relative risk of a URI being preceded by a high threat event within a 6-week period *over symptom groups* was considered to be of limited value. Analsyses were therefore confined to examining the risk of this relationship occurring in the group of children in general.

The children reported a mean of 4.8 high threat events. While both the child and family tended to bring about the majority of positive life events, in the case of negative events approximately one-third of all such events were related to the behaviour of the child or family. On breaking these events down according to the temporal nature of the threat involved, this showed that the children reported a mean of 3.3 high threat events of a short-term nature and a mean of 1.5 high threat events of a long-term nature. These figures in this one year study are again very consistent with findings in the London PACE reliability study where controls reported a mean of 4.0 short-term high threat events and 2.1 long-term high threat events as opposed to a mean of 4.4 in each of these types of events in psychiatric cases, over a longer 18-month period. Overall, children with asthma appear to be reporting normal levels of stress in comparison with healthy controls. However, the burden of chronic illness combined with airways vulnerability may still leave these children at increased risk in the stress-illness relationship.

In this study, high threat events related to school, leisure, pets and frightening or unexpected events were more likely to be of a short-term nature. High threat events

arising from family relationships, marriage, friendships and sexual relationship tended to give rise to events of a long-term nature. Results indicate that children, aged 9 to 11 years, were at increased risk of reporting increased numbers of high threat events. Girls were also at significant risk of reporting such events, specifically those events of a high long-term threat nature. It may be, therefore, that girls are exposed to a different kind of psychological stress compared to boys. The same group of children i.e. 9 to 11 year olds and girls, were also found to be at increased risk of reporting a higher number of URI. Further, subsequent analyses indicated that these children were significantly more likely to report a high threat event of a ***long-term*** nature in the 6-week period prior to the commencement of a URI compared to the same period following the start of a URI.

There was also some indication that high chronic adversity and levels of positive experiences may play a role in the temporal relationship between acute event and the occurrence of infection. However, the evidence for this was relatively weak. These results, therefore, are somewhat inconsistent with reports in the literature that suggest long-term stress may provide a mediating link between life events and adverse illness outcomes (Glickman, Tanaka & Chan, 1991; Brown & Harris, 1978, 1989; McGonagle & Kessler, 1990; Pearlin, Menaghan, Lieberman & Mullan, 1981) especially those events which arise from ongoing stress (Goodyer, 1990; Sandberg et al, 1993). Therefore, while chronic adversity may predispose all children with asthma to increased levels of upper respiratory symptom morbidity, for girls, such stress appears to play no particularly significant role in the temporal relationship between high threat acute event and the occurrence of an upper respiratory infection. Such matters, however, would have to be the subject of further study.

The results of this study are consistent with the community study conducted by Graham, Douglas & Ryan (1986) who found that female sex and age were important correlates of respiratory illness. The present results are also consistent with reports in the life event literature. High threat acute events, relatively long-term in threat impact

i.e. where the threat impact endures for at least 10 days to 2 weeks after the initial occurrence of the event, and not those with short-term threat, have been considered to give rise to the risk in the relationship between psychological stress and illness in ***adults*** (Brown & Harris, 1989). Whether this is also the case for children has yet to be established. However, findings in this study indicate a similar role for high threat long-term events in the stress-illness relationship in children. Girls with asthma appear to be more inclined to react to psychological stress of a more ***acute*** high threat nature, the negative effects of which tend to linger for a period of about two weeks or so. Circumstances surrounding family relationships, friendships and sexual relationship tend to give rise to such events of a long-term nature. Clearly such relationship events play an important role in stress-illness processes in girls.

Before moving on to further discussion of these results, a comment should be made about the 'before/after' analysis employed in this study. This analysis was based on the proposal that the occurrence of events prior to the start of an illness will exceed those following the start of the illness. However, if an event is capable of precipitating a URI, it may also be the case that ***anticipation*** of an event rather than the actual occurrence of the event itself will also precipitate an episode of illness. A child's prior knowledge that a dance exam will occur in three weeks time may be related to the development of a URI before that date. The nature of an event and prior knowledge of its occurrence may be factors which contribute to ***an illness preceding an event***, rather than the opposite being the case. The PACE instrument for the measurement of stress, nor any other for that matter, takes account of this factor. A separate rating should perhaps be included in life event interview-based instruments for the measurement of stress relating to 'prior knowledge of the occurrence of an event'. Consideration must also be given to the fact that the occurrence of a high threat life event may subsequently give rise to or be associated with the occurrence of a further event(s). An event occurring prior to a URI, therefore, could be causally related to the occurrence of an event after the start of the illness. High threat events related to family relationships can give rise to such a sequence of events. For

example, the occurrence of a high threat event related to a family or marital problem, such as father leaving the home, may precede a URI but also subsequently give rise to another related high threat event(s), such as the news that father was living with another woman. It was not considered that these methodological shortcomings would have a significant effect on the results of this study and, if anything, may add support to them.

Because of attrition of subjects in this study, another source of error may be the slight underrepresentation of children from lower social class groups. Results show that such children are at increased risk of reporting significantly higher levels of chronic stress and lower levels of positive experiences. The presence of such stress may have given rise to circumstances or events which resulted in non-completion of diaries. The external validity of results relating to within-groups analyses may be affected in that such results may be slightly underrepresented in terms of these social class groups. However, results relating to psychological adjustment and the comparison of Harter scores with the normative sample are unaffected since the children in that sample were also underrepresented in terms of children in lower social class groups. The internal validity of results relating to between-groups analyses may also be slightly affected. However, the ranked division of children into equal groups based on symptom presentation should minimise any between-group effect normally associated with the random allocation of subjects into groups.

In conclusion, therefore, two questions must be asked. (1) Why should girls be more vulnerable to the occurrence of acute life events of a more long-term high threat nature in comparison with boys, while boys appear to be more responsive to psychological stress of a long-term nature? (2) Why are girls significantly more likely to report an increased number of such events compared to boys?. Perhaps an answer to both questions rests in the possibility that girls are more likely to become enmeshed in relationships, particularly family relationships, compared to boys who might be more inclined to be involved in outdoor activities. Girls, thus may be exposed to a

higher number of such relationship events than boys. They may also tend to respond more immediately and emotionally to these relationship events in which they have become involved. Boys, on the other hand, may be more cognisant of and responsive to the presence of more *long-term psychological stress* in their family, school and social background. Reports in the literature have already suggested that sympathetic nervous system activation in response to psychological stress in females, both children and adults, may be different to that for males and thus boys and girls may be coping differently both psychologically and physiologically to such stress (Johansson, 1972; Johansson & Post, 1972; Frankenhaeuser, 1975; Cox 1987). In another study, Zlatich et al (1982) reported that, on the basis of medical management of illness in children and adolescents, female non-responders reported their mother's behaviour as more intrusive compared to females who responded well to medical treatement. Interestingly, males who did not respond well to medical treatment perceived their mothers as granting a higher degree of autonomy than those who did respond well. These researchers also found that the mothers of non-responders experienced a significantly greater number of undesirable life events than mothers of responders. Female non-responders also reported significantly more undesirable life events in the previous year than female responders. Zlatich et al (1982) concluded that in these female children with asthma, greater numbers and severity of life events appeared to be associated with less favourable responses to medical treatment. This study was based on a checklist measure of stress and did not examine the temporal relationship between such events and disease course. It is difficult, therefore, to draw any conclusions. However, this study is of interest in that it concludes that these female children and adolescents with asthma experience an increased level of background stress and that family interaction in the form of the mother-child relationship plays a role in asthma severity and management of the disease. It is also interesting to note gender differences in the nature of the mother-child relationship and the subsequent effect on severity of disease. The present study employed a more methodologically advanced measurement of acute and chronic stress. However, whether subjective or objective ratings of threat impact in this interview-based measure are more predictive

of illness would have to be the subject of further investigation. Nevertheless, a similar finding that girls in this study are at increased risk of reporting increased levels of high threat acute life events, particularly of a long-term nature, should certainly be a matter for further study.

On the question of gender difference in susceptibility to URI in children in the community, the literature lacks clarity. Findings of the Tuscon study (Martinez et al, 1995) do not rule out a role for upper respiratory infection in the onset and course of asthma morbidity together with a role, along with other factors, in determining the age when wheezing symptoms may begin at a later age. It is also interesting to note that the studies by Johnson and colleagues (1992, 1995) which found the presence of viral pathogens in 80% of asthma exacerbations, were conducted on a community sample of 9 to 11 year olds. If examined, would a similarly high percentage of exacerbations be found in older or younger children and would these rates be similar for both boys and girls? In this study, girls reported a higher mean number of asthma episodes (mean 3.5) compared to boys (mean 2.0). These levels of asthma morbidity are consistent with the finding in this study of increased levels of URI in girls, particularly 9 to 11 year olds. Such increased upper and lower respiratory morbidity in girls compared to boys and the possible effect on lung function may begin to explain the gender crossover in prevalence of asthma which generally starts in the mid-teen years and results in a female predominance in prevalence by the age of 20 years.

In relation to the latter point, a number of interesting reports have emerged from the Medical Research Council, Medical Sociology Unit, in Glasgow (MacIntyre, 1993; Sweeting, 1995) MacIntyre examined data obtained from 1700 subjects, men and women who had participated in research at the Common Cold Unit in Salisbury. This showed that females were significantly more likely than men to get colds when they were at the Unit. Results also indicated that these colds were more likely to be rated by a trained clinical observer as being more severe. However, men were significantly

more likely than women to 'overrate' their signs and symptoms compared to the clinical observer. She felt that these results supported a "whingeing male" hypothesis and suggested that differing thresholds for perceiving and reporting symptoms may produce underestimates of gender differences in morbidity. These differing thresholds are thought to arise from childhood socialisation as well as from adult role expectations and obligations.

Sweeting (1995), on the other hand, has investigated health in childhood and adolescence. Her paper reviewed findings on sex differences in health in 7 to 15 year olds. Sweeting concluded that there was a gradual emergence of excess morbidity in females over this life stage. Examining some large scale surveys, she reported that, among females, an excess of psychological disturbances and overall levels of chronic illness (including asthma and migraine) arise in early-mid adolescence with sex differences in the utilisation of health services appearing to mirror this excess morbidity. Sweeting concluded that this pattern may be related to the relative lowering of the psychological well-being of females during early adolescence.

In their normative study, Hoare et al (1993) also discuss epidemiological findings showing an increase in mood disturbance among adolescent girls (Rutter, Graham, Chadwick & Yule, 1976) to explain the general decline in Subscale scores evident in girls over Primary and Secondary school years. Both Harter's standardisation study (1985) and the normative Scottish study indicate that boys' perceptions of themselves are different from girls. Generally, boys rate themselves higher than girls on most subscales except on the Behaviour subscale. This widening of the gap in levels of self-perceptions between boys and girls, may leave girls more vulnerable in the stress illness process as they grow older. This is similar to what Sweeting (1995) is suggesting.

A number of factors, therefore, may contribute to this gender crossover in asthma morbidity. In addition to an early airways vulnerability in boys, these may include:

early socialisation processes related to illness behaviours; decreasing levels of self-perceptions in girls; chronic adversity and negative family relationships; increased levels of high threat life events in girls and increased risk in the temporal relationship between acute high threat life event and illness. This study shows that while both boys and girls may be vulnerable to chronic adversity in terms of general upper respiratory symptom presentation, girls appear to be more vulnerable to acute stress and are at increased risk of responding to such stress with upper respiratory infection. This increased vulnerability may be related to the finding that girls are at increased risk of reporting higher levels of such stress.

The combination of all of these factors and processes may result in increased asthma morbidity *over time* in female children. Research has clearly demonstrated that the majority of exacerbations of asthma are brought about by upper respiratory infection to which such children are vulnerable. It is interesting to note that some researchers investigating the prevalence of diagnosed asthma, wheezy illness and atopic disease in general have found some gender differences in the relative ratio increases in prevalence rates of diagnosed asthma, hay-fever like symptoms and eczema (Ninian & Russell, 1992; Powell & Primhak, 1996). It has been suggested that the mechanisms which mediate the relationships between these different types of atopic illness may be different for boys than for girls and may not be attributed solely to genetic predisposition (Ninian & Russell, 1992).

These findings suggest that the gender crossover in asthma prevalence and morbidity will occur at an earlier age in males and females as time and asthma morbidity increases. Perhaps the nature of these mechanisms and the role played not just by physical environmental factors but also by psychological factors in the recorded prevalence and morbidity of asthma should be made the subject of future study.

CHAPTER 15

CONCLUSION

No relationship was found in this study between psychological adjustment as reflected in anxiety measures and upper respiratory symptoms or infection. Otherwise, all of the null hypotheses in the present study were rejected and results show that psychological factors may play a role in a number of aspects of upper respiratory symptom presentation and in the occurrence of URI and that these differences may be gender related:

15.1 Clinical Implications

On the basis of the findings of this study, therefore, a number of clinical implications are outlined below:

- Overall, asthma treatment strategies should be approached differently for boys and girls since each appear to be presenting with different patterns of upper respiratory and asthma morbidity. For example, boys may benefit more from treatment strategies, both medical and psychological, aimed at reducing the day to day occurrence of upper respiratory symptom morbidity. Those with lower levels of Global Self-worth and who perceive themselves as relatively less well-behaved than their peers, particularly within a context of high chronic stress, should perhaps be the particular target of such treatment. It may be that such children also have problems relating to compliance with medication and treatment strategies aimed at dealing with such problems might be beneficial.

- Since 9 to 11 year old girls are at increased risk of reporting higher levels of upper respiratory infection, treatment aimed at reducting or preventing inflammatory responses may be generally more beneficial to these children. It should also be considered that these girls are significantly more likely to have an infection preceded by a particularly highly threatening event within a 6-week period. Effective management of asthma at periods when such girls might be especially vulnerable may help to reduce the inflammatory sequelae to upper respiratory infection.

- Paediatricians should encourage inoculation against 'flu with the aim of reducing increased susceptibility, particularly in girls. In addition, since *symptomatic* infection plays an important role in asthma morbidity, steps should be taken, as far as is possible in children with asthma, to vigorously attack URI symptoms immediately they appear. Prior stress, through its immunosuppressive effects, may possibly play a role in the development of symptoms in those infected. However, the development of symptoms may also arise, for example, from factors such as nasal blockage, etc., which may leave children at increased risk of infection and inflammatory processes via a more direct route i.e. mouth-breathing. Results showed that in this sample of children with asthma, those with high upper respiratory symptom levels differed from those with low levels in both the number of days on which upper respiratory symptoms were reported and on the number of symptoms reported on such days. Children with low and mid levels of symptoms differed only in the number of days on which symptoms were reported. Reducing the number of days on which children report upper respiratory symptoms, whatever the cause and by whatever means, may in the long-term help to reduce general levels of symptom morbidity in children with asthma.

15.2 Research Recommendations

The following research recommendations are made.

- Patterns of symptom reporting over days in the week should be investigated.
- Measures of high threat negative experiences together with positive experiences of a long-term nature should be included in studies investigating both psychological 'adjustment' and the role of social class in asthma morbidity. Gender differences in these relationships should also be investigated.
- The occurrence of psychological stress in children with asthma and gender differences in the occurrence of acute stress in such children should be studied.

- Gender differences in sympathetic nervous system responses to psychological stress and coping with such stress should be the subject of further study especially in relation to children with asthma.
- Gender differences in susceptibility to URI over time in children and the role of psychological factors in these processes should be studied, particularly in children with asthma.
- The role of levels of prior chronic psychological stress both in the development of symptoms in those virally infected and in the symptomatic response to a number of allergens and irritants in the environment should be investigated.
- Non-compliance with medication and its relationship to measures of self-esteem and chronic stress should be examined, particularly in boys.

Findings from such studies should be fully integrated into a biopsychosocial model of disease. As Lask (1992) has suggested that while there is little the paediatrician can do to cure the ills of society befalling some of the children who may walk through his door, he may well be able to detect at an earlier stage illness behaviours which in the long term, within an adverse psychosocial context, may exacerbate the course of asthma.

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TABLES

Table 1: Atopy prevalence rates of 8 to 13 year olds in Aberdeen in two surveys 25 years apart (1964-1989). (Extracted from data of Ninian & Russell, 1992.)

Prevalence of:	1964 %	1989 %	Ratio Increase
Wheeze	10.4	19.8	1 : 1.9
Shortness of Breath	5.4	10.0	1 : 1.9
Diagnosed Asthma	4.1	10.2	1 : 2.5
Boys	2.8	6.6	1 : 2.4
Girls	1.3	3.8	1 : 2.9
Boy/Girl Ratio	2.1 : 1	1.7 : 1	
Eczema	5.3	12.0	1 : 2.3
Boys	2.5	7.2	1 : 2.9
Girls	2.8	4.6	1 : 1.6
Boy/Girl Ratio	0.9 : 1	1.6 : 1	
Hay Fever	3.2	11.9	1 : 3.7
Boys	1.6	7.2	1 : 4.5
Girls	1.6	4.7	1 : 2.9
Boy/Girl Ratio	1 : 1	1.5 : 1	

Table 2: Demographic details of children participating in study of upper respiratory morbidity and psychological stress.

	Girls n=37	Boys n=41	All n=78
Age			
< 9 yrs	14	13	27
9 to11 yrs	12	18	30
Over 11 yrs	11	10	21
Social Class			
I & II	9	16	25
III & IV	19	16	35
V & VI	9	9	18
BTS Score*			
2	1	0	1
3	14	15	29
4	12	15	27
5(a & b)	10	11	21
Atopic status**			
Positive	31	37	68
Negative	3	2	5
No skin-tests	3	2	5

***BTS score is a score based on the treatment step of the British Thoracic Society guidelines for patients**

****Atopic status is determined by nature of inflammatory response to skin test involving a number of allergens**

Table 3: Distribution of *chronicity of symptoms in subjects (n=78).**

Symptoms were reported by:	Days (%)
45 subjects (57.7%)	**≥ 25**
21 subjects (26.9%)	**≥ 50**
11 subjects (14.1%)	**≥ 75**

***Chronicity** - *proportion of days on which symptoms were reported*

Table 4: Distribution of *severity of symptoms in subjects (n=78).**

Symptoms were reported by:	**Symptoms** (Mean)
48 subjects (61.5%)	**> 1.5**
20 subjects (25.6%)	**> 2**
6 subjects (7.7%)	**>2.5**

**Severity* - mean number of symptoms reported on symptom days

Table 5: Tukey (Honestly Significant Difference) Table of *differences* in average total symptoms reported by subjects over days in the week.

DAY (mean)	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Sun (31.96)	-	(-)0.93	(-) 0.12	1.34	0.73	1.63	2.19
Mon (32.89)	-	-	0.81	**2.27***	1.66	**2.56***	**3.12****
Tues 32.08)	-	-	-	1.46	0.85	1.75	**2.31***
Wed (30.62)	-	-	-	-	0.61	0.29	0.85
Thurs (31.23)	-	-	-	-	-	0.90	1.46
Fri (30.33)	-	-	-	-	-	-	0.56
Sat (29.77)	-	-	-	-	-	-	-

***p = ≤0.05; **p = ≤0.01**
Tukey HSD (≤0.05) = 2.24
Tukey HSD (≤0.01) = 2.62

Table 6: Demographic details of subjects (by symptom group levels).

	Low symptom level (n=26)	Mid symptom level (n=26)	High symptom level (n=26)
Age*			
< 9 yrs	10	9	8
9 to11 yrs	10	8	12
Over 11 yrs	6	9	6
Sex**			
Female	14	12	11
Male	12	14	15
Social Class***			
I & II	8	12	4
III & IV	12	7	13
V & VI	6	7	9
BTS Score****			
2	1	0	0
3	12	11	6
4	5	9	13
5(a,b)	8	6	7
Atopic status			
Positive	24	22	22
Negative	0	2	3
Not skin-tested	2	2	1

*** $x^2 = 1.88$, NS; ** $x^2 = 0.72$, NS; *** $x^2 = 8.01$, NS; **** $x^2 = 6.44$, NS**

Table 7: Mean symptoms over symptom groups.

	Low	Mid	High
Mean dailysymptoms			
Mean	0.2	0.5	1.4
Median	0.2	0.5	1.1
Standard Deviation	0.1	0.1	0.6
Range	0.0 - 0.3	0.3 - 0.7	0.7 - 2.8

Table 8: Chronicity and severity of symptoms over symptom groups.

	Low	Mid	High
Symptom chronicity (% of days on which symptoms reported)			
Mean	11.5	30.4	68.8
Median	11.01	31.3	72.9
Standard Deviation	5.3	9.6	22.8
Range	0.6 - 22.3	13.6 - 52.1	32.9 - 100.0
Symptom severity (number of symptoms on symptom days)			
Mean	1.5	1.6	2.0
Median	1.4	1.6	2.0
Standard Deviation	0.4	0.4	0.4
Range	1.0 - 2.5	1.1 - 2.7	1.2 - 2.9

Table 9: Results of Analysis of Variance investigating the effects of symptom group levels, gender, age and social class on *SYMPTOM CHRONICITY.*

Source	d.f.	F	p
Symptom chronicity			
Symptom groups	2,52	71.24	**0.000*** **
Gender	1,52	0.36	0.553
Age	2,52	0.41	0.665
Social class	2,52	0.55	0.578
Groups x gender	2,52	0.13	0.878
Groups x age	4,52	1.27	0.294
Groups x social class	4.52	0.87	0.474
Gender x age	2,52	1.90	0.159
Gender x social class	2,52	0.17	0.845
Age x social class	4,52	0.40	0.806

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 10: Results of Analysis of Variance investigating the effects of symptom group levels, gender, age and social class on *SYMPTOM SEVERITY*.

Source	d.f.	F	p
Symptom severity			
Symptom groups	2,52	4.61	**0.014***
Gender	1,52	0.07	0.788
Age	2,52	2.31	0.110
Social class	2,52	1.48	0.236
Groups x gender	2,52	0.01	0.985
Groups x age	4,52	0.61	0.655
Groups x social class	4.52	1.20	0.322
Gender x age	2,52	0.17	0.840
Gender x social class	2,52	0.09	0.913
Age x social class	4,52	0.96	0.436

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 11: Symptom measures within and between respiratory episodes (REs).

Symptom measures	All (n=78)	Low (n=26)	Mid (n=26	High (n=26)
No. of REs (mean)	**7.7**	**7.0**	**7.3**	**8.9**
Boys	8.3	7.3	7.9	9.5
Girls	7.1	6.8	6.6	8.0
Symptoms/day in REs (mean)	**2.5**	**1.6**	**2.4**	**3.5**
Boys	2.6	1.6	2.4	3.5
Girls	2.5	1.6	2.5	3.6
% of all symptom days spent in REs (mean)	**49.0**	**85.1**	**39.2**	**22.6**
Boys	45.6	79.2	42.3	24.0
Girls	52.6	89.3	35.7	20.8
Symptoms/day in periods between REs (mean)	**1.2**	**0.8**	**1.1**	**1.6**
Boys	1.2	0.9	1.1	1.5
Girls	1.1	0.7	1.1	1.6

Table12: Results of Logistic Regression investigating the proportion of children over symptom groups with above median levels of acute *RESPIRATORY EPISODES* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			0.5904	2	0.7444	
< 9 years / 9 to 11 years	0.0455	0.5742	0.0063	1	0.9368	1.0466
9 to 11 years / >11years	0.4069	0.6336	0.4125	1	0.5207	1.5022
< 9 years / >11years	0.4525	0.6298	0.5161	1	0.4725	1.5722
Gender	0.4168	0.4953	0.7083	1	0.4000	1.5171
Social class			2.8837	2	0.2365	
Class I & II / Class III & IV	-1.0276	0.6142	2.7991	1	0.0943	0.3579
Class III & IV / Class V & VI	0.1937	0.6114	0.1004	1	0.7513	1.2138
Class I & II / Class V & VI	-0.8339	0.6976	1.4289	1	0.2319	0.4344
Symptom group			2.6894	2	0.2606	
Low/Mid symptom levels	-0.1968	0.6007	0.1074	1	0.7431	0.8213
Mid/High symptom levels	-0.7439	0.6225	1.4282	1	0.2321	0.4753
Low/High symptom levels	-0.9407	0.5961	2.4902	1	0.1146	0.3903
Constant	-0.1789	0.2515	0.5060	1	0.4769	

Table 13: Results of Analysis of Variance investigating the effects of symptom groups, gender and age on *RESPIRATORY EPISODE SYMPTOM LEVELS.*

Source	d.f.	F	p
Mean daily symptoms per RE			
Symptom groups	2,64	45.38	**0.000*** **
Gender	1,64	0.76	0.387
Age	2,64	2.30	0.109
Groups x gender	2,64	0.15	0.860
Groups x age	4,64	0.55	0.698
Gender x age	2,64	1.76	0.180
% of symptomatic days spent in REs			
Symptom groups	2,64	73.43	**0.000*** **
Gender	1,64	0.00	0.997
Age	2,64	0.32	0.731
Groups x gender	2,64	0.95	0.392
Groups x age	4,64	2.10	0.091
Gender x age	2,64	1.14	0.325
Mean daily symptoms in periods between REs			
Symptom groups	2,64	20.46	**0.000*** **
Gender	1,64	0.22	0.640
Age	2,64	3.16	**0.049***
Groups x gender	2,64	0.78	0.463
Groups x age	4,64	0.29	0.884
Gender x age	2,64	0.49	0.614

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 14: Upper respiratory illness periods across symptom level groups.

Upper respiratory illness periods	All (n=78)	Low (n=26)	Mid (n=26)	High (n=26)
Number(mean)	228 (2.9)	72 (2.8)	81 (3.1)	75 (2.9)
REs per Illness (mean)	2.9	2.7	2.5	3.6

Table15: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *ILLNESS PERIODS* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			1.1381	2	0.5661	
< 9 years/9 to 11 years	0.2701	0.6700	0.1625	1	0.6869	1.3101
9 to 11 years/>11years	0.4820	0.6929	0.4840	1	0.4866	1.6194
< 9 years/>11years	0.7521	0.7114	1.1178	1	0.2904	2.1215
Gender	-1.0159	0.5845	3.0212	1	0.0822	0.3621
Social class			2.6417	2	0.2669	
Class I & II / Class III & IV	1.0476	0.7415	1.9962	1	0.1577	2.8508
Class III & IV / Class V & VI	0.1942	0.6574	0.0873	1	0.7676	1.2144
Class I & II / Class V & VI	1.2418	0.8137	2.3292	1	0.1270	3.4620
Symptom group			4.6626	2	0.0972	
Low/Mid symptom levels	-1.2096	0.6963	3.0178	1	0.0824	0.2983
Mid/High symptom levels	-0.0539	0.7505	0.0052	1	0.9428	0.9475
Low/High symptom levels	-1.2635	0.6750	3.5038	1	0.0612	0.2827
Constant	1.0859	0.3028	12.864	1	0.0003	

Table 16: Results of Analysis of Variance investigating the effects of symptom groups, gender and age on the *MEAN NO. OF RESPIRATORY EPISODES IN ILLNESS PERIODS*.

Source	d.f.	F	p
Symptom groups	2,64	1.61	0.208
Gender	1,64	4.21	**0.044***
Age	2,64	0.93	0.400
Groups x gender	2,64	0.61	0.545
Groups x age	4,64	0.81	0.521
Gender x age	2,64	2.25	0.113

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 17: Classification of all upper respiratory illness periods by subject report.

Reported reason for upper respiratory illness periods	All (n=78)	Low (n=26)	Mid (n=26)	High (n=26)
'Cold' or 'Flu' swabbed				
GP visit	58	10	18	30
No GP visit	27	10	6	11
'Cold' or 'Flu' not swabbed				
GP visit	36	6	20	10
No GP visit	33	12	16	5
Total 'colds'	**154**	**38**	**60**	**56**
(Mean)	(2.0)	(1.5)	(2.3)	(2.2)
(% of all illnesses)	(66.4)	(52.8)	(73.2)	(71.8)
GP visit/hospital admission (antiobiotics prescribed)	**21**	**8**	**6**	**7**
(% of all illnesses)	(9)	(11.1)	(7.3)	(9)
Other illnesses (e.g. 'hay-fever')/no reason	**57**	**26**	**16**	**15**
(% of all illnesses)	(24.6)	(36.1)	(19.5)	(19.2)
Total upper respiratory illness periods	**232**	**72**	**82**	**78**

Table18: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *URI* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			5.2848	2	0.0712	
< 9 years/9 to 11 years	-1.3037	0.6724	3.7593	1	**0.0525**	0.2715
9 to 11 years/>11years	1.5182	0.7716	3.8717	1	**0.0491**	4.5642
< 9 years/>11years	0.2145	0.7660	0.0784	1	0.7794	1.2393
Gender	-1.4758	0.5816	6.4396	1	**0.0112**	0.2286
Social class			2.5499	2	0.2794	
Class I & II / Class III & IV	0.5582	0.7037	0.6292	1	0.4276	1.7475
Class III & IV / Class V & VI	-1.1287	0.7114	2.5174	1	0.1126	0.3235
Class I & II / Class V & VI	-0.5705	0.7780	0.5377	1	0.4634	0.5653
Symptom group						
Low/Mid symptom levels	-1.5663	0.7375	4.5107	1	**0.0337**	0.2088
Mid/High symptom levels	0.4289	0.6991	0.3764	1	0.5396	1.5355
Low/High symptom levels	-1.1374	0.7308	2.4225	1	0.1196	0.3207
Constant	-0.8871	0.2978	8.8739	1	0.0029	

Table 19: Results of microbiological tests on reported URI.

Proportion of swabbed URI with positive microbiological test	**All (n=78)**	**Low (n=26)**	**Mid (n=26)**	**High (n=26)**
URI with GP visit	24/51	3/10	7/15	14/26
URI with no GP visit	13/27	5/10	1/6	7/11
Total swabbed URI with + microbiological test (% of all URI)	**37/78** (47.4)	**8/20** (40.0)	**8/21** (38.1)	**21/37** (56.8)

Table 20: Results of Microbiological Tests (Viruses).

Type of viruses isolated in positive microbiological tests	All (n=78)	Low (n=26)	Mid (n=26)	High (n=26)
Flu A	1	0	0	1
Flu B	7	1	2	4
Rhinovirus	23	6	6	11
Picornavirus	6	1	0	5
Total swabbed URI with + microbiological test	**37**	**8**	**8**	**21**

Table 21: Distribution of paediatrician-recorded episodes of asthma over subjects.

Number of Episodes of Asthma	Number of all children		Number of low symptom presenters		Number of mid symptom presenters		Number of high symptom presenters	
	Girls (n)	Boys (n)	Girls (n)	Boys (n)	Girls (n)	Boys (n)	Girls (n)	Boys (n)
0 - 1	22	9	8	5	6	4	8	0
2 - 3	12	12	2	3	6	4	4	5
≥ 4	7	16	2	6	2	4	3	6

Table 22: Coincidence between reported upper respiratory illnesses and paediatrician-recorded episodes of asthma.

Illnesses coinciding with episode of asthma	All (n=78)	Low (n=26)	Mid (n=26)	High (n=26)
URI swabbed				
GP visit	43/58 (74.1%)	8/10 (80.0%)	14/18 (77.8%)	21/30 (70.0%)
No GP visit	15/27 (55.6%)	6/10 (60.0%)	2/6 (33.3%)	7/11 (63.6%)
URI not swabbed				
GP visit	25/36 (69.4%)	3/6 (50.0%)	15/20 (75.0%)	7/10 (70.0%)
No GP visit	13/33 (39.4%)	7/12 (58.3%)	4/16 (25.0%)	2/5 (40.0%)
Total URI	**96/154 (62.3%)**	**24/38 (63.2%)**	**35/60 (58.3%)**	**37/56 (66.1%)**
Hospital admissions/ GP visits	10/21 (47.6%)	6/8 (75.0%)	3/6 (50.0%)	1/7 (14.3%)
Other illnesses	13/57 (22.8%)	5/26 (19.2%)	4/16 (25.0%)	4/15 (26.7%)
Total upper respiratory illnesses	**119/232 (51.3%)**	**35/72 (48.6%)**	**42/82 (51.2%)**	**42/78 (53.8%)**

Table 23: Results of microbiological tests on reported URI.

Proportion of swabbed URI with positive microbiological test	**All (n=78)**	**Low (n=26))**	**Mid (n=26)**	**High (n=26**
URI with GP visit				
Coinciding asthma episode	16/36	3/8	4/11	9/17
No asthma episode	8/15	0/2	3/4	5/9
URI with no GP visit				
Coinciding asthma episode	8/15	3/6	1/2	4/7
No asthma episode	5/12	2/4	0/4	3/4
Total swabbed URI with + microbiological test (%)	**37/78** (47.4)	**8/20** (40.0)	**8/21** (38.1)	**21/37** (56.8)

Table 24: Classification of URI and other upper respiratory illnesses.

Total URI (biologically verified)		**37**
URI (non-biologically verified)		
Reported URI (GP visit with antibiotics prescribed and coinciding episode of asthma)	52	
Reported URI (GP visit with antiobiotics prescribed)	18	
Reported URI (coinciding asthma episode)	20	
Reported URI	27	
Total URI (non-biologically verifed)		**117**
Total reported URI		**154**
GP visit with antibiotics prescribed/hospital admission		**21**
Other reports ('hay-fever', etc.)/no reason given		**57**
Total Illnesses		**232**

Table 25: Comparison between individual subscale scores of children with asthma and a normative sample (Hoare, Elton, Greer & Kerley, 1993).

	Harter Scores (Mean)					
Harter subscale	**Asthma Girls** n=38	**Normative Girls** n=1875	**Asthma Boys** n=40	**Normative Boys** n=1897	**Asthma Whole Group** n=78	**Normative Whole Group** n=3772
Scholastic	**2.96***	2.70	**3.00***	2.74	**2.98****	2.72
Social	**3.38*****	2.95	**3.22***	3.01	**3.30*****	2.98
Athletic	2.66	2.57	3.06	2.96	2.87	2.77
Appearance	**3.18*****	2.54	**3.10***	2.86	**3.14*****	2.70
Behaviour	**3.19*****	2.79	**2.95****	2.63	**3.07*****	2.71
Global	**3.31*****	2.87	**3.28***	3.03	**3.29*****	2.95

***p<0.05**
****p<0.005**
*****p<0.001**

Table 26: Results of a Multivariate Analysis of Variance investigating the effects of age and social class on the six HARTER SUBSCALE SCORES for *BOYS*.

Source	d.f.	F	p
Age			
Scholastic Competence	2,32	0.16	0.85
Social Acceptance	2,32	1.04	0.36
Athletic Competence	2,32	1.62	0.21
Physical Appearance	2,32	1.17	0.32
Behavioural Conduct	2,32	0.22	0.81
Global Self Worth	2,32	0.61	0.55
Social Class			
Scholastic Competence	2,32	0.09	0.91
Social Acceptance	2,32	1.55	0.23
Athletic Competence	2,32	0.46	0.64
Physical Appearance	2,32	0.42	0.66
Behavioural Conduct	2,32	0.98	0.39
Global Self Worth	2,32	0.84	0.44
Age x Social Class			
Scholastic Competence	4,32	1.08	0.38
Social Acceptance	4,32	0.91	0.47
Athletic Competence	4,32	2.50	0.06
Physical Appearance	4,32	0.88	0.49
Behavioural Conduct	4,32	0.69	0.60
Global Self Worth	4,32	1.32	0.29

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 27: Results of a Multivariate Analysis of Variance investigating the effects of age and social class on the six *HARTER SUBSCALE SCORES* for *GIRLS*.

Source	d.f.	F	p
Age			
Scholastic Competence	2,28	1.56	0.23
Social Acceptance	2,28	0.10	0.90
Athletic Competence	2,28	0.26	0.77
Physical Appearance	2,28	8.01	**0.002****
Behavioural Conduct	2,28	2.40	0.11
Global Self Worth	2,28	1.14	0.33
Social Class			
Scholastic Competence	2,28	0.25	0.78
Social Acceptance	2,28	1.92	0.17
Athletic Competence	2,28	1.24	0.30
Physical Appearance	2,28	0.50	0.61
Behavioural Conduct	2,28	0.93	0.41
Global Self Worth	2,28	3.23	**0.05***
Age x Social Class			
Scholastic Competence	4,28	5.41	**0.002*****
Social Acceptance	4,28	3.65	**0.02***
Athletic Competence	4,28	1.28	0.30
Physical Appearance	4,28	1.43	0.25
Behavioural Conduct	4,28	2.30	0.08
Global Self Worth	4,28	6.05	**0.001*****

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 28: Scores across Harter subscales by symptom groups and gender.

Harter Scores Mean Standard Deviation												
Harter Subscale	**Whole Group**			**Low**			**Mid**			**High**		
	Girls n=38	**Boys n=40**	**All n=78**	**Girls n=15**	**Boys n=11**	**All n=26**	**Girls n=12**	**Boys n=14**	**All n=26**	**Girls n=11**	**Boys n=15**	**All n=26**
Scholastic	2.96	3.00	**2.98**	3.14	3.31	**3.22**	2.96	2.93	**2.94**	2.71	2.81	**2.77**
	0.76	0.66	**0.70**	0.66	0.62	**0.63**	0.91	0.61	**0.75**	0.69	0.68	**0.67**
Social	3.38	3.22	**3.30**	3.38	3.54	**3.46**	3.39	3.25	**3.31**	3.38	2.94	**3.13**
	0.60	0.68	**0.64**	0.44	0.40	**0.42**	0.80	0.86	**0.82**	0.58	0.56	**0.60**
Athletic	2.66	3.06	**2.87**	2.80	3.25	**3.01**	2.89	3.10	**3.00**	2.23	2.87	**2.60**
	0.85	0.69	**0.79**	0.76	0.68	**0.74**	0.90	0.58	**0.74**	0.82	0.79	**0.85**
Appearance	3.18	3.10	**3.14**	3.26	3.36	**3.31**	3.28	3.01	**3.13**	2.95	2.98	**2.97**
	0.66	0.56	**0.61**	0.48	0.38	**0.43**	0.74	0.65	**0.69**	0.77	0.54	**0.64**
Behaviour	3.19	2.95	**3.07**	3.25	3.31	**3.28**	3.47	2.94	**3.19**	2.82	2.67	**2.73**
	0.69	0.62	**0.66**	0.61	0.57	**0.58**	0.72	0.50	**0.65**	0.65	0.65	**0.64**
Global	3.31	3.28	**3.29**	3.26	3.67	**3.45**	3.40	3.25	**3.32**	3.26	3.00	**3.11**
	0.62	0.53	**0.57**	0.51	0.41	**0.50**	0.71	0.47	**0.58**	0.67	0.51	**0.59**

Table 29: Results of a Multivariate Analysis of Variance investigating the effects of symptom group on the six *HARTER SUBSCALE SCORES* for *GIRLS* and *BOYS* separately.

Source	d.f.	F	p
Girls			
Scholastic Competence	2,34	1.00	0.38
Social Acceptance	2,34	0.00	0.99
Athletic Competence	2,34	2.18	0.13
Physical Appearance	2,34	0.87	0.43
Behavioural Conduct	2,34	2.93	0.07
Global Self Worth	2,34	0.21	0.81
Boys			
Scholastic Competence	2,38	2.11	0.14
Social Acceptance	2,38	2.88	0.07
Athletic Competence	2,38	1.06	0.36
Physical Appearance	2,38	1.95	0.16
Behavioural Conduct	2,38	3.98	**0.03***
Global Self Worth	2,38	6.71	**0.003****

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 30: State/Trait Anxiety Inventory scores.

State/ Trait Anxiety	All (n=76) Mean (SD)		Low (n=25) Mean (SD)		Mid (n=25) Mean (SD)		High (n=26) Mean (SD)	
	Girls (n=37)	**Boys (n=39)**	**Girls (n=14)**	**Boys (n=11)**	**Girls (n=12)**	**Boys (n=13)**	**Girls (n=11)**	**Boys (n=15)**
State 'How I feel' "now"	27.1 (4.7)	28.0 (3.3)	26.1 (5.6)	27.8 (3.2)	27.8 (4.6)	28.5 (2.1)	27.7 (3.6)	27.7 (4.1)
Trait 'How I feel' "usually"	31.7 (8.6)	32.3 (8.3)	34.1 (9.4)	30.7 (10.2)	28.8 (9.6)	31.4 (8.3)	31.8 (5.8)	34.3 (6.8)

Table 31: Results of Multivariate Analysis of Variance investigating the effects of age and social class on *STATE/TRAIT ANXIETY SCORES*.

Source	d.f.	F	p
Age			
State anxiety	2,67	10.32	**0.000*****
Trait anxiety	2,67	0.12	0.884
Social class			
State anxiety	2,67	2.43	0.095
Trait anxiety	2,67	1.92	0.155
Age x social class			
State anxiety	4,67	1.13	0.349
Trait anxiety	4,67	3.12	**0.020***

***p = ≤0.05; **p = ≤0.01; ***p = ≤0.005**

Table 32: Distribution of positive, negative and high negative impact (HNI) long-term experiences over gender, age, social class and symptom groups.

	NO. OF SUBJECTS WITH POSITIVE LTEs (%)					NO. OF SUBJECTS WITH NEGATIVE LTEs (%)							NO. OF SUBJECTS WITH HNI LTEs (%)						
No. of LTEs	**0**	**1**	**2***	**3***	**4***	**0**	**1**	**2**	**3**	**4**	**5***	**>5***	**0**	**1**	**2***	**3***	**4***	**5***	**>5***
Gender																			
Female	6 (16.2)	12 (32.4)	**12 (32.4)**	**6 (16.2)**	**1 (2.7)**	2 (5.4)	4 (10.8)	4 (10.8)	5 (13.5)	5 (13.5)	**7 (18.9)**	**10 (27.0)**	8 (21.6)	12 (32.4)	**6 (16.2)**	**3 (8.1)**	**3 (8.1)**	**4 (10.8)**	**1 (2.7)**
Male	10 (24.4)	7 (17.1)	**13 (31.7)**	**7 (17.1)**	**4 (9.8)**	1 (2.4)	7 (17.1)	4 (9.8)	3 (7.3)	9 (22.0)	**8 (19.5)**	**9 (22.0)**	11 (26.8)	7 (17.1)	**10 (24.4)**	**3 (7.3)**	**4 (9.8)**	**1 (2.4)**	**5 (12.2)**
Age																			
< 9 years	9 (33.3)	3 (11.1)	**11 (40.7)**	**4 (14.8)**	**0 -**	2 (7.4)	4 (14.8)	1 (3.7)	3 (11.1)	5 (18.5)	**6 (22.2)**	**(22.2)**	9 (33.3)	6 (22.2)	**3 (11.1)**	**3 (11.1)**	**2 (7.4)**	**2 (7.4)**	**2 (7.4)**
9 to 11 years	3 (10.0)	8 (26.7)	**9 (30.0)**	**6 (20.0)**	**4 (13.3)**	0 -	4 (13.3)	7 (23.3)	3 (10.0)	6 (20.0)	**4 (13.3)**	**6 (20.0)**	8 (26.7)	7 (23.3)	**10 (33.3)**	**0 -**	**2 (6.7)**	**2 (6.7)**	**1 (3.3)**
> 11 years	4 (19.0)	8 (38.1)	**5 (23.8)**	**3 (14.3)**	**1 (4.8)**	1 (4.8)	3 (14.3)	0 -	2 (9.5)	3 (14.3)	**5 (23.8)**	**7 (33.4)**	2 (9.5)	6 (28.6)	**3 (14.3)**	**3 (14.3)**	**3 (14.3)**	**1 (4.8)**	**3 (14.3)**
Social Class																			
I & II	1 (4.0)	2 (8.0)	**11 (44.0)**	**7 (28.0)**	**4 (16.0)**	1 (4.0)	6 (24.0)	2 (8.0)	2 (8.0)	8 (32.0)	**5 (20.0)**	**1 (4.0)**	11 (44.0)	6 (24.0)	**6 (24.0)**	**1 (4.0)**	**1 (4.0)**	**0 -**	**0 -**
III & IV	8 (22.9)	10 (28.6)	**10 (28.6)**	**6 (17.1)**	**1 (2.9)**	2 (5.7)	3 (8.6)	6 (17.1)	5 (14.3)	3 (8.6)	**7 (20.0)**	**9 (25.7)**	7 (20.0)	7 (20.0)	**8 (22.9)**	**4 (11.4)**	**3 (8.6)**	**3 (8.6)**	**3 (8.6)**
V & VI	7 (38.9)	7 (38.9)	**4 (22.2)**	**0 -**	**0 -**	0 -	2 (11.1)	0 -	1 (5.6)	3 (16.7)	**3 (16.7)**	**9 (50.0)**	1 (5.6)	6 (33.3)	**2 (11.1)**	**1 (5.6)**	**3 (16.7)**	**2 (11.1)**	**3 (16.7)**
Groups																			
Low	4 (15.4)	7 (26.9)	**8 (30.8)**	**6 (23.1)**	**1 (3.8)**	2 (7.7)	6 (23.1)	3 (11.5)	2 (7.7)	3 (11.5)	**2 (7.7)**	**8 (30.8)**	10 (38.5)	6 (23.1)	**3 (11.5)**	**2 (7.7)**	**1 (3.8)**	**2 (7.7)**	**2 (7.7)**
Mid	7 (26.9)	4 (15.4)	**8 (30.8)**	**3 (11.5)**	**4 (15.4)**	1 (3.8)	4 (15.4)	2 (7.7)	4 (15.4)	7 (26.9)	**4 (15.4)**	**4 (15.4)**	8 (30.8)	8 (30.8)	**6 (23.1)**	**1 (3.8)**	**1 (3.8)**	**1 (3.8)**	**1 (3.8)**
High	5 (19.2)	8 (30.8)	**9 (34.6)**	**4 (15.4)**	**0 -**	0 -	1 (3.8)	3 (11.5)	2 (7.7)	4 (15.4)	**9 (34.6)**	**7 (26.9)**	1 (3.8)	5 (19.2)	**7 (26.9)**	**3 (11.5)**	**5 (19.2)**	**2 (7.7)**	**3 (11.5)**

*** Above sample median LTE score**

Table 33: Mean number of long-term experiences over gender, age, social class and symptom groups.

	POSITIVE LTEs Mean (SD)			NEGATIVE LTEs Mean (SD)			HNI LTEs Mean (SD)		
	All	**Boys**	**Girls**	**All**	**Boys**	**Girls**	**All**	**Boys**	**Girls**
ALL LTEs	1.64 (1.17)	1.71 (1.29)	1.57 (1.04)	4.05 (2.35)	4.15 (2.58)	3.95 (2.09)	2.13 (2.15)	2.27 (2.36)	1.97 (1.91)
AGE									
< 9 years	1.37 (1.12)	1.23 (1.24)	1.50 (1.02)	4.00 (2.48)	4.00 (3.00)	4.00 (2.00)	1.93 (2.07)	1.92 (2.33)	1.93 (1.90)
9 to 11 years	2.00 (1.20)	2.17 (1.34)	1.75 (0.97)	3.70 (2.07)	3.89 (2.19)	3.42 (1.93)	1.83 (2.10)	2.11 (2.47)	1.42 (1.38)
> 11 years	1.48 (1.12)	1.50 (1.08)	1.46 (1.21)	4.62 (2.56)	4.80 (2.82)	4.46 (2.42)	2.81 (2.25)	3.00 (2.26)	2.64 (2.34)
SOCIAL CLASS									
I & II	2.44 (1.00)	2.75 (0.86)	1.89 (1.05)	3.16 (1.72	3.13 (1.86)	3.22 (1.56)	1.00 (1.12)	1.13 (1.26)	0.78 (0.83)
III & IV	1.49 (1.12)	1.19 (1.17)	1.74 (1.05)	4.11 (2.65)	4.88 (3.18)	3.47 (1.98)	2.43 (2.28)	3.13 (2.78)	1.84 (1.61)
V & VI	0.83 (0.79)	0.78 (0.83)	0.89 (0.78)	5.17 (2.07)	4.67 (2.12)	5.67 (2.00)	3.11 (2.37)	2.78 (2.44)	3.44 (2.40)
SYMPTOM GROUPS									
Low	1.73 (1.12)	1.58 (1.31)	1.86 (0.95)	3.54 (2.45)	3.83 (2.59)	3.29 (2.40)	1.73 (2.09)	1.92 (2.47)	1.57 (1.79)
Mid	1.73 (1.40)	2.00 (1.52)	1.42 (1.24)	3.77 (2.30)	3.50 (2.77)	4.08 (1.68)	1.50 (1.70)	1.50 (1.87)	1.50 (1.57)
High	1.46 (0.99)	1.53 (1.06)	1.36 (0.92)	4.85 (2.17)	5.00 (2.33)	4.64 (2.01)	3.15 (2.29)	3.27 (2.46)	3.00 (2.14)

Table 34: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *POSITIVE LTEs* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			0.0855	2	0.9581	
< 9 years/9 to 11 years	-0.1574	0.6411	0.0603	1	0.8061	0.8544
9 to 11 years/>11years	0.1729	0.6804	0.0646	1	0.7994	1.1888
< 9 years/>11years	0.0156	0.6873	0.0005	1	0.9819	1.0157
Gender	0.0408	0.5425	0.0056	1	0.9401	1.0416
Social class			14.022	2	**0.0009**	
Class I & II / Class III & IV	2.1763	0.7755	7.8758	1	**0.0050**	8.8141
Class III & IV / Class V & VI	1.1801	0.6749	3.0573	1	0.0804	3.2546
Class I & II / Class V & VI	3.3564	0.9002	13.902	1	**0.0002**	28.686
Symptom group			0.6803	2	0.7106	
Low/Mid symptom levels	0.5781	0.7061	0.6705	1	0.4129	1.7827
Mid/High symptom levels	-0.4080	0.7143	0.3263	1	0.5678	0.6650
Low/High symptom levels	0.1701	0.6467	0.0692	1	0.7925	1.1855
Constant	0.2247	0.3060	0.5390	1	0.4628	

Table 35: Negative long term experiences by type.

Long Term Experiences by Type	(n)
Illness	140
Family Relationships	48
Marriage/separation	25
School routine	20
Inappropriate parenting (e.g. abuse)	17
Moves/living conditions	17
Caretaking (e.g. lack of supervision)	14
Work	8
Friendships	8
School work	6
Social isolation	6
Poverty/financial difficulty	5
Law contact	1
Witnessing unpleasant/frightening incident*	1
Pregnancy/Birth	0
Pets	0
Unpleasant or frightening experiences*	0
Sexual harassment/abuse	0
Burglary/theft/damage to property	0
Receiving/breaking unexpected news*	0
Meeting key person from the past*	0
Good experience	0
Holidays*	0
Family ceremonies*	0
Periods, menarche	0
Sexual relationships	0
Leisure activities	0
Total negative experiences (excluding all positive experiences)	316

* Only applicable if occurring frequently

Table36: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *NEGATIVE (ANY IMPACT) LTEs* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			2.2232	2	0.3290	
< 9 years/9 to 11 years	0.5474	0.6090	0.8077	1	0.3688	1.7287
9 to 11 years/>11years	-0.9857	0.6682	2.1764	1	0.1401	0.3732
< 9 years/>11years	0.4383	0.6529	0.4507	1	0.5020	0.6451
Gender	-0.1277	0.5150	0.0614	1	0.8042	0.8801
Social class			4.2240	2	0.1210	
Class I & II / Class III & IV	-0.4851	0.6468	0.5625	1	0.4533	0.6157
Class III & IV / Class V & VI	-0.9848	0.6484	2.3067	1	0.1288	0.3735
Class I & II / Class V & VI	-1.4699	0.7340	4.0098	1	**0.0452**	0.2299
Symptom group			4.7813	2	0.0916	
Low/Mid symptom levels	0.3142	0.6446	0.2375	1	0.6260	1.3691
Mid/High symptom levels	-1.3940	0.6826	4.1703	1	**0.0411**	0.2481
Low/High symptom levels	-1.0798	0.6258	2.9775	1	0.0844	0.3397
Constant	-0.1478	0.2688	0.3023	1	0.5824	

Table 37: Classification of negative LTEs by threat impact on child and/or family.

		NEGATIVE IMPACT ON THE FAMILY		
		Low	**High**	
NEGATIVE IMPACT ON CHILD	**Low**	66	84	**150 [47.5%]**
	High	77	89	**166 [52.5%]**
		143 [45.3%]	**173 [54.7%]**	**316**

Table 38: High negative impact long term experiences *(HNI LTEs)* by type.

HNI LTEs by type	Low n=26	Mid n=26	High n=26	All n=78
Illness	13	16	25	54
Family Relationships	10	7	13	30
Inappropriate parenting (e.g. abuse)	4	1	10	15
Marriage/separation	3	3	9	15
School routine	3	3	8	14
Moves/living conditions	3	3	5	11
Caretaking (e.g. lack of supervision)	0	2	5	7
School work	2	1	2	5
Social isolation	2	0	3	5
Work	2	1	0	3
Friendships	1	1	1	3
Poverty/financial difficulty	1	1	1	3
Witnessing unpleasant/frightening incident*	1	0	0	1
Pregnancy/Birth	0	0	0	0
Pets	0	0	0	0
Law contact	0	0	0	0
Unpleasant or frightening experiences*	0	0	0	0
Sexual harassment/abuse	0	0	0	0
Burglary/theft/damage to property	0	0	0	0
Receiving/breaking unexpected news*	0	0	0	0
Meeting key person from the past*	0	0	0	0
Good experience	0	0	0	0
Holidays*	0	0	0	0
Family ceremonies*	0	0	0	0
Periods, menarche	0	0	0	0
Sexual relationships	0	0	0	0
Leisure activities	0	0	0	0
Total HNI LTE experiences	45	39	82	166

Table 39: Relationship of *HNI LTEs* to the behaviour of child and/or family.

		BEHAVIOUR OF FAMILY		
		Related	**Independent**	
BEHAVIOUR OF CHILD	**Related**	9	9	18
	Independent	81	31	112
		90	40	130

Table 40: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *HNI LTEs* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			1.0289	2	0.5978	
< 9 years/9 to 11 years	-0.0857	0.6021	0.0202	1	0.8869	0.9179
9 to 11 years/>11years	-0.5552	0.6734	0.6797	1	0.4097	0.5740
< 9 years/>11years	-0.6409	0.6639	0.9319	1	0.3344	0.5268
Gender	0.5436	0.5215	1.0866	1	0.2972	1.7222
Social class			2.2996	2	0.3167	
Class I & II / Class III & IV	-0.8185	0.6392	1.6396	1	0.2004	0.4411
Class III & IV / Class V & VI	-0.1926	0.6458	0.0889	1	0.7656	0.8248
Class I & II / Class V & VI	-1.0110	0.7274	1.9321	1	0.1645	0.3638
Symptom group			7.1582	2	0.0279	
Low/Mid symptom levels	-0.0574	0.6136	0.0087	1	0.9255	0.9442
Mid/High symptom levels	-1.5245	0.6757	5.0908	1	**0.0241**	0.2177
Low/High symptom levels	-1.5819	0.6420	6.0717	1	**0.0137**	0.2056
Constant	0.1130	0.2674	0.1785	1	0.6726	

Table 41: Type and impact of all events.

TYPE OF EVENT	Positive Events	All Neg Events	HNI LEs	HNI S/T LEs	HNI LT LEs
Illness/accident/death	-	119	**102**	73	29
Family Relationships	**1**	15	**15**	8	7
Inappropriate parenting	-	-	-	-	-
Marriage/separation	**1**	16	**16**	6	10
School routine	**10**	44	**42**	35	7
Moves/living conditions	**4**	20	**16**	8	8
Caretaking	-	-	-	-	-
School work	**25**	9	**9**	8	1
Social isolation	-	-	-	-	-
Work	**3**	12	**8**	3	5
Friendships	**8**	32	**29**	15	14
Major financial loss	**1**	-	-	-	-
Witnessing unpleasant/ frightening incident	-	17	**14**	14	-
Pregnancy/birth	**4**	1	**1**	-	1
Pets	**17**	18	**15**	11	4
Law contact	-	3	**2**	1	1
Unpleasant or frightening experiences	-	24	**20**	13	7
Sexual harassment/abuse	-	-	**1**	1	-
Burglary/theft/ damage to property	-	9	**7**	6	1
Receiving/ breaking unexpected news	**4**	26	**21**	15	6
Meeting person from the past	**5**	2	**2**	2	-
Good event	**107**	-	-	-	-
Holidays and holiday events	**28**	8	**8**	5	3
Family ceremonies	**21**	3	**3**	2	1
Periods, menarche	-	3	**3**	2	1
Sexual relationships	-	3	**3**	1	2
Leisure activities	**108**	41	**37**	30	7
TOTAL	**347**	425	**374**	259	115

HNI LEs= High negative impact life events
HNI ST LEs= High negative impact short-term life events
HNI LT LEs= High negative impact long-term life events

Table 42: Distribution of positive, negative and high negative impact (HNI) life events over gender, age, social class and symptom groups.

	NO. OF SUBJECTS WITH POSITIVE LEs (%)						NO. OF SUBJECTS WITH NEGATIVE LEs (%)						NO. OF SUBJECTS WITH HNI LEs (%)					
No. of LTEs	**1**	**2**	**3**	**4**	**5***	**>5***	**1**	**2**	**3**	**4**	**5**	**>5***	**1**	**2**	**3**	**4**	**5***	**>5***
Gender																		
Female	2 (5.4)	6 (16.2)	6 (16.2)	9 (24.3)	**8 (21.6)**	**6 (16.2)**	1 (2.7)	4 (10.8)	1 (2.7)	6 (16.2)	6 (16.2)	**19 (55.3)**	2 (5.4)	3 (8.1)	4 (10.8)	5 (13.5)	**7 (18.9)**	**16 (43.2)**
Male	1 (2.4)	7 (17.1)	6 (14.6)	8 (19.5)	**5 (12.2)**	**14 (34.2)**	3 (7.3)	2 (4.9)	7 (17.1)	7 (17.1)	6 (14.6)	**16 (39.0)**	3 (7.3)	6 (14.6)	9 (22.0)	4 (9.8)	**7 (17.1)**	**12 (29.2)**
Age																		
< 9 years	2 (7.4)	5 (18.5)	4 (14.8)	6 (22.2)	**5 (18.5)**	**5 (18.5)**	2 (7.4)	5 (18.5)	4 (14.8)	5 (18.5)	5 (18.5)	**6 (22.2)**	3 (11.1)	5 (18.5)	7 (25.9)	2 (7.4)	**5 (18.5)**	**5 (18.5)**
9 to 11 years	1 (3.3)	6 (20.0)	2 (6.7)	6 (20.0)	**2 (6.7)**	**13 (43.3)**	2 (6.7)	0 -	2 (6.7)	2 (6.7)	4 (13.3)	**20 (66.7)**	2 (6.7)	1 (3.3)	3 (10.0)	3 (10.0)	**6 (20.0)**	**15 (50.0)**
> 11 years	0 -	2 (9.5)	6 (28.6)	5 (23.8)	**6 (28.6)**	**2 (9.5)**	0 -	1 (4.8)	2 (9.5)	6 (28.6)	3 (14.3)	**9 (42.9)**	0 -	3 (14.3)	3 (14.3)	4 (19.0)	**3 (14.3)**	**8 (38.1)**
Social Class																		
I & II	0 -	5 (20.0)	4 (16.0)	6 (24.0)	**2 (8.0)**	**8 (32.0)**	2 (8.0)	3 (12.0)	2 (8.0)	4 (16.0)	4 (16.0)	**10 (40.0)**	2 (8.0)	4 (16.0)	4 (16.0)	2 (8.0)	**5 (20.0)**	**8 (32.0)**
III & IV	2 (5.7)	4 (11.4)	4 (11.4)	6 (17.1)	**10 (28.6)**	**9 (25.8)**	1 (2.9)	1 (2.9)	5 (14.3)	5 (14.3)	5 (14.3)	**18 (51.5)**	2 (5.7)	1 (2.9)	8 (22.9)	5 (14.3)	**5 (14.3)**	**14 (40.0)**
V & VI	1 (5.6)	4 (22.2)	4 (22.2)	5 (27.8)	**1 (5.6)**	**3 (16.7)**	1 (5.6)	2 (11.1)	1 (5.6)	4 (22.2)	3 (16.7)	**7 (39.0)**	1 (5.6)	4 (22.2)	1 (5.6)	2 (11.1)	**4 (22.2)**	**6 (33.5)**
Groups																		
Low	1 (3.8)	4 (15.4)	3 (11.5)	8 (30.8)	**4 (15.4)**	**6 (23.0)**	2 (7.7)	2 (7.7)	2 (7.7)	4 (15.4)	4 (15.4)	**12 (46.1)**	2 (7.7)	3 (11.5)	3 (11.5)	4 (15.4)	**6 (23.1)**	**8 (30.7)**
Mid	0 -	4 (15.4)	8 (30.8)	7 (26.9)	**3 (11.5)**	**4 (15.4)**	2 (7.7)	4 (15.4)	2 (7.7)	5 (19.2)	4 (15.4)	**9 (34.4)**	3 (11.5)	6 (23.1)	4 (15.4)	1 (3.8)	**5 (19.2)**	**7 (26.8)**
High	2 (7.7)	5 (19.2)	1 (3.8)	2 (7.7)	**6 (23.1)**	**10 (38.4)**	0 -	0 -	4 (15.4)	4 (15.4)	4 (15.4)	**14 (54.5)**	0 -	0 -	6 (23.1)	4 (15.4)	**3 (11.5)**	**13 (49.9)**

*** Above sample median LE score**

Table 43: Mean number of life events over gender, age, social class and symptom groups.

	POSITIVE LEs Mean (SD)			NEGATIVE LEs Mean (SD)			HNI LEs Mean (SD)		
	All	**Boys**	**Girls**	**All**	**Boys**	**Girls**	**All**	**Boys**	**Girls**
ALL LEs	**4.45** (**2.25**)	4.81 (2.56)	4.05 (1.81)	**5.45** (**2.70**)	4.88 (2.16)	6.1 (3.10)	**4.80** (**2.43**)	4.17 (1.94)	5.49 (1.74)
AGE									
< 9 years	**4.15** (**2.33**)	4.85 (2.85)	3.50 (1.56)	**4.52** (**2.71**)	4.15 (2.51)	4.86 (2.93)	**3.93** (**2.30**)	3.62 (2.14)	4.21 (2.49)
9 to 11 years	**4.97** (**2.61**)	4.94 (2.84)	5.00 (2.34)	**6.20** (**2.70**)	5.33 (2.17)	7.50 (2.97)	**5.43** (**2.32**)	4.56 (1.95)	6.75 (2.26)
> 11 years	**4.10** (**1.41**)	4.50 (1.72)	3.73 (1.01)	**5.57** (**2.42**)	5.00 (1.49)	6.09 (3.02)	**5.00** (**2.51**)	4.20 (1.62)	5.73 (3.00)
SOCIAL CLASS									
I & II	**4.72** (**2.53**)	4.81 (2.64)	4.56 (2.46)	**5.00** (**2.60**)	4.56 (2.48)	5.78 (2.77)	**4.48** (**2.31**)	4.06 (2.21)	5.22 (2.44)
III & IV	**4.66** (**2.45**)	5.13 (2.78)	4.26 (1.66)	**5.86** (**2.72**)	5.31 (1.92)	6.32 (3.23)	**4.97** (**2.28**)	4.31 (1.54)	5.53 (2.67)
V & VI	**3.67** (**1.75**)	4.22 (2.17)	3.11 (1.05)	**5.28** (**2.80**)	4.67 (2.06)	5.89 (3.41)	**4.89** (**2.91**)	4.11 (2.26)	5.67 (3.39)
SYMPTOM GROUPS									
Low	**4.42** (**2.27**)	4.58 (2.68)	4.29 (1.94)	**5.19** (**2.26**)	4.50 (2.02)	5.79 (2.36)	**4.62** (**2.10**)	3.83 (1.75)	5.29 (2.20)
Mid	**3.96** (**1.61**)	4.36 (1.95)	3.50 (1.00)	**4.96** (**2.91**)	4.36 (2.06)	5.67 (3.63)	**4.27** (**2.82**)	3.43 (1.83)	5.25 (3.49)
High	**4.96** (**2.72**)	5.40 (3.00)	4.36 (2.29)	**6.19** (**2.82**)	5.67 (2.26)	6.91 (3.42)	**5.50** (**2.21**)	5.13 (1.89)	6.00 (2.61)

Table 44: Relationship of all events to the behaviour of child and family.

Behaviour related to:	Positive events	All negative events	All HNI events	Short-term HNI events	Long-term HNI events
Child and Family	7/347 **[0.020]**	7/425 **[0.016]**	7/374 **[0.019]**	4/259 **[0.015]**	3/115 **[0.026]**
Child only	141/347 **[0.406]**	50/425 **[0.118]**	46/374 **[0.123]**	42/259 **[0.162]**	4/115 **[0.035]**
Family only	152/347 **[0.438]**	88/425 **[0.207]**	82/374 **[0.219]**	39/259 **[0.151]**	43/115 **[0.374]**
Neither	47/347 **[0.135]**	234/425 **[0.551]**	199/374 **[0.532]**	143/259 **[0.552]**	56/115 **[0.487]**
Related to physical illness in child and/or parent	-	46/425 **[0.108]**	40/374 **[0.107]**	31/259 **[0.120]**	9/115 **[0.078]**

Table 45: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *HNI LEs* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			6.6951	2	**0.0352**	
< 9 years/9 to 11 years	-1.5550	0.6010	6.6945	1	**0.0097**	0.2112
9 to 11 years/>11years	0.8260	0.6446	1.6418	1	0.2001	2.2841
< 9 years/>11years	-0.7290	0.6321	1.3302	1	0.2488	0.4824
Gender	-0.9307	0.5172	3.2386	1	0.0719	0.3943
Social class			0.4141	2	0.8130	
Class I & II / Class III & IV	0.2907	0.6306	0.2125	1	0.6448	1.3374
Class III & IV / Class V & VI	-0.3687	0.6297	0.3429	1	0.5581	0.6916
Class I & II / Class V & VI	-0.0780	0.7115	0.0120	1	0.9127	0.9249
Symptom group			1.0954	2	0.5783	
Low/Mid symptom levels	0.2750	0.6121	0.2018	1	0.6533	1.3165
Mid/High symptom levels	-0.6749	0.6483	1.0837	1	0.2979	0.5092
Low/High symptom levels	-0.3999	0.6182	0.4185	1	0.5177	0.6704
Constant	0.2108	0.2550	0.6830	1	0.4086	

Table 46: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *LT HNI LEs* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			3.7410	2	0.1540	
< 9 years/9 to 11 years	-1.2433	0.6638	3.5076	1	0.0611	0.2884
9 to 11 years/>11years	0.8823	0.7098	1.5453	1	0.2138	2.4165
< 9 years/>11years	-0.3609	0.7337	0.2420	1	0.6228	0.6970
Gender	-1.7311	0.6010	8.2961	1	**0.0040**	0.1771
Social class			1.6014	2	0.4490	
Class I & II / Class III & IV	0.7835	0.7202	1.1836	1	0.2766	2.1892
Class III & IV / Class V & VI	-0.7067	0.6947	1.0348	1	0.3090	0.4933
Class I & II / Class V & VI	0.0768	0.7835	0.0096	1	0.9219	1.0798
Symptom group			5.8977	2	**0.0524**	
Low/Mid symptom levels	0.8192	0.7222	1.2867	1	0.2567	2.2687
Mid/High symptom levels	-1.8505	0.7734	5.7245	1	**0.0167**	0.1572
Low/High symptom levels	-1.0313	0.6606	2.4372	1	0.1185	0.3565
Constant	-0.7260	0.2862	6.4373	1	0.0112	

Table 47: Results of Logistic regression investigating the proportion of children over symptom groups with above median levels of *ST HNI LEs* and controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			3.9880	2	0.1361	
< 9 years/9 to 11 years	-1.0735	0.6015	3.1847	1	0.0743	0.3418
9 to 11 years/>11years	-0.0481	0.6129	0.0062	1	0.9375	0.9530
< 9 years/>11years	-1.1215	0.6578	2.9072	1	0.0882	0.3258
Gender	0.0545	0.4978	0.0120	1	0.9129	1.0560
Social class			0.7649	2	0.6822	
Class I & II / Class III & IV	-0.4448	0.6160	0.5215	1	0.4702	0.6410
Class III & IV / Class V & VI	0.4432	0.6329	0.4905	1	0.4837	1.5577
Class I & II / Class V & VI	-0.0016	0.7266	0.0000	1	0.9983	0.9984
Symptom group			0.1042	2	0.9492	
Low/Mid symptom levels	0.1811	0.6179	0.0859	1	0.7695	1.1985
Mid/High symptom levels	-0.1739	0.6383	0.0742	1	0.7853	0.8404
Low/High symptom levels	0.0072	0.6020	0.0001	1	0.9905	1.0072
Constant	-0.5534	0.2586	4.5790	1	0.0324	

Table 48: Total URI preceded by/followed by HNI event within 6-week period.

	URI		
TYPE OF EVENT	**Boys**	**Girls**	**All**
All HNI events			
Preceded by event	24/76	37/75	61/151
	(0.316)	**(0.493)**	**(0.404)**
Followed by event	23/76	31/75	54/151
	(0.303)	**(0.413)**	**(0.358)**
HNI ST Events			
Preceded by event	15/76	23/75	38/151
	(0.197)	**(0.307)**	**(0.252)**
Followed by events	21/76	24/75	45/151
	(0.276)	**(0.320)**	**(0.298)**
IINI LT events			
Preceded by event	9/76	20/75	29/151
	(0.118)	**(0.267)**	**(0.192)**
Followed by event	5/76	12/75	17/151
	(0.066)	**(0.160)**	**(0.113)**

Table 49: Results of Logistic regression investigating the effect of 'before'/'after' period on the proportion of URI temporally related to a *HNI LE (any impact)* controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			7.4907	2	**0.0236**	
< 9 years/9 to 11 years	-0.7890	0.2920	7.3007	1	**0.0069**	0.4543
9 to 11 years/>11years	0.2036	0.3162	0.4148	1	0.5195	1.2258
< 9 years/>11years	-0.5853	0.3373	3.0120	1	0.0827	0.5569
Gender	-0.7116	0.2553	7.7710	1	**0.0053**	0.4908
Social class			0.1281	2	0.9379	
Class I & II / Class III & IV	0.0603	0.3232	0.0348	1	0.8520	1.0622
Class III & IV / Class V & VI	0.0852	0.3307	0.0664	1	0.7967	1.0889
Class I & II / Class V & VI	0.1455	0.4091	0.1265	1	0.7221	1.1566
High threat LTE levels	-0.2702	0.2570	1.1054	1	0.2931	0.7633
Positive LTE levels	0.0497	0.2971	0.0280	1	0.8670	1.0510
Period ('6-weeks before URI'/'6-weeks after URI')	-0.2074	0.2437	0.7241	1	0.3948	0.8127
Constant	-0.5223	0.1280	16.653	1	0.0000	

Table 50: Results of Logistic regression investigating the effect of 'before'/'after' period on the proportion of URI temporally related to a *LT HNI LE* controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			2.1063	2	0.3488	
< 9 years/9 to 11 years	-0.5911	0.4203	1.9777	1	0.1596	0.5537
9 to 11 years/>11years	0.1151	0.4225	0.0742	1	0.7854	1.1219
< 9 years/>11years	-0.4761	0.4521	1.1087	1	0.2924	0.6212
Gender	-1.0532	0.3636	8.3893	1	**0.0038**	0.3488
Social class			1.5731	2	0.4554	
Class I & II / Class III & IV	-0.1551	0.4812	0.1038	1	0.7473	0.8564
Class III & IV / Class V & VI	-0.4670	0.4184	1.2454	1	0.2644	0.6269
Class I & II / Class V & VI	-0.6220	0.5666	1.2050	1	0.2723	0.5369
High threat LTE levels	-0.6630	0.3530	3.5284	1	0.0603	0.5153
Positive LTE levels	0.2297	0.3953	0.3376	1	0.5612	1.2582
Period ('6-weeks before URI'/ '6-weeks after URI')	-0.6734	0.3421	3.8754	1	**0.0490**	0.5100
Constant	-1.8708	0.1923	94.654	1	0.0000	

Table 51: Results of Logistic regression investigating the effect of 'before'/'after' period on the proportion of URI temporally related to a *ST HNI LE* controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			3.9612	2	0.1380	
< 9 years/9 to 11 years	-0.6174	0.3116	3.9250	1	**0.0476**	0.5394
9 to 11 years/>11years	0.3066	0.3451	0.7892	1	0.3743	1.3588
< 9 years/>11years	-0.3108	0.3729	0.6945	1	0.4046	0.7329
Gender	-0.4609	0.2754	2.8002	1	0.0943	0.6307
Social class			0.8304	2	0.6602	
Class I & II / Class III & IV	-0.0095	0.3414	0.0008	1	0.9777	0.9905
Class III & IV / Class V & VI	0.3335	0.3713	0.8067	1	0.3691	1.3958
Class I & II / Class V & VI	0.3239	0.4516	0.5145	1	0.4732	1.3825
High threat LTE levels	-0.1452	0.2773	0.2742	1	0.6006	0.8649
Positive LTE levels	-0.1895	0.3217	0.3469	1	0.5559	0.8274
Period ('6-weeks before URI'/'6-weeks after URI')	0.2401	0.2625	0.8372	1	0.3602	1.2714
Constant	-1.0665	0.1424	56.073	1	0.0000	

Table 52: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of URI preceded by a *HNI LE* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			5.0738	2	0.0791	
< 9 years/9 to 11 years	-0.9200	0.4150	4.9137	1	**0.0266**	0.3985
9 to 11 years/>11years	0.2230	0.4489	0.2468	1	0.6193	1.2499
< 9 years/>11years	-0.6969	0.4779	2.1271	1	0.1447	0.4981
Gender	-0.9167	0.3648	6.3145	1	**0.0120**	0.3998
Social class			0.8274	2	0.6612	
Class I & II / Class III & IV	0.3924	0.4608	0.7249	1	0.3945	1.4805
Class III & IV / Class V & VI	0.0573	0.4686	0.0150	1	0.9027	1.0590
Class I & II / Class V & VI	0.4497	0.5794	0.6024	1	0.4377	1.5678
High threat LTE levels	-0.4316	0.3666	1.3860	1	0.2391	0.6495
Positive LTE levels	0.2658	0.4223	0.3961	1	0.5291	1.3044
Constant	-0.4081	0.1809	5.0919	1	0.0240	

Table 53: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of URI preceded by a *LT HNI LE* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			3.3353	2	0.1887	
< 9 years/9 to 11 years	-0.9452	0.5572	2.8770	1	0.0899	0.3886
9 to 11 years/>11years	0.0159	0.5346	0.0009	1	0.9763	1.0160
< 9 years/>11years	-0.9293	0.6054	2.3563	1	0.1248	0.3948
Gender	-1.1629	0.4702	6.1176	1	**0.0134**	0.3126
Social class			0.2998	2	0.8608	
Class I & II / Class III & IV	0.3125	0.5808	0.2895	1	0.5905	1.3669
Class III & IV / Class V & VI	-0.0084	0.5722	0.0002	1	0.9883	0.9917
Class I & II / Class V & VI	0.3041	0.7239	0.1765	1	0.6744	1.3555
High threat LTE levels	-0.7169	0.4584	2.4456	1	0.1179	0.4883
Positive LTE levels	0.3498	0.5160	0.4597	1	0.4978	1.4188
Constant	-1.5566	0.2403	41.951	1	0.0000	

Table 54: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of URI preceded by a *ST HNI LE* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			1.9158	2	0.3837	
< 9 years/9 to 11 years	-0.6330	0.4577	1.9130	1	0.1666	0.5310
9 to 11 years/>11years	0.2791	0.5006	0.3108	1	0.5772	1.3219
< 9 years/>11years	-0.3540	0.5401	0.4294	1	0.5123	0.7019
Gender	-0.6979	0.4044	2.9778	1	0.0844	0.4977
Social class			0.4258	2	0.8082	
Class I & II / Class III & IV	0.1939	0.5005	0.1501	1	0.6985	1.2140
Class III & IV / Class V & VI	0.2324	0.5340	0.1895	1	0.6633	1.2617
Class I & II / Class V & VI	0.4263	0.6534	0.4258	1	0.5141	1.5316
High threat LTE levels	-0.3287	0.4050	0.6586	1	0.4171	0.7199
Positive LTE levels	0.0155	0.4663	0.0011	1	0.9736	1.0156
Constant	-1.1658	0.2063	31.948	1	0.0000	

Table 55: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of URI followed by a *HNI LE* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			2.6328	2	0.2681	
< 9 years/9 to 11 years	-0.6654	0.4135	2.5891	1	0.1076	0.5141
9 to 11 years/>11years	0.1910	0.4494	0.1806	1	0.6709	1.2105
< 9 years/>11years	-0.4744	0.4798	0.9777	1	0.3228	0.6223
Gender	-0.5101	0.3607	1.9996	1	0.1573	0.6004
Social class			0.3629	2	0.8341	
Class I & II / Class III & IV	-0.2711	0.4592	0.3486	1	0.5549	0.7625
Class III & IV / Class V & VI	0.1125	0.4692	0.0574	1	0.8106	1.1190
Class I & II / Class V & VI	-0.1587	0.5842	0.0738	1	0.7859	0.8533
High threat LTE levels	-0.1135	0.3634	0.0975	1	0.7548	0.8927
Positive LTE levels	-0.1665	0.4215	0.1560	1	0.6929	0.8466
Constant	-0.6378	0.1825	12.207	1	0.0005	

Table 56: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of URI followed by a *LT HNI LE* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			0.1205	2	0.9415	
< 9 years/9 to 11 years	-0.0932	0.6748	0.0191	1	0.8901	0.9110
9 to 11 years/>11years	0.2451	0.7104	0.1191	1	0.7300	1.2778
< 9 years/>11years	0.1519	0.6965	0.0476	1	0.8273	1.1641
Gender	-0.9054	0.5933	2.3287	1	0.1270	0.4044
Social class			4.9652	2	0.0835	
Class I & II / Class III & IV	-1.4865	1.1370	1.7093	1	0.1911	0.2262
Class III & IV / Class V & VI	-0.9995	0.6314	2.5063	1	0.1134	0.3680
Class I & II / Class V & VI	-2.4860	1.2131	4.1995	1	**0.0404**	0.0832
High threat LTE levels	-0.5479	0.5742	0.9105	1	0.3400	0.5782
Positive LTE levels	0.0577	0.6289	0.0084	1	0.9269	1.0594
Constant	-2.4589	0.4029	37.254	1	0.0000	

Table 57: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of URI preceded by a *ST HNI LE* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			2.0746	2	0.3544	
< 9 years/9 to 11 years	-0.6087	0.4275	2.0270	1	0.1545	0.5441
9 to 11 years/>11years	0.3381	0.4790	0.4982	1	0.4803	1.4023
< 9 years/>11years	-0.2706	0.5176	0.2732	1	0.6012	0.7629
Gender	-0.2479	0.3794	0.4268	1	0.5135	0.7804
Social class			0.7566	2	0.6850	
Class I & II / Class III & IV	-0.1959	0.4709	0.1731	1	0.6774	0.8221
Class III & IV / Class V & VI	0.4309	0.5185	0.6905	1	0.4060	1.5386
Class I & II / Class V & VI	0.2350	0.6279	0.1401	1	0.7082	1.2649
High threat LTE levels	0.0187	0.3828	0.0024	1	0.9611	1.0189
Positive LTE levels	-0.3789	0.4468	0.7190	1	0.3965	0.6846
Constant	-0.9794	0.1984	24.369	1	0.0000	

Table 58: Total HNI events preceded by/followed by URI within 6-week period.

TYPE OF EVENT	URI Boys	URI Girls	URI All
All HNI events			
Followed by URI	28/130	61/173	89/303
	(0.215)	**(0.353)**	**(0.294)**
Preceded by URI	34/147	42/177	76/324
	(0.231)	**(0.237)**	**(0.235)**
HNI ST Events			
Followed by URI	19/98	32/110	51/208
	(0.194)	**(0.291)**	**(0.245)**
Preceded by URI	28/109	27/116	55/225
	(0.257)	**(0.232)**	**(0.244)**
HNI LT events			
Folowed by URI	9/32	29/63	38/95
	(0.281)	**(0.460)**	**(0.40)**
Preceded by URI	6/38	15/61	21/99
	(0.158)	**(0.246)**	**(0.212)**

Table 59: Results of Logistic regression investigating the effect of 'before'/'after' period on the proportion of *HNI LE (any impact)* temporally related to a *URI* controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			5.1296	2	0.0769	
< 9 years/9 to 11 years	-0.3597	0.2276	2.4974	1	0.1140	0.6979
9 to 11 years/>11years	0.5047	0.2397	4.4335	1	**0.0352**	1.6565
< 9 years/>11years	0.1450	0.2594	0.3123	1	0.5762	1.1560
Gender	-0.3785	0.1997	3.5925	1	0.0580	0.6849
Social class			0.1025	2	0.9500	
Class I & II / Class III & IV	0.0364	0.2490	0.0213	1	0.8839	1.0370
Class III & IV / Class V & VI	-0.0752	0.2411	0.0974	1	0.7550	0.9275
Class I & II / Class V & VI	-0.0389	0.3010	0.0167	1	0.8972	0.9619
High threat LTE levels	-0.0622	0.1967	0.0999	1	0.7520	0.9397
Positive LTE levels	0.0467	0.2138	0.0476	1	0.8272	1.0478
Period ('6-weeks before URI'/ '6-weeks after URI')	-0.2703	0.1874	2.0798	1	0.1493	0.7631
Constant	-0.9307	0.1018	83.547	1	0.0000	

Table 60: Results of Logistic regression investigating the effect of 'before'/'after' period on the proportion of *LT HNI LE* temporally related to a *URI* controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			0.3500	2	0.8394	
< 9 years/9 to 11 years	-0.1638	0.4436	0.1364	1	0.7119	0.8489
9 to 11 years/>11years	-0.1257	0.4184	0.0903	1	0.7638	0.8819
< 9 years/>11years	-0.2896	0.4896	0.3497	1	0.5543	0.7486
Gender	-0.6639	0.3961	2.8091	1	0.0937	0.5149
Social class			0.2145	2	0.8983	
Class I & II / Class III & IV	-0.2086	0.4882	0.1826	1	0.6692	0.8117
Class III & IV / Class V & VI	-0.0369	0.4376	0.0071	1	0.9327	0.9637
Class I & II / Class V & VI						
High threat LTE levels	-0.5353	0.3646	2.1553	1	0.1421	0.5855
Positive LTE levels	0.1826	0.4197	0.1892	1	0.6636	1.2003
Period ('6-weeks before URI'/ '6-weeks after URI')	-0.7142	0.3397	4.4195	1	**0.0355**	0.4896
Constant	-0.8475	0.1986	18.201	1	0.0000	

Table 61: Results of Logistic regression investigating the effect of 'before'/'after' period on the proportion of *ST HNI LE* temporally related to a *URI* controlling for the effects of age, gender and social class.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			7.2661	2	**0.0264**	
< 9 years/9 to 11 years	-0.3948	0.2745	2.0680	1	0.1504	0.6738
9 to 11 years/>11years	0.8114	0.3064	7.0133	1	**0.0081**	2.2511
< 9 years/>11years	0.4167	0.3280	1.6135	1	0.2040	1.5169
Gender	-0.2091	0.2414	0.7507	1	0.3862	0.8113
Social class			0.0142	2	0.9929	
Class I & II / Class III & IV	0.0108	0.3005	0.0013	1	0.9713	1.0109
Class III & IV / Class V & VI	0.0317	0.3170	0.0100	1	0.9203	1.0322
Class I & II / Class V & VI	0.0425	0.3745	0.0129	1	0.9097	1.0434
High threat LTE levels	0.1375	0.2442	0.3168	1	0.5735	1.1474
Positive LTE levels	-0.0946	0.2622	0.1303	1	0.7181	0.9097
Period ('6-weeks before URI'/'6-weeks after URI')	-0.0146	0.2317	0.0040	1	0.9498	0.9855
Constant	-1.0536	0.1291	66.611	1	0.0000	

Table 62: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of *HNI LEs* (any impact) *followed by a URI* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			5.2524	2	0.0724	
< 9 years/9 to 11 years	-0.7172	0.3298	4.7298	1	**0.0296**	0.4881
9 to 11 years/>11years	0.5005	0.3556	2.2244	1	0.1358	1.6495
< 9 years/>11years	-0.2167	0.3711	0.3412	1	0.5592	0.8051
Gender	-0.8029	0.2934	7.4902	1	**0.0062**	0.4480
Social class			1.9280	2	0.3814	
Class I & II / Class III & IV	0.4471	0.3554	1.5822	1	0.2084	1.5637
Class III & IV / Class V & VI	0.0950	0.3529	0.0724	1	0.7879	1.0996
Class I & II / Class V & VI	0.5420	0.4367	1.5407	1	0.2145	1.7195
High threat LTE levels	-0.1705	0.2817	0.3665	1	0.5449	0.8432
Positive LTE levels	0.5666	0.3052	3.4459	1	0.0634	1.7622
Constant	-0.8399	0.1476	32.365	1	0.0000	

Table 63: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of *LT HNI LEs followed by a URI* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			5.7009	2	0.0578	
< 9 years/9 to 11 years	-1.5350	0.6720	5.2169	1	**0.0224**	0.2155
9 to 11 years/>11years	0.0089	0.5587	0.0003	1	0.9873	1.0090
< 9 years/>11years	-1.5260	0.7350	4.3114	1	**0.0379**	0.2174
Gender	-0.8338	0.5414	2.3717	1	0.1236	0.4344
Social class			0.1128	2	0.9452	
Class I & II / Class III & IV	-0.1376	0.6438	0.0457	1	0.8308	0.8715
Class III & IV / Class V & VI	0.1904	0.6237	0.0932	1	0.7602	1.2097
Class I & II / Class V & VI	0.0528	0.7727	0.0047	1	0.9455	1.0543
High threat LTE levels	-0.6107	0.5047	1.4642	1	0.2263	0.5429
Positive LTE levels	0.1743	0.5759	0.0916	1	0.7622	1.1904
Constant	-0.7088	0.2854	6.1689	1	0.0130	

Table 64: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of *ST HNI LEs followed by a URI* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			2.9144	2	0.2329	
< 9 years/9 to 11 years	-0.3841	0.3959	0.9412	1	0.3320	0.6811
9 to 11 years/>11years	0.7616	0.4564	2.7850	1	0.0952	2.1418
< 9 years/>11years	0.3776	0.4764	0.6282	1	0.4280	1.4587
Gender	-0.6759	0.3673	3.3867	1	0.0657	0.5087
Social class			1.6774	2	0.4323	
Class I & II / Class III & IV	0.4433	0.4470	0.9836	1	0.3213	1.5579
Class III & IV / Class V & VI	0.2664	0.4891	0.2967	1	0.5860	1.3053
Class I & II / Class V & VI	0.7097	0.5698	1.5512	1	0.2130	2.0335
High threat LTE levels	0.0925	0.3596	0.0661	1	0.7970	1.0969
Positive LTE levels	0.5467	0.3839	2.0276	1	0.1545	1.7275
Constant	-1.0333	0.1933	28.589	1	0.0000	

Table 65: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of *HNI LEs (any impact) preceded by a URI* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			2.7649		0.2510	
< 9 years/9 to 11 years	0.0646	0.3242	0.0398	1	0.8419	1.0668
9 to 11 years/>11years	0.5091	0.3544	2.0638	1	0.1508	1.6639
< 9 years/>11years	0.5738	0.3737	2.3580	1	0.1246	1.7750
Gender	0.0628	0.2830	0.0492	1	0.8244	1.0648
Social class			2.2816	2	0.3196	
Class I & II / Class III & IV	-0.4016	0.3618	1.2317	1	0.2671	0.6693
Class III & IV / Class V & VI	-0.2440	0.3407	0.5130	1	0.4738	0.7835
Class I & II / Class V & VI	-0.6456	0.4309	2.2451	1	0.1340	0.5244
High threat LTE levels	0.0605	0.2844	0.0452	1	0.8316	1.0623
Positive LTE levels	-0.5509	0.3105	3.1481	1	0.0760	0.5764
Constant	-1.0496	0.1464	51.428	1	0.0000	

Table 66: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of *LT HNI LEs* preceded by a *URI* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			4.1203	2	0.1274	
< 9 years/9 to 11 years	1.3760	0.6849	4.0360	1	**0.0445**	3.9590
9 to 11 years/>11years	-0.4570	0.6982	0.4284	1	0.5128	0.6332
< 9 years/>11years	0.9190	0.7224	1.6184	1	0.2033	2.5069
Gender	-0.4981	0.6549	0.5786	1	0.4469	0.6077
Social class			0.3001	2	0.8607	
Class I & II / Class III & IV	-0.3468	0.8855	0.1534	1	0.6953	0.7069
Class III & IV / Class V & VI	-0.2092	0.6547	0.1021	1	0.7493	0.8112
Class I & II / Class V & VI	-0.5560	1.0188	0.2979	1	0.5852	0.5735
High threat LTE levels	-0.4963	0.5826	0.7258	1	0.3942	0.6088
Positive LTE levels	0.1563	0.6905	0.0512	1	0.8209	1.1692
Constant	-1.1228	0.3118	12.967	1	0.0003	

Table 67: Results of Logistic regression investigating the effect of LTE levels, age gender and social class on the proportion of *ST HNI LEs* preceded by a *URI* within a 6-week period.

Variable	B	SE	Wald	df	Sig	Exp.B
Age			4.2391	2	0.1201	
< 9 ycars/9 to 11 years	-0.3540	0.3916	0.8171	1	0.3660	0.7019
9 to 11 years/>11years	0.8694	0.4240	4.2047	1	**0.0403**	2.3854
< 9 years/>11years	0.5153	0.4635	1.2363	1	0.2662	1.6742
Gender	0.1711	0.3311	0.2669	1	0.6054	1.1866
Social class			1.1208	2	0.5710	
Class I & II / Class III & IV	-0.3265	0.4189	0.6076	1	0.4357	0.7214
Class III & IV / Class V & VI	-0.2088	0.4307	0.2351	1	0.6278	0.8115
Class I & II / Class V & VI	-0.5354	0.5154	1.0791	1	0.2989	0.5854
High threat LTE levels	0.1642	0.3410	0.2318	1	0.6302	1.1784
Positive LTE levels	-0.6716	0.3716	3.2657	1	0.0707	0.5109
Constant	-1.0901	0.1807	36.397	1	0.0000	

FIGURES

Figure 1: Biopsychosocial model of disease

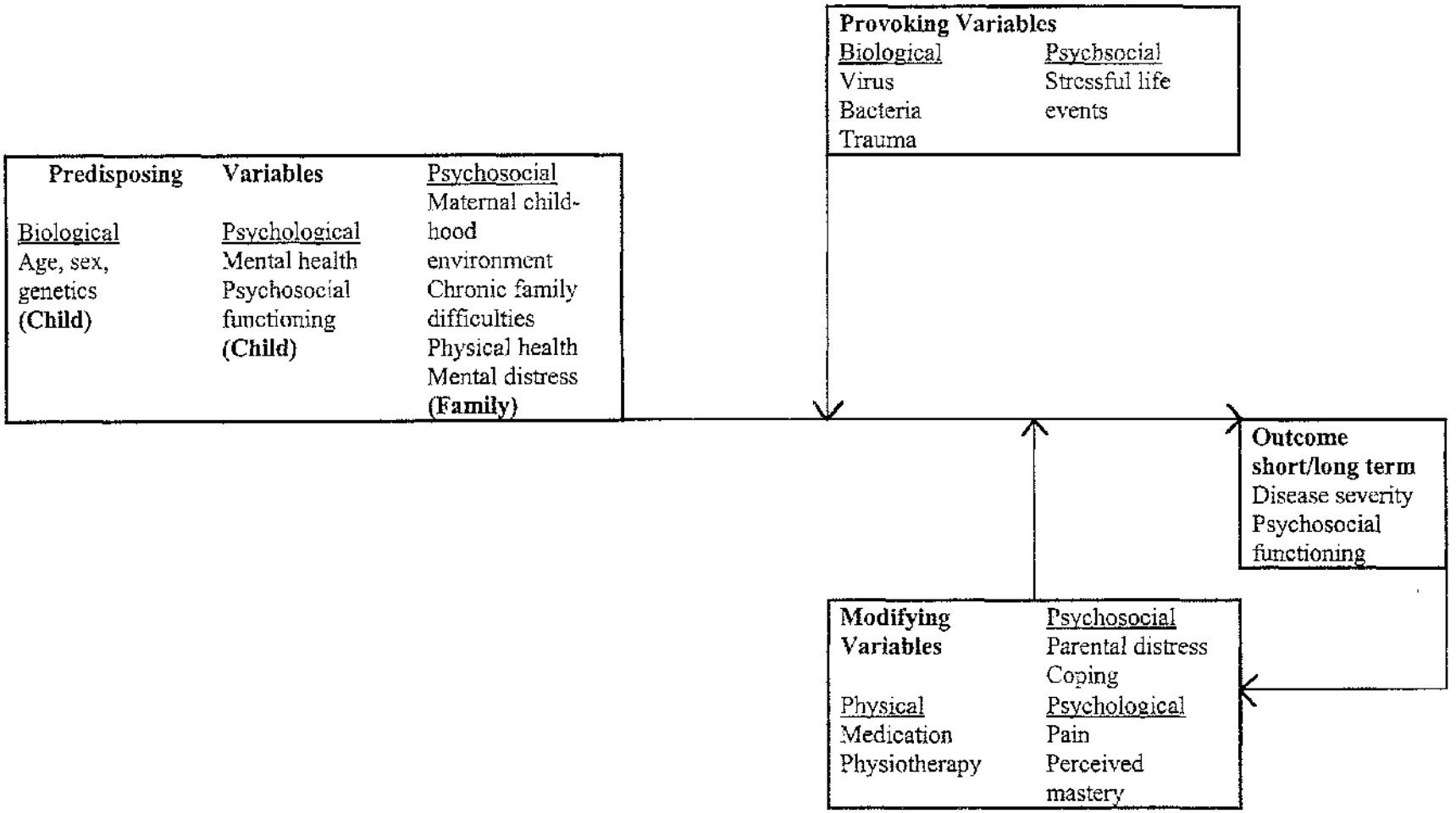


Figure 2: Average total symptoms reported by subjects over each weekday

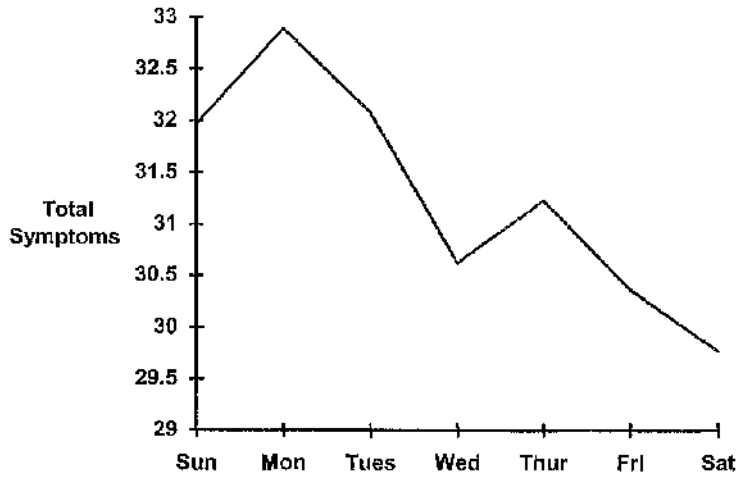


Figure 3: Mean daily symptoms over Symptom Groups

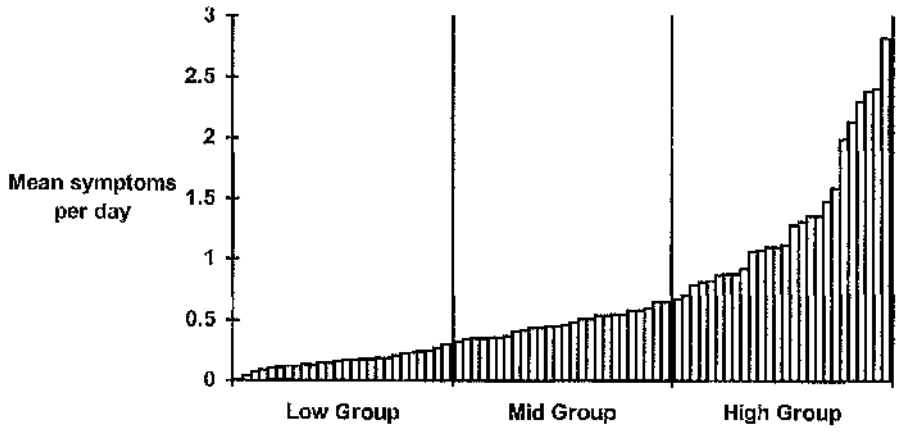
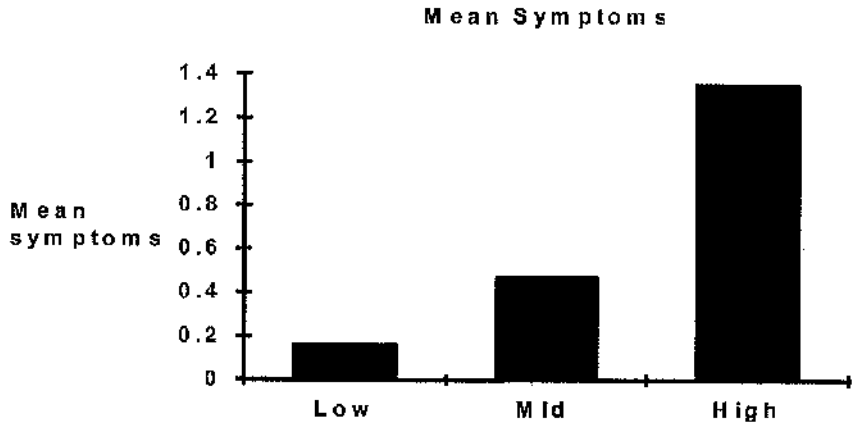
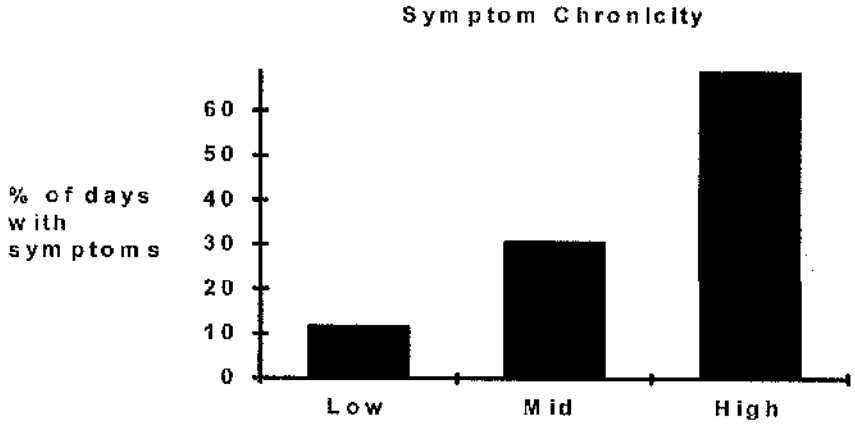


Figure 4: Patterns of symptom presentation over 'low', 'mid' and 'high' symptom presenters





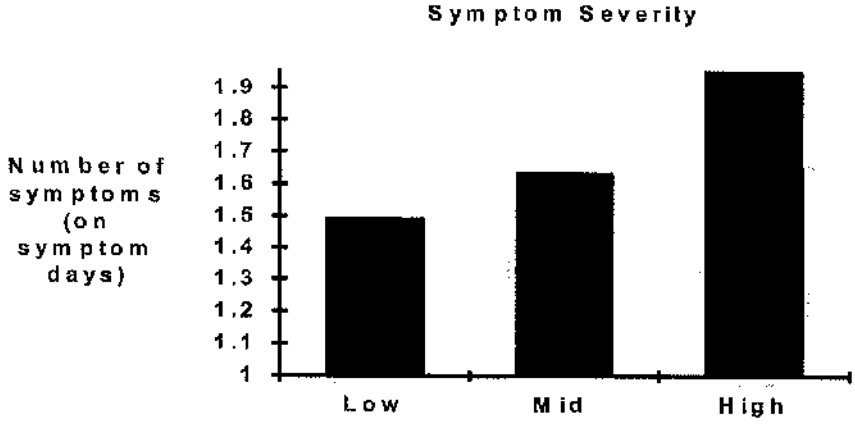


Figure 5: Diagrammatic representation of a Respiratory Episode (RE)

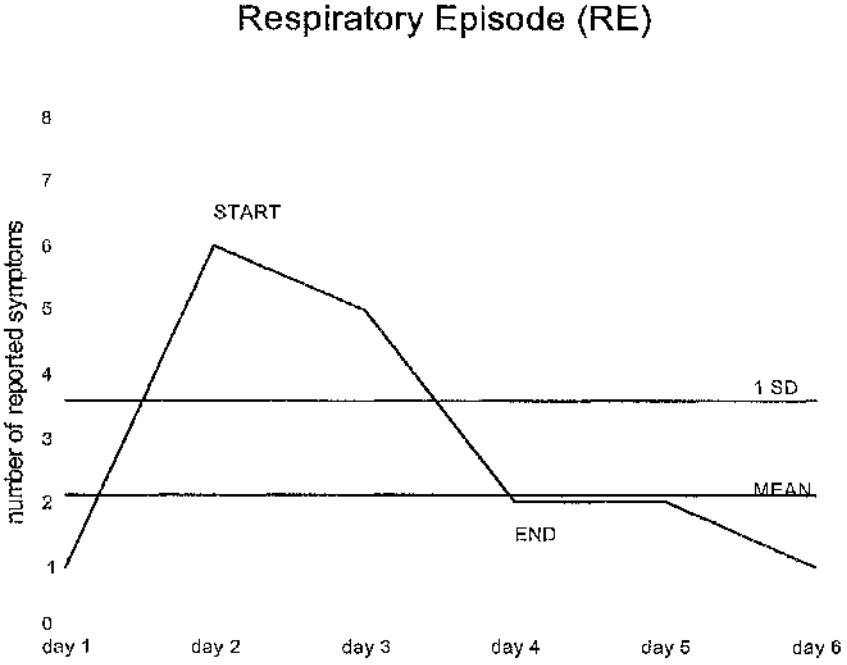


Figure 6: Subject graph for Low Symptom Group (20 week period February to May)

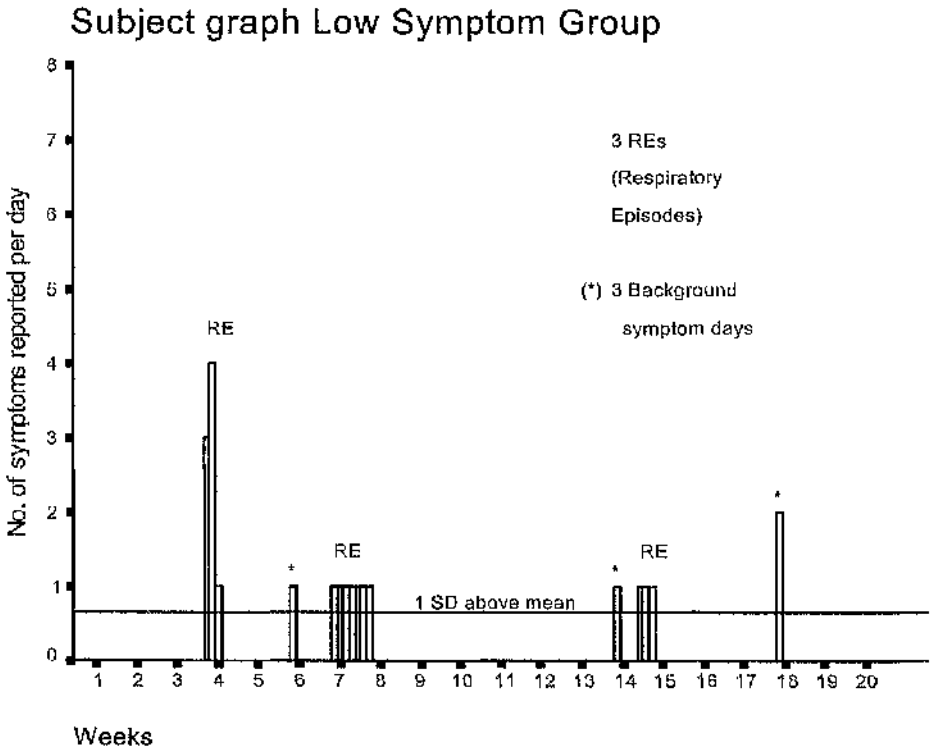


Figure 7: Subject graph for Mid Symptom Group (20 week period February to May)

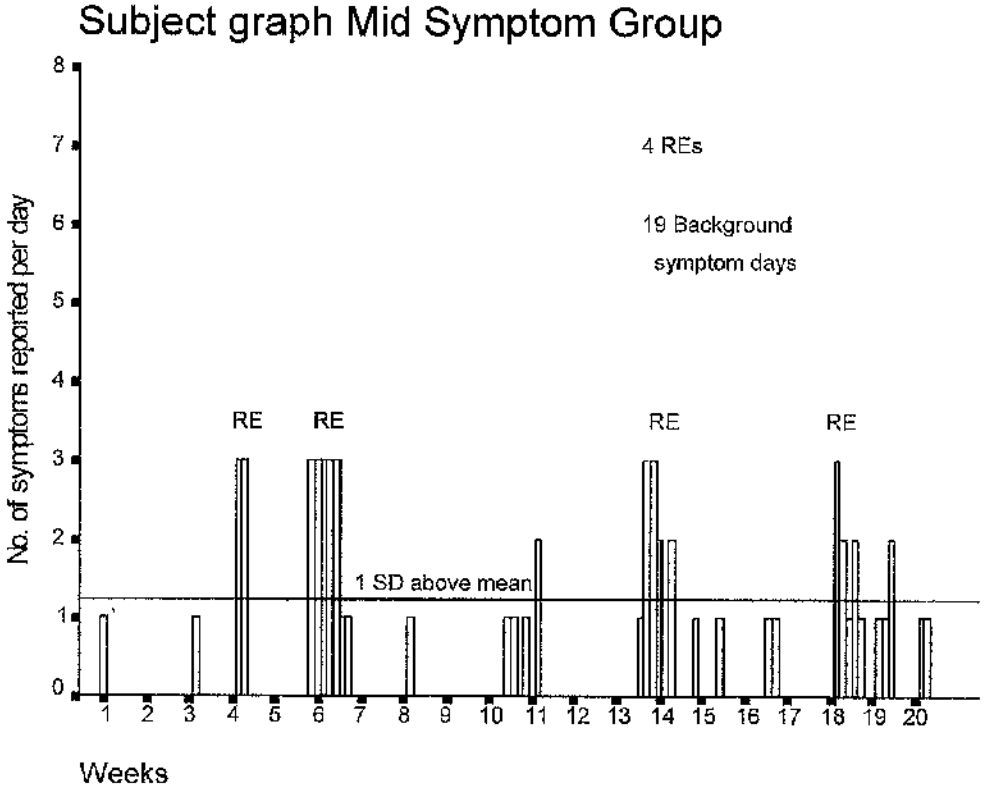


Figure 8: Subject graph for High Symptom Group (20 week period February to May)

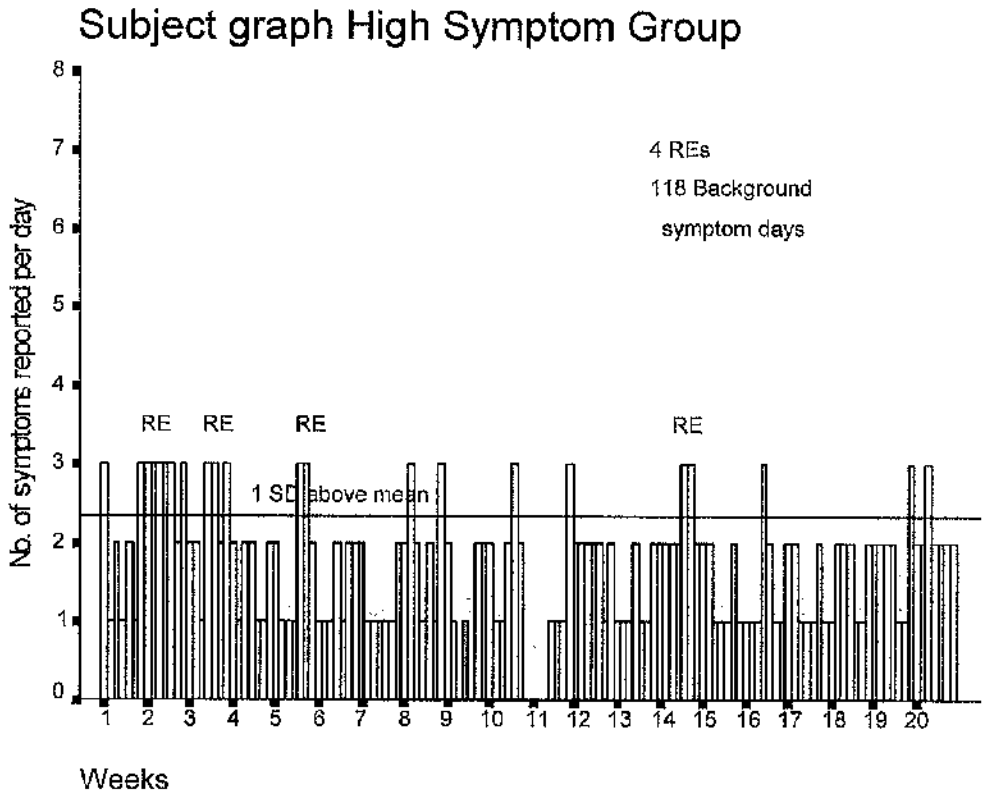


Figure 9: Mean scores over Harter subscales and Symptom Groups