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# Psychosocial factors, respiratory viruses and exacerbation of asthma

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## Abstract

The aim of this research was study the role of psychosocial factors in exacerbations of asthma in adults induced by upper respiratory tract infections (URTIs). It involved a longitudinal study (one year) of 92 adults with asthma. The volunteers were 27 men and 65 women 19–46 years of age with a mean duration of wheeze of 19 years. The main outcome measure was symptomatic colds producing asthma exacerbations (infections confirmed by laboratory assays and exacerbation of asthma confirmed by objective changes in peak expiratory flow rate). The results showed that about 20% of the sample did not report an episode. This subgroup had a high proportion of males, low negative affectivity scores and consumed more alcohol. When volunteers with at least one episode were considered it was found that those who reported more negative life events and had low levels of social support had more episodes. Smokers were more likely to have to visit their doctor when they developed a cold-induced exacerbation of asthma. Overall, these results show that health-related behaviours, demographic and psychosocial factors influence susceptibility to and severity of exacerbations of asthma by URTIs. © 2001 Elsevier Science Ltd. All rights reserved.

*Keywords:* Stress; Social support; Negative affectivity; Gender; Smoking; Upper respiratory tract infections; Asthma

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## 1. Introduction

Recent research has shown that psychological stress influences susceptibility to experimentally induced upper respiratory tract illnesses (Cohen et al., 1991). We have also shown that respiratory virus infections commonly cause or are associated with exacerbations of asthma in adults (Nicholson et al., 1993). Taken together these two results suggest that stress should increase the frequency of URTI induced exacerbations of asthma. The present article presents preliminary data on this issue.

It is widely believed that life stressors increase susceptibility to infectious disease. This view is supported by research which has demonstrated direct connections between stress and immune system functioning (Kiecolt-Glaser and Glaser, 1991; Manuck et al., 1991). Similarly, some studies of community samples show that social stressors increase the risk for verified upper respiratory disease (Meyer and Haggerty, 1962; Graham et al., 1986). A viral challenge study provides the strongest evidence for a link between stress and susceptibility to the common cold. Cohen et al. (1991) controlled for exposure to the infecting agent, removed the effect of important predictors of susceptibility such as pre-existing antibodies to the infectious agent, and demonstrated that the effect of stress was not produced by differences in personality or health-related behaviours. Recent studies have extended these results by considering a wider range of psychosocial factors. Cohen et al. (1995) assessed the influence of trait negative affectivity and temporary fluctuations in negative mood (state negative affectivity). Both baseline trait and state negative affectivity were associated with the number of symptoms reported but they were found to have independent effects. State negative affectivity not only predicted symptoms but showed a positive relation with an objective marker of illness, nasal secretion weight. In contrast, trait negative affectivity was associated with symptom reporting but not nasal secretion weight. The effects of stress on health are often mediated by a number of other psychological factors. Social support can often act as a buffer against the effects of stress (Cohen and Wills, 1985) and Cohen et al. (1997) conducted a viral challenge study to determine whether social support played an important role in the development of colds. Social diversity, but not the total number of network members, was associated with a reduction in virus replication, fewer symptoms and lower nasal secretion weights, and increased mucociliary clearance. Turner-Cobb and Steptoe (1996) examined the effects of stress and social support in a diary study of upper respiratory tract illnesses. Under low levels of stress, high levels of social support were associated with a decreased risk of infection, whereas social support had no effect when levels of stress were high. An initial aim of the present study was to examine the associations between psychosocial factors (stress, social support, negative affectivity) and viral excacerbations of asthma.

The present study involved naturally occurring illnesses rather than experimentally-induced ones but it maintained several important features of the methodology used by Cohen et al. (1991). First, stress was measured at the start of the study in order to examine the extent to which it could predict subsequent illness. Secondly, two dimensions of personality, namely introversion and neuroticism, which have been shown to be important predictors of susceptibility to colds (Broadbent et al.,

1984) were also measured at the start of the study. Smoking status and alcohol consumption were also recorded as these have been shown to be important predictors of colds (Cohen et al., 1993a).

Before considering the effects of psychosocial factors on respiratory virus induced exacerbations of asthma it is essential to have strong evidence for the role of these viruses in asthma. Until recently there appeared to be only a weak association between asthma and upper respiratory tract infection in adults (Hudgel et al., 1979; Beasley et al., 1988). The absence of a stronger association in these epidemiological studies of adult asthmatics could, at least in part, have been due to difficulties in isolating human rhinoviruses and coronaviruses. Indeed, results from a study using enzyme linked immunosorbent assays for antibodies to human coronavirus and sem-inested reverse transcriptase polymerase chain reactions for detections of rhinovirus suggested a stronger role of these viruses in asthma in adults (Nicholson et al., 1993). Details of these results are given below as they not only confirm the importance of URTIs in exacerbating asthma but validate the main outcome measure considered here.

A longitudinal study of 138 adults with asthma showed that colds were reported in 80% of episodes with symptoms of wheeze, chest tightness or breathlessness. Indeed, 89% of colds were associated with asthma symptoms. About 70% of labora-tory confirmed infections were associated with chest tightness, wheeze and breath-lessness. Similarly, acute upper respiratory tract viral infections were associated with objective measures (decreases in peak expiratory flow) of exacerbation of asthma. These results demonstrate that subjective reports of a cold and exacerbation of asthma have been validated using objective indicators of infection and asthma. The data presented in this article were collected to test the hypothesis that psychosocial factors would influence the susceptibility to cold induced exacerbations of asthma.

## 2. Method

Details of the patients and study design have already been published (Nicholson et al., 1993). The psychological measures are described here and a brief summary of other features of the study given.

### 2.1. Patients

Of the 138 subjects recruited into the study, 92 participated for at least one year. These subjects provided the data reported here. They did not differ in age from the original sample, having an age range of 19–46 years. Twenty seven were males and 65 females, reflecting the gender bias in the original study. Those who completed the study did not differ from those who dropped out with regard to history of asthma, psychosocial factors or health-related behaviours.

## 2.2. Procedure

At baseline subjects were asked about the duration and frequency of their asthma, medication, hospitalisation and history of atopy. They were examined clinically and peak expiratory flow rates measured. Blood samples and nose and throat swabs were collected for serology and virological testing. The subjects also completed the psychological questionnaires (see below).

Once they had completed their baseline measurements subjects were instructed to contact the researchers immediately they developed symptoms of an acute upper respiratory tract illness or increased symptoms of asthma. Symptoms were recorded on diary cards and symptomatic patients were seen at home or work as soon as possible after the onset of the symptoms. A cold was defined as having two or more of the following symptoms, with at least one being moderately severe or severe: runny nose, stuffy nose, sneezing, sore throat, cough, systemic features. Exacerbation of asthma was defined as either (a) an increase in one or more symptoms of wheeze, chest tightness and breathlessness in association with an increase in bronchodilator use, or (b) the subject was noted to be wheezing on clinical examination, or (c) the subject was admitted to hospital with asthma.

Nose and throat swabs were collected as was a 10 ml acute phase blood sample. A convalescent blood sample was collected 21 days later. All subjects were seen routinely and during these a 10 ml blood sample and nose and throat swabs were collected.

Paired acute and convalescent serum samples were stored at $-20°C$ and tested later by complement fixation tests for antibodies to adenovirus, influenza A and B, respiratory syncytial virus, parainfluenza viruses types 1,2 and 3, *Mycoplasma pneumoniae* and *Chalmydia psittaci*. An ELISA not commercially available was used to detect rises in antibodies to coronavirus 229E and OC43 (Kraaijeveld et al., 1980). Human rhinoviruses in the nose and throat swabs were identified by using a seminested reverse transcriptase (RT) polymerase chain reaction (PCR) that is described fully elsewhere (Ireland et al., 1993).

## 2.3. Questionnaires

### 2.3.1. Negative life events

The major stressful life events scale (Cohen et al., 1993b) consisted of 41 items that might happen in the life of the respondent. Respondents were asked which of the items had occurred during the last 12 months and they were asked to rate each event they reported as having either a positive or negative impact on their lives. The score was the number of negative events reported by the subject.

### 2.3.2. Eysenck personality inventory (Eysenck and Eysenck, 1963)

This measures introversion and neuroticism.

### 2.3.3. Interpersonal self-evaluation list (Cohen and Hoberman, 1983)

This measures perceived social support. The score used here was the total support score.

### 2.3.4. Health-related behaviours

Smoking status and history were recorded, as was alcohol consumption.

## 3. Results

Interest here lies in the relationship between the psychosocial scores and the frequency of colds with asthma. The mean number of colds/asthma episodes was 1.68 (s.d. 1.45; median: 1.0; range 0–7; 95% confidence limits: 1.38, 1.99). Over 20% of the volunteers did not report an episode of asthma associated with a cold. Initial analyses were conducted to determine whether this group had a different psychosocial profile from those who had one episode or more. The data for these two subgroups are shown in Table 1.

The analyses revealed that those who reported no episodes had a higher proportion of males (chi squre=8.11 d.f.1 $P<0.005$), lower negative affectivity scores ($t=-2.18$ d.f.1,90 $P<0.05$) and consumed more alcohol ($t=2.60$ d.f.1,90 $P<0.05$). When these variables were entered into a logistic regression all had a significant effect (gender: $F=8.70$ d.f.1,90 $P<0.005$; negative affectivity: $F=4.32$ d.f.1,89 $P<0.05$; alcohol consumption: $F=5.36$ d.f.1,89 $P<0.05$). Negative life events, social support and their

Table 1
Demographic, psychosocial, and health-related behaviour characteristics of those who reported no cold/asthma episodes and those who reported one or more

|  | No episodes | At least one episode | Whole sample |
|---|---|---|---|
| Males (*N*) | 11 | 16 | 27 |
| Females (*N*) | 9 | 56 | 65 |
| Age (years) (mean scores, s.d.s in parentheses) | 33.4 (8.2) | 33.2 (6.6) | 33.3 (7.0) |
| Negative affectivity: (mean scores, s.d.s in parentheses) | 8.1 (4.6) | 10.8 (5.1) | 10.3 (5.1) |
| Introversion: (mean scores, s.d.s in parentheses) | 9.3 (4.0) | 10.5 (4.1) | 10.3 (4.3) |
| Negative life even (mean scores, s.d.s in parentheses) | 1.6 (1.2) | 2.3 (2.2) | 2.2 (2.0) |
| Social Support: | | | |
| Total ISEL score: (mean scores, s.d.s in parentheses) | 91.1 (23.9) | 94.6 (14.8) | 93.8 (17.1) |
| Units of alcohol a week: (mean scores, s.d.s in parentheses) | 10.15 (10.6) | 5.2 (6.5) | 6.3 (7.8) |

interaction did not have a significant effect. Similarly, introversion, smoking and age had no effect.

The next set of analyses was restricted to those who reported at least one episode. An analysis of covariance was conducted to determine whether stress influenced the number of colds with asthma and whether this effect was modified by social support. The other variables were entered as covariates. Median splits were used to categorise the high/low negative life events groups (median=2) and high/low social support groups (median=97). The mean negative life events scores and the mean total ISEL scores for these four groups are shown in Table 2. A significant interaction ($F$=5.9 d.f.1,62 $P<0.05$) between negative life events and social support was observed (see Fig. 1). This reflected the greater number of episodes in the high stress low support group. None of the covariates had a significant effect on the number of episodes.

The next set of analyses considered the severity of the episodes by distinguishing those that required a visit to the doctor and those which did not. Twenty-seven of the patients were either current or ex-smokers. While this group did not differ in the frequency of cold/asthma episodes they did have more severe episodes which resulted in them having to see their GP more frequently following the illness (chi square=3.84 d.f.1 $P$=0.05). This is shown in Table 3. When a logistic regression was carried out including the other independent variables only the effect of smoking was significant ($F$1,70=3.94 $P$=0.05).

Table 2
Negative life-events and total ISEL scores for the high/low social support and high/low negative life events sub-groups (scores are the means, s.d.s. in parentheses)

|  | low stress/low support | low stress/high support | high stress/low support | high stress/high support |
|---|---|---|---|---|
| Negative life events: | 1.00 (0.84) | 0.88 (0.88) | 4.53 (2.17) | 4.10 (1.10) |
| Total ISEL: | 85.97 (15.64) | 104.64 (4.99) | 83.13 (12.50) | 106.50 (5.70) |

Table 3
Effects of smoking on number of GP visits following cold/asthma exacerbation

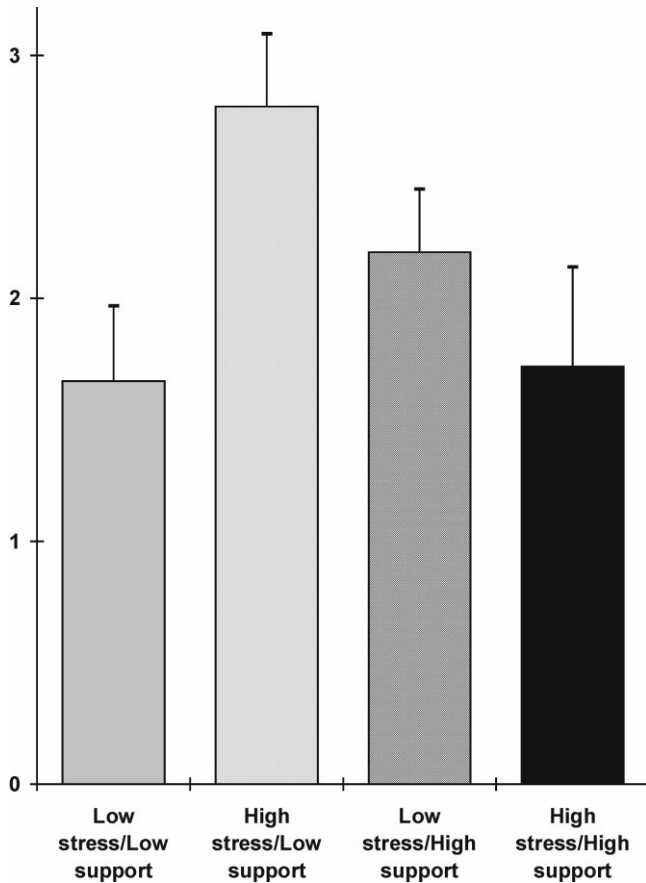|  | Smoker (N=27) | Non-smoker (N=45) |
|---|---|---|
| GP visits: |  |  |
| None: | 11 | 29 |
| One or more | 16 | 16 |

Fig. 1. Mean number of cold/asthma episodes in subjects who reported high/low numbers of negative life events and with high/low levels of social support (scores are the adjusted means from the analysis of covariance, s.e.s shown as bars).

## 4. Discussion

Previous research has shown that psychosocial factors and health-related behaviours are related to subsequent susceptibility to upper respiratory tract illness. Associations between acute respiratory infections and exacerbation of asthma have been noted in previous studies and in an earlier report of the present investigation. The analyses reported here show three different types of effect. The first effect examined was whether psychosocial characteristics and health-related behaviours were associated with the occurrence of cold-induced exacerbations of asthma. These results showed that those who didn't report such an episode were more likely to be male, have lower negative affectivity scores and consume more alcohol. Stress and social report were not significant factors in these first analyses.

The second set of analyses considered only those volunteers who reported at least

one episode. Negative life events were associated with increased episodes of colds and asthma but only when levels of social support were low. This interaction between stress and social support did not reflect demographic factors, personality or health-related behaviours. Smoking was associated with increased severity but not frequency of exacerbation. Again, this effect could not be attributed to the other factors measured (psychosocial factors, demographics).

The present results are important because they were achieved in the context of a study with a number of crucial methodological features. First, volunteers in this study were enrolled from the community, general practice and hospital. Indeed, the sample was representative of young adults with asthma in the general population, although the trial population did have more women and more subjects with a history of severe asthma than one would expect in the general asthmatic population.

The second important feature of the methodology was the use of objective measures to confirm upper respiratory tract infections and exacerbations of asthma. The diagnostic rate for viruses and asthma exacerbations was much higher than in other studies although not as high as might be expected on the basis of symptoms. This probably reflects methodological features of the virology and serology and improvements in the development of sensitive tests may well lead to the view that these non-bacterial pathogens have an even greater role in the exacerbation of asthma. Similarly, the method used to assess peak expiratory flow rates may have missed brief exacerbations, although it did prevent problems of asthma control being included as exacerbations.

In summary, the present study confirmed the view that psychosocial factors and health-related behaviours are associated with increased susceptibility to colds, which then leads to an exacerbation of asthma. This was done in the context of a study where both diseases (cold and asthma) were verified using objective measures. The well-established buffering effect of social support was observed in the high stress group and possible confounders such as demographics, health-related behaviours or personality could not account for this effect. In addition to this, alcohol consumption, personality and demographic factors were shown to be important predictors of susceptibility. In contrast to this smoking was related to illness severity. These results show that one must consider a range of psychosocial factors, personality traits, demographic factors and health-related behaviours in studies of individual differences in susceptibility and severity of upper respiratory tract infections. Such a conclusion fits with the existing literature and the present study has extended the research by considering a population, namely asthmatics, where a cold can have far greater consequences. The literature on asthma also suggests that a variety of factors may have an influence. For example, Klinnert et al. (1994) found associations between life events and asthma and some evidence that social support buffered against stress. Brook and Tepper (1997) found that adolescents with asthma had significantly lower self-esteem than those who did not suffer from asthma. Asthma also tends to be more frequent in females than males and the metabolic changes associated with the menstrual cycle provide a plausible mechanism for gender to be an important factor in susceptibility to asthma attacks (Nagata et al., 1997). Smoking may be important in asthma for two reasons. First, smoking causes direct damage to the respiratory

tract which may lead to greater severity of symptoms. Second, smoking will influence the immune system which again may alter the severity of the disease. Moderate consumption of alcohol has been shown to be beneficial in other studies of susceptibility to respiratory diseases (Cohen et al., 1993a) and it is possible that alcohol has an anti-inflammatory action that may be important in asthma. All of these results show the importance of considering a range of variables in this type of study. Identification of the mechanisms underlying the effects reported here is difficult in this type of study. For example, if one examines the variables found to be important in whether a cold/asthma episode was reported or not, one finds that several different interpretations are possible. If one considers the finding that low negative affectivity was associated with a reduced likelihood of reporting an episode then this could reflect several things. First, it could suggest that biases in self-report related to negative affectivity are operating. Secondly, it may be the case that negative affectivity reflects the extent of reactions to stress and those with high levels may be more vulnerable to illness because of this greater reactivity. Similarly, the effects of gender and alcohol consumption are difficult to ascribe to single mechanisms. For example, do the gender differences reflect the biological differences between males and females or correlated psychosocial attributes not measured here? Further research is now needed to determine the mechanisms which underlie these associations.

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## References

Beasley, R., Coleman, E.D., Hermon, Y., Holst, P.E., O'Donnell, T.V.O., Tobias, M., 1988. Viral respiratory tract infection and exacerbations of asthma in adult patients. Thorax 43, 679–683.

Broadbent, D.E., Broadbent, M.H.P., Phillpotts, R.J., Wallace, J., 1984. Some further studies on the prediction of experimental colds in volunteers by psychological factors. J. Psychosom. Res. 28, 511–523.

Brook, U., Tepper, I., 1997. Self-image, coping and familial interaction among asthmatic children and adolescents in Israel. Patient Educ. Couns. 30, 187–192.

Cohen, S., Hoberman, H.M., 1983. Positive events and social supports as buffers of life change stress. J. Appl. Soc. Psychol. 13, 99–125.

Cohen, S., Wills, T., 1985. Stress, social support and the buffering hypothesis. Psychol. Bull. 98, 310–357.

Cohen, S., Tyrrell, D.A.J., Smith, A.P., 1991. Psychological stress and susceptibility to the common cold. N. Engl. J. Med. 325, 606–612.

Cohen, S., Tyrrell, D.A.J., Russell, M.A.H., Jarvis, M.J., Smith, A.P., 1993a. Smoking, alcohol consumption and susceptibility to the common cold. Am. J. Public Health 83, 1277–1283.

Cohen, S., Tyrrell, D.A.J., Smith, A.P., 1993b. Negative life events, perceived stress, negative affect, and susceptibility to the common cold. J. Pers. Soc. Psychol 64, 131–140.

Cohen, S., Gwaltney, J.M., Doyle, W.J., Newsom, J.T., 1995. State and trait negative affect as predictors of objective and subjective symptoms of respiratory viral infections. J. Pers. Soc. Psychol. 68, 159–169.

Cohen, S., Doyle, W.J., Skoner, D.P., Rabin, B.S., Gwaltney, M.D., 1997. Social ties and susceptibility to the common cold. J. Am. Med Assoc. 277, 24.

Eysenck, H.J., Eysenck, S.B.G., 1963. Manual of the Eysenck Personality Inventory. University of London Press, London.

Graham, N.M.H., Douglas, R.B., Ryan, P., 1986. Stress and acute respiratory infection. Am. J. Epidemiol. 124, 389–401.

Hudgel, D.W., Langston, L., Seiner, J.C., McIntosh, K., 1979. Viral and bacterial infections in adults with chronic asthma. Am. Rev. Respir. Dis. 120, 393–397.

Ireland, D.C., Kent, J., Nicholson, K.G., 1993. Improved detection of rhinovirus in nasal and throat swabs by semi-nested RT–PCR. J. Med. Virol. 40, 96–101.

Kiecolt-Glaser, J.K., Glaser, R., 1991. Psychosocial factors, stress, disease, and immunity. In: Ader, R., Felten, D.L., Cohen, N. (Eds.), Psychoneuroimmunology. Academic Press, San Diego, CA, pp. 849–867.

Klinnert, M.D., Mrazek, P.J., Mrazek, D.A., 1994. Early asthma onset: The interaction between family stressors and adaptive parenting. Psychiatry 57, 51–61.

Kraaijeveld, C.A., Reed, S.E., MacNaughton, M.R., 1980. Enzyme-linked immunosorbent assay for detection of antibody in volunteers experimentally infected with human coronavirus 229E. J. Clin. Microbiol. 12, 493–497.

Manuck, S.B., Cohen, S., Rabin, B.S., Mouldeen, M., Bachen, E., 1991. Individual differences in cellular immune response to stress. Psychol. Sci. 2, 111–115.

Meyer, R.J., Haggerty, R.J., 1962. Streptococcal infections in families. Pediatrics 29, 539–549.

Nagata, K., Ishitobi, K., Yamamoto, Y., Ikeda, T., Hori, S., Matsumoto, Y., Sasaki, T., 1997. Increased theophylline metabolism in the menstrual phase of healthy women. J. Allergy Clin. Immunol. 100, 39–43.

Nicholson, K.G., Kent, J., Ireland, D.C., 1993. Respiratory viruses and exacerbations of asthma in adults. Br. Med. J. 307, 982–986.

Turner-Cobb, J.M., Steptoe, A., 1996. Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample. Psychosom. Med. 58, 404–412.