

## ORIGINAL ARTICLE

## Case-control study of severe life threatening asthma (SLTA) in adults: psychological factors

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**Background:** Severe life threatening asthma (SLTA) is important in its own right and as a proxy for asthma death. In order to target hospital based intervention strategies to those most likely to benefit, risk factors for SLTA among those admitted to hospital need to be identified. Adverse psychological factors are purported risk factors for asthma death and SLTA /near fatal asthma. A study was undertaken to determine whether, in comparison with patients admitted to hospital with acute asthma, those with SLTA have specific adverse psychological factors.

**Methods:** A case-control study was undertaken. Cases (n=77) were admitted to the intensive care unit with SLTA (mean (SD) pH 7.17 (0.15), PaCO<sub>2</sub> 10.7 (5.0) kPa). Controls (n=239) were admitted to general wards with acute asthma and were matched only by date of index attack. An interviewer administered questionnaire was undertaken 24–48 hours after admission. A random sample of community based asthmatics was recruited to provide normative data on asthmatics for comparison with cases and hospital controls.

**Results:** The risk of SLTA increased with age (OR 1.04/year, 95% CI 1.01 to 1.07) and was less for women (OR 0.36, 95% CI 0.20 to 0.68). These variables were controlled for in all further analyses. There was a high prevalence of psychological disorder in both cases and matched controls, but there was no difference in prevalence of caseness for anxiety or depression, total (or individual) life events in last 12 months, availability of general or disease specific social support, nor in any of the domains of the Attitudes and Beliefs about Asthma Questionnaire (emotional (mal) adjustment, doctor-patient relationship, stigma, self-efficacy). Cases (SLTA) were less likely to have had previous emotional counselling (25% v 35%, p<0.05). However, when comparison was made with a community based group of asthmatic patients, those admitted to hospital with acute asthma (SLTA and hospital controls) had a higher prevalence of anxiety and depression, higher total life events, and higher prevalence of certain specific life events.

**Conclusions:** There was considerable psychological morbidity generally (and anxiety specifically) in those admitted with acute asthma. Specific adverse psychological factors were not risk factors for SLTA, when comparison was made with those admitted to hospital with acute asthma, but adverse psychological factors were a risk factor for hospitalisation for acute asthma (including SLTA). Psychological risk factors for adverse events in asthma are dependent both on the type of event under study and the comparison group used.

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While severe life threatening asthma (SLTA) is an important entity in its own right, it may be regarded as a "proxy for asthma death". This contention is based on the shared sociodemographic and other characteristics between those with SLTA and those dying of asthma<sup>1-4</sup>; that death would almost certainly ensue in those presenting with SLTA in the absence of prompt medical intervention; that SLTA is a risk factor for asthma death<sup>5</sup>; and that a significant proportion of persons dying of asthma have had prior SLTA.<sup>6,7</sup> The study of SLTA has a number of practical advantages over the study of asthma death—greater numbers, the subject is available for interview, and thus more detailed accurate and less biased data can be obtained. The precise definition of risk factors for SLTA (and asthma death), particularly in the population admitted to hospital for acute asthma, should allow the development of specific interventional strategies to reduce the incidence of both forms of adverse event.

Adverse psychological factors are common in those with severe asthma and have been defined as a risk factor for asthma death<sup>3,5,8-14</sup> and life threatening asthma.<sup>15-19</sup> However, few studies have used validated instruments to carefully assess these factors; most factors have been crudely defined<sup>5,9,11,13,14,18</sup> and based on data obtained from relatives,<sup>5,9,11,14,18</sup> the deceased patient's own doctor,<sup>5,9,11,13,14,18</sup> or a medical record which did not necessarily pertain to the event

itself.<sup>5,9,11,13,14,18,19</sup> As such, the information is often inaccurate, incomplete, and subject to important bias. In many studies the lack of an adequate control group meant that it was not possible to determine whether the reported prevalence of psychological factors was specifically associated with SLTA/death or merely due to chronic and/or severe asthma and its associated morbidity.<sup>11,13,14,15,18</sup>

The primary aim of this study was to determine whether, in comparison with patients admitted to hospital with acute asthma, patients experiencing SLTA had either higher levels or a greater prevalence of psychological morbidity.

## METHODS

A prospective case-control study design was undertaken because of its efficiency.<sup>20</sup> Data on sociodemographics, health care, and management of the acute attack have been published elsewhere.<sup>21</sup>

## Cases

Cases were persons normally resident in the Auckland region, aged 15–49 years, admitted to one of the two intensive care units (ICUs) in the region with SLTA.<sup>1</sup> For the purposes of this study, SLTA was defined as admission to an ICU with acute severe asthma plus at least one of the following: (i) cardiorespiratory arrest; (ii) requirement for mechanical ventilation;

(iii) impaired conscious level at presentation; (iv) pH <7.2, and (v)  $\text{Paco}_2 \geq 6.0$  kPa. Exclusion criteria have been previously detailed.<sup>21</sup>

### Controls

#### Matched hospital control group

This group comprised persons normally resident in the Auckland region aged 15–49 years who were admitted to a general medical ward of the same hospital as the case with acute asthma on the same day, the day before, or within the subsequent 2 weeks of admission of the case—that is, days 1–14. Apart from matching in terms of timing of presentation, no other matching was undertaken but sociodemographic characteristics were measured and, if found to be independent, risk factors were controlled for in subsequent analyses. Up to four matched controls were selected for each case in order to maximise efficiency.<sup>20</sup> Exclusion criteria have been detailed elsewhere.<sup>21</sup>

#### Community comparison group

A random sample of community based asthmatics was recruited to provide normative data on asthmatics for comparison with that of cases and controls. Recruitment was based on those identified in a previous study of the prevalence of adult asthma.<sup>22</sup>

### Questionnaire

A detailed questionnaire was administered to cases and hospital controls within 24–72 hours of admission to general medical wards (either directly or after discharge from the ICU) by the same research associate (WF) who was blinded to the hypotheses being tested. Members of the community comparison group were interviewed at home. All components were administered by the interviewer and included:

- (1) Patient demographic data.
- (2) Level of anxiety and depression using the Hospital Anxiety and Depression (HAD) scale<sup>23</sup> (which is specific for distress in physically ill subjects) and state and trait anxiety assessed on a visual analogue scale. Caseness for anxiety and/or depression was defined as an HAD score of >11.
- (3) Social support measured by a modification of the scale of O'Reilly and Thomas<sup>24</sup> which was designed to evaluate social support in patients with cardiac disease. This included an assessment of general support as well as disease specific support, both day to day and during acute attacks.<sup>25</sup>
- (4) Life events using a validated modification for New Zealand of the life event scale of Tenant and Andrews.<sup>26</sup>
- (5) Attitudes and beliefs about asthma using a modification of the instrument developed by Sibbald *et al.*<sup>27</sup> This questionnaire has been extensively modified, consensual validity tested, and trialled in different patient groups.<sup>25–30</sup> The results of factor analysis of the modified questionnaire are presented in detail in an appendix to Kolbe *et al.*<sup>31</sup>

The instruments used in (2), (3), and (4) have previously been trialled and found to be feasible, acceptable, and reliable in patients attending an asthma clinic<sup>25–28</sup> and in different ethnic groups.<sup>29</sup>

Information was also obtained on psychosocial factors based on the definition of Rea *et al.*<sup>3</sup> and whether the person had previously received “counselling for emotional problems”.

### Ethics

All subjects provided written informed consent to participate in the study which was approved by the Auckland Healthcare ethics committee.

### Statistical analysis

Data are expressed as mean (SD) values. The modified Attitudes and Beliefs questionnaire underwent factor analysis

**Table 1** State-trait anxiety, anxiety and depression scores (HAD scale), and caseness for anxiety and depression for cases (SLTA), matched hospital controls, and community comparison group

	Cases (SLTA)	Matched hospital controls	Community comparison group
<b>Anxiety</b>			
State	3.6 (1.6)	3.5 (1.5)	2.1 (1.4)
Trait	2.8 (1.5)	2.7 (1.6)	2.8 (1.2)
<b>Anxiety</b>			
HAD score	7.8 (4.5)	8.3 (4.3)	7.4 (3.5)
Caseness	36%	38%	28%*
<b>Depression</b>			
HAD score	4.0 (3.7)	4.1 (3.7)	3.5 (2.7)
Caseness	8%	8%	2%*

\*p<0.05 compared with both cases and controls.

with orthogonal transformation. Using a cut off point of eigenvalue >0.5, a four factor solution was obtained. Factor 1 contained items related to emotional (mal) adjustment to asthma, factor 2 doctor-patient relationship, factor 3 stigmatisation, and factor 4 self-efficacy.<sup>31</sup> After the variables representing these factors were defined, they were combined using unit weighting to provide the factor score. Remarkably similar solutions of factor analysis have been obtained in the different patient groups studied (data not presented).

For the matched cases and controls, conditional logistic regression was performed to identify factors related to SLTA compared with the matched hospital control group. Basic demographic variables were analysed initially and any statistically significant variables were included in all further analyses. Variables considered to be the best measures of adverse psychologic factors were grouped and analysed in conjunction with the significant demographic variables. Differences between cases and the community comparison group were analysed using unpaired *t* tests and the Wilcoxon signed rank test on parametric and non-parametric data, respectively. The  $\chi^2$  test was used to test the differences in proportions between the groups. A *p* value of  $\leq 0.05$  was regarded as statistically significant.

### RESULTS

Seventy seven patients fulfilled the criteria for cases; 239 matched hospital controls were recruited representing 1–4 controls/case. One hundred subjects were recruited in the community comparison group. Details of potential subjects excluded, demographic data, and health care have been presented elsewhere.<sup>21</sup> In comparison with matched hospital controls, the risk of SLTA increased with age (OR 1.04/year, 95% CI 1.01 to 1.07) and was less for women (OR 0.36, 95% CI 0.20 to 0.68).<sup>21</sup> These variables were controlled for in all subsequent analyses. (Although adjusted odds ratios are presented, adjustment made only minor difference to the effect sizes).

There was a high prevalence of psychological disorder in cases and matched hospital controls. Data on state/trait anxiety, anxiety and depression scores (HAD scale), and caseness for anxiety and depression (based on the HAD score<sup>23</sup>) are shown in table 1. There were no differences between cases and controls, but caseness for anxiety and depression was less prevalent in the community group. Life events (total and certain individual) in the last year are shown in table 2. There were no differences between cases and controls; however, total life events and the prevalence of certain life events were less in the community group. Psychosocial factors (based on the criteria of Rea *et al.*<sup>3</sup>) recorded in the hospital record of the index attack were not different between cases and matched controls. However, cases were less likely than matched controls to have

**Table 2** Life events (total and individual) in the last year, recording of psychosocial factors in the medical record of the index attack, and previous counselling for emotional problems for cases (SLTA), matched hospital controls, and community comparison group

	Cases (SLTA)	Matched hospital controls	Community comparison group
Total life events (last year) <sup>26</sup>	3.9 (2.3)	3.7 (2.5)	2.8 (1.9)*
Certain individual life events (last year):			
Close relative or friend imprisoned	14%	16%	2%***
Looked for work >1 month	29%	24%	3%***
Death of close relative or friend	27%	29%	22%
Separated from partner for >1 month	18%	15%	7%
Psychosocial factors recorded in medical record (after Rea <i>et al</i> ) <sup>6</sup>	42%	36%	–
Previous “counselling for emotional problems”	25%	35%*	–

\*p<0.05 compared with cases; \*\*\*p<0.005 compared with both cases and controls.

**Table 3** Availability and adequacy of social support for cases (SLTA) and matched hospital controls

	Cases (SLTA)	Matched hospital controls
Social support* available for:		
Important decisions	90%	93%
Personal matters	91%	90%
Help with asthma	76%	70%
Asthma specific social support:		
Lack of availability	24%	30%
Inadequate quality	22%	24%
High level of conflict	6%	6%
Inadequate asthma specific social support	39%	44%

\*Not conducted in community control group.

**Table 4** Factor analysis of Attitudes and Beliefs about Asthma questionnaire for cases (SLTA), matched hospital controls, and community comparison group

Factors	Cases (SLTA)	Matched hospital control	Community comparison group
Emotional (Mal) adjustment	-28.9 (7.0)	-27.6 (7.5)	-18.7 (6.5)
Doctor-patient relationship	13.2 (3.9)	13.4 (4.4)	14.6 (3.8)
Stigma	-2.9 (2.8)	-2.8 (2.6)	-2.9 (2.6)
Self-efficacy	8.03 (2.1)	7.8 (2.3)	8.5 (2.0)

For emotional adjustment and stigma a more negative score indicates greater emotional maladjustment and greater stigmatisation, respectively. For doctor-patient relationship and self-efficacy a more positive score indicates a better doctor-patient relationship and greater self-efficacy, respectively.

had previous “counselling for emotional problems” (table 2). Availability and quality of social support (both general and asthma-specific) did not differ between cases and matched hospital controls (table 3). There were no differences between the groups in any of the four domains of the Attitudes and Beliefs about Asthma questionnaire (table 4).

## DISCUSSION

There are four major conclusions to be drawn from these results. Firstly, there was a high level of psychological morbidity in all groups although the prevalence was related to “severity” of disease as indicated by morbidity indices. Secondly, there were no differences in any of the adverse psychological parameters between cases with SLTA and hospital controls, with the exception that those with SLTA had a lower rate of previous emotional counselling. Thirdly, adverse

psychological factors were more common in those admitted (SLTA and hospital controls) than in the community based control group—that is, adverse psychological factors are a risk factor for admission for acute severe asthma. Finally, as has been shown previously,<sup>6,21</sup> risk factors for adverse asthma events are dependent upon the type of event under study and the comparison group used.

The lack of differences in the adverse psychological parameters between cases with SLTA and matched hospital controls admitted to hospital with acute asthma indicates that adverse psychological factors are not a risk factor for SLTA when comparison is made with patients admitted to hospital. This may seem initially to be at variance with the results of previous cross sectional studies. However, careful scrutiny of the results of recent case-control studies of SLTA reveals a remarkable consistency of results. In the study by Boulet *et al*<sup>19</sup> the difference in “dependency” between those with near fatal asthma and controls matched for age, sex, atopic status, baseline FEV<sub>1</sub>, and medication use was due to better than average coping or adaptive personality characteristics in the control group; the group with near fatal asthma scored as would have been expected from normal subjects. Rocco *et al*<sup>22</sup> in a case-control study of near fatal asthma found no differences in terms of psychiatric symptoms, personality characteristics, or levels of anxiety and depression between 17 asthmatics who had experienced near fatal asthma and those who had not. Furthermore, Campbell *et al*<sup>17</sup> found that 43% of patients studied 10–12 weeks after a near fatal attack of asthma scored in the psychiatric case range on the General Health Questionnaire 28. Although there was no control group in this study, it was pointed out that the prevalence of psychiatric morbidity in the general hospital population was estimated to be 20–40%.<sup>17</sup> The consistency of these results, together with the results of the present study, strongly supports the conclusion that adverse psychological/psychiatric factors are not a reliable risk factor for patients with SLTA, particularly when compared with those admitted to hospital or those with severe disease.

The prevalence of anxiety, depression (table 1), the total number of life events, and the incidence of certain life events (table 2) were significantly lower in the community comparison group—that is, these features are risk factors for admission to hospital for acute asthma (including SLTA) when community based patients with milder disease are studied in comparison. This difference may be simply related to the less severe asthma in this group (as previously shown<sup>21</sup>) or may be a consequence of the different demographic and socioeconomic characteristics of this group.<sup>21</sup> In other words, the psychological factors may be intermediate in the causal pathway. The prevalence of anxiety and depression of attendees at a hospital based asthma clinic<sup>25</sup> was very similar to that of the community sample in this study. This is somewhat unexpected in that a substantial proportion (45%, unpublished

observations) of asthma clinic attendees were referred after hospital admission, and attendees at hospital clinics are a very biased sample of community based patients, even if severity is controlled for. Nevertheless, these results highlight the crucial fact that the determination of risk factors for adverse events in asthma is highly dependent upon the event being studied and the control (or comparison) group used.

The absolute requirement in studies of asthma death to obtain information from other than the subject introduces bias as well as potential inaccuracies and incompleteness of the data, and this (along with the lack of a control or comparison group) may have led to erroneous conclusions. SLTA is studied because it is important in its own right, is more common than asthma death, and the consistent similarities with asthma death<sup>1-4</sup> suggest that it is a legitimate proxy for asthma death. However, studies of SLTA in which the information has been obtained from the medical record or information has been obtained from others have similar deficiencies to studies of asthma death. This may be particularly the case when psychosocial issues are under study. In a study of patients admitted to hospital with acute severe asthma, psychosocial problems as defined by Rea *et al*<sup>5</sup> were recorded in the medical record in only 13%. However, on subsequent interview it was found that 33% had previously received "treatment or counselling for an emotional problem" and 56% had clinically significant anxiety and 19% depression (Kolbe, unpublished observations).

Obtaining information from relatives is not necessarily a satisfactory or unbiased solution, despite the fact that this source has been used in most studies of asthma death.<sup>5 9 11 14 18</sup> Campbell *et al*<sup>23</sup> found that reliable information about "more visible" asthma manifestations of those surviving near fatal asthma attacks was supplied by close acquaintances. However, much lower levels of agreement between the survivors and close acquaintances were found for psychosocial factors; a kappa statistic of 0.50 for denial score and only 0.44 for a history of psychiatric consultation. In studies of SLTA/near fatal asthma the assessment of psychological factors is frequently delayed—for example, 6 months to 5 years after the event in the study by Boulet *et al*<sup>19</sup>, an average of 13 months often in the studies by Yellowlees *et al*,<sup>15 16</sup> and within 10–12 weeks in the study by Campbell *et al*.<sup>17</sup> To what extent psychological status at that time accurately reflected that at or prior to SLTA is unclear, but intuitively one might expect significant change including the psychological sequelae of the attack itself.

A high prevalence of anxiety (36–38%) was found in both the cases with SLTA and hospital controls. This is consistent with the results of previous cross sectional studies.<sup>15 16 34</sup> In an epidemiological study using the same instrument (HAD scale), Janson *et al*<sup>25</sup> found an association between reported respiratory symptoms and psychological status but no evidence that patients with diagnosed asthma had more anxiety and depression than those without asthma. However, the majority of asthmatics identified by Janson *et al* were likely to be classified as mild. The community comparison group in the current study who generally had mild disease (as indicated by very low morbidity indices<sup>21</sup>) had a rate of definite caseness (28%) somewhat higher than that of Janson *et al*,<sup>25</sup> but the rates of milder anxiety symptoms were similar. There does appear to be a relationship between rate of caseness for anxiety and asthma severity/degree of morbidity from asthma, with significantly higher rates in cases (SLTA) (36%) and hospitalised controls (38%) than in the community comparison group (28%). This suggests that, while states of fear of a mild sort are common in all who have asthma, more severe anxiety is a greater problem in those with clinically more serious disease. While these data do not clarify the nature or direction of this relationship, they do underline the need to address anxiety in asthma management, particularly as anxiety may cause dysfunctional breathing patterns difficult to distinguish from airflow obstruction. High levels of anxiety may impair the

ability to make correct self-management decisions, specifically impairing the ability to put into practice what is known.<sup>29</sup> We have previously demonstrated that "panic" during an acute attack of asthma is a risk factor for SLTA.<sup>21</sup> Furthermore, doctors may be influenced by excessive patient anxiety and alter medical regimens inappropriately.<sup>36</sup>

Although depression is reported as a risk factor for asthma death,<sup>37-40</sup> we did not find depression to be a prevalent problem in any of the groups studied—similar to our findings in clinic outpatients<sup>25</sup> and those of Janson *et al*.<sup>25</sup> This contrasts with findings of high rates of depression among school age asthmatics, albeit in a highly selected inpatient group<sup>39</sup> and with the reported beneficial responses to antidepressant medications in individual patients.<sup>37 38</sup> Garden and Ayres<sup>34</sup> found that 15% of their cohort of "brittle" asthmatics had current mood disorder, although this increased rate of depression may have been related to the apparent inability of health professionals to improve their clinical status. Given that the prevalence of depression in medical patients has been variously documented to be 5–20% depending on the population studied and the instrument used,<sup>41</sup> and that higher rates are present in the seriously ill,<sup>42</sup> it is unlikely that the prevalence rates documented in the current study represent a clinically important asthma specific problem. To what extent the borderline statistically significantly higher rates in cases (SLTA) and hospital controls (compared with the community comparison group) can be related to the effect of corticosteroids used to treat the index attack<sup>43</sup> or the impact of the attack itself is unknown.

Joseph *et al*<sup>44</sup> have reported increased morbidity and mortality related to asthma among patients who used major tranquillisers (relative risk (RR) 3.2, 95% CI 1.4 to 7.5) and sedatives (RR 1.9, 95% CI 1.2 to 3.1), but not among users of antidepressants. However, after adjustment for confounding (use of asthma drugs, hospitalisation), this excess risk disappeared, which suggests that the association may have been due to differential prescribing of major tranquillisers and sedatives to patients with more severe asthma and thus at increased risk of death (or possibly the differential prescribing of asthma drugs between patients with or without psychiatric problems requiring major tranquillisers or sedatives). In the current study only 3% of cases and 2% of hospital controls had been prescribed a major tranquilliser or sedative.

There were no differences between cases and hospital controls in total life events and no evidence that any particular life event was more common. Garden and Ayres<sup>34</sup> also found no difference in life events between those with "brittle" asthma and an outpatient comparison group. However, the total life events and the prevalence of certain individual life events were greater in the cases and hospital controls than in the comparison group. To what extent this may be due to differences in severity of disease (as suggested by others<sup>45</sup>) or to differences in socioeconomic or demographic features is unknown.

It was clear from the results of this study that a variety of adverse psychological factors were present. Rather than an assessment of individual specific factors, some assessment of the total psychosocial burden may have been useful. In this study we did not specifically assess the duration and frequency of psychosocial stresses which are important determinants of impact on health.<sup>46</sup> Nevertheless, if substantial differences did exist, one would have expected that this would have been reflected in the total life event score or a "catch all" assessment such as "previous emotional counselling". Whether the lower rate of emotional counselling in the SLTA meant that these issues were less appropriately managed is a matter of speculation, but in view of the lack of difference in all other parameters, it is unlikely that this finding is of aetiological significance. The rate of previous emotional counselling found in this study is similar to the rate of psychiatric consultation reported by Campbell *et al*<sup>17</sup> in a study of asthma death and near fatal asthma.

Good family support may be protective, particularly against the adverse effects of life events,<sup>47</sup> while poor family support<sup>48</sup> and abnormal family function<sup>9,49</sup> have been suggested as risk factors for morbidity and mortality. The levels of social support in all groups were generally high and there were no differences between cases and controls. Conflict with support persons has been suggested as a risk factor,<sup>9,11</sup> but little recent conflict was reported in any of the groups in this study. Of greater concern were the higher rates of inadequate disease specific social support. This deficiency may contribute to the high rate of serious self-management errors during an acute attack<sup>21,27</sup> and underlines the importance of involving support persons in the asthma education and management processes.

Patient attitudes to and beliefs about their disease and its treatment impact upon their medical care and may thus be reflected in morbidity indices. Sibbald *et al*<sup>48</sup> found that those patients with the greater feelings of stigma, less positive attitudes to their doctor, and less self-efficacy have the highest morbidity from asthma. Using a modified Sibbald questionnaire<sup>30</sup> which has been independently validated and tested in different patient groups,<sup>25,28,29</sup> we were not able to show significant differences between the three groups studied, despite the differences in demographics and severity. Therefore, either the differences in these factors are not causal or the instrument does not have sufficient sensitivity to detect differences, notwithstanding the results of Sibbald *et al*<sup>48</sup> who obtained a very similar factor solution and despite the fact that we have previously shown the impact of these factors have on patient self-management knowledge and self-management behaviour.<sup>27,30</sup>

While we agree with Harrison<sup>49</sup> that the major factors associated with preventable asthma death (and SLTA) are behavioural rather than pharmacotherapeutic, specific adverse psychological factors are not risk factors for SLTA when comparison is made with those admitted to hospital with acute asthma, but are risk factors when comparison is made with a community based group of asthmatics. Although we regard SLTA as a valid "proxy for asthma death", some caution needs to be exercised when extrapolating these findings in SLTA to asthma death. The definition of risk factors for adverse asthma events is dependent both on the event and the control or comparison group studied. There is a high prevalence of adverse psychological and social factors in patients with severe asthma (or high morbidity from asthma) and this has major implications for asthma education and other strategies designed to improve self-management behaviour.

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