Eur Respir J 2011; 37: 986–990
DOI: 10.1183/09031936.00018511

EDITORIAL

Asthma nervosa: old concept, new insights

J. Douwes*, C. Brooks* and N. Pearce*,#

Stress has long been recognised to be associated with asthma. Hippocrates stated that to prevent an asthma attack ''the asthmatic should guard himself against his own anger'' [1]. Maimonides in his treatise of asthma suggested that ''mental anguish, fear, mourning or distress'' may cause asthma whereas ''gaiety and joy'' which ''gladden the heart and stimulate the blood and mental activity'' may have the opposite effect [2]. In his treatise, H.H. Salter wrote that ''asthma is essentially, and with perhaps the exception of a single class of cases, exclusively a nervous disease; the nervous system is the seat of the essential pathological condition'' [3], and W. Osler referred to asthma as ''a neurotic affection'' [4]. Thus, until the second half of the 20th century, asthma was predominantly viewed as a psychosomatic disorder in which emotional stress and imbalances in the nervous system were key factors in its aetiology. As a result, relief of anxiety was considered the main therapeutic intervention for ''asthma nervosa''; as it has been referred to historically.

Although the increased awareness in the second half of the 20th century of other triggers of asthma (allergens and air pollution) has shifted the focus away from psychosocial factors, these old concepts are going through a renaissance, with an increasing number of publications reporting consistent positive associations between psychosocial stress and asthma. Associations with asthma have been shown for a wide range of stressors including: post-traumatic stress disorder (PTSD) [5, 6]; psychiatric disorders [7, 8]; community violence [9]; stressful life events [10]; partner violence and housing quality [11]; war-related stress [12]; neuroticism and relational problems [13]; perceived safety [14]; social depravity and high crime rates [15]; anxiety and attention disorders [16]; psychological distress [17]; maternal anxiety [18]; maternal depression and paternal PTSD [19]; and work-related stress [20]. Conversely, the prevalence of asthma has been shown to be elevated in those suffering from anxiety disorders [21].

The cross sectional nature of most of these studies has prevented firm conclusions from being drawn regarding causality and direction of the relationship. However, there is now a growing body of evidence within the last decade (table 1), and even prior to this [27], suggesting that emotional stress, anxiety and PTSD precedes the development of asthma both in children and adults. Similarly, there is evidence that asthma precedes panic disorders and that panic disorders may exacerbate pre-existing asthma [21]. These associations remain even after adjusting for potential confounders such as smoking, socioeconomic status, body mass index, and familial and genetic factors, as assessed in twin studies [5]. Thus, prospective studies appear to support a causal bidirectional association with psychosocial factors playing a role in both the development and prognosis of asthma [28]. However, there are critical issues that have not been adequately addressed in the currently available studies. In particular, although many studies have used standardised questionnaires to assess asthma, or respiratory health more generally, few have included objective measures. This is generally not a major issue in most population-based asthma studies where standardised asthma questions show good agreement with a more objective clinical diagnosis of asthma [29]; however, it may be problematic in studies of stress and asthma since psychosocial conditions are known to affect accurate symptom perception [30, 31]. A difference in the incidence or prevalence of respiratory symptoms may, therefore, be at least partially accounted for by a difference in symptom perception between those with and without stress, rather than an objective difference in airway obstruction. Furthermore, psychological disorders have been associated with poor asthma self management [32], a factor that is not usually controlled for in studies of stress and asthma. Thus, any observed effects of stress on asthma (severity) may be indirectly mediated through poor asthma self management rather than being direct effects of stress itself. Finally, it is not clear whether the effects associated with emotional stress are specific to asthma, with some reports also showing associations with chronic obstructive pulmonary disease (COPD) and chronic bronchitis [24]. These problems are exacerbated by uncertainty about the neuroimmunomodulatory mechanisms underlying the association between stress and asthma.

Studies involving objective measures of respiratory health effects, such as the one by SPITZER *et al.* [33] published in this issue of the *European Respiratory Journal*, may shed some light on these issues. The authors conducted cross-sectional analyses (nested within a cohort study) of the associations between lung function, as an objective measure of airway obstruction, and trauma exposure and PTSD in 1,772 adults from the general population. Trauma exposure, PTSD and respiratory symptoms were assessed using standardised questions, and lung function was assessed using spirometry. Similar to previous studies, those with PTSD (n=28) had a significantly greater risk of having asthma symptoms, after adjustment for confounders. However, those with trauma (n=887) had only slightly elevated risk and most associations were not statistically significant. Unadjusted analyses indicated that subjects with PTSD had lower forced expiratory volume in 1 s (FEV_1),

*Centre for Public Health Research, Massey University, Wellington, New Zealand. #Dept of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK.

CORRESPONDENCE: J. Douwes, Centre for Public Health Research, Massey University, Wellington Campus, Private Box 756, Wellington, New Zealand. E-mail: j.douwes@massey.ac.nz

TABLE 1 Summary of longitudinal studies of stress and asthma published in the last decade

First author [ref.]	Sample size n	Study design	Definition of stress	Definition of respiratory outcome	Variable associated with asthma/respiratory outcome	Adjusted OR/RR/HR (95% CI)
HUOVINEN [22]	11540	Combined prevalence and incidence study: cohort-twin registry, ~15 yr follow-up.	Neuroticism and extraversion according to Eysenck Personality Inventory, self-reported stress and life satisfaction.	Physician-diagnosed asthma, bronchitis symptoms, self-reported.	Low life satisfaction and neuroticism associated with increased asthma prevalence. High extroversion score associated with increased asthma incidence.	OR 2.27 (1.04–4.93) OR 1.78 (1.12–2.84) OR 2.72 (1.44–5.12)
HASLER [23]	591	Prospective community study with over represented number of psychiatric disorder cases: 20 yr follow-up.	SPIKE structured interview for assessment of panic and anxiety based on DSM-III.	Physician-diagnosed asthma, symptoms or medication use, self-reported.	Asthma predicted subsequent panic disorder Panic disorder predicted active asthma. Stronger association in females and smokers than males and nonsmokers.	OR 4.5 (1.1–20.1) OR 6.3 (2.8–14)
PEMBROKE [24]	3885	Cohort study of middle-aged adults: follow-up at 3–4 yrs.	Psychological distress assessed using the GHQ-30 questionnaire, self reported.	Bronchitis and COPD related symptoms assessed using MRC questionnaire, self-reported Lung function assessed by spirometry.	Reduced FEV_1. Breathlessness Chronic bronchitis associated with psychological distress in females only.	OR 1.31 (1–1.73) OR 3.02 (1.99–4.59) OR 2.00 (1.16–3.46)
THORN [25]	231	Prospective females study: ~30 yr follow-up.	Self-reported history of stressed periods.	Self-reported asthma, wheezing or bronchitis.	Mental stress associated with obstructive symptoms (also obesity and low socioeconomic status).	OR 2.2 (1.0–5.1)
LOERBROKS [13]	4010	Prospective study: middle-aged adults.	Neuroticism and extraversion according to Eysenck Personality Inventory, stressful life events.	Physician-diagnosed asthma and asthma symptoms, self reported.	High level of neuroticism associated with increased risk of asthma. Relationship split associated with increased risk of asthma.	RR 3.07 (1.71–5.48) RR 2.24 (1.20–4.21)
COOKSON [18]	5810	Cohort study: children assessed at 7.5 yrs.	Maternal anxiety during pregnancy, self-reported.	Physician-diagnosed asthma, symptoms and treatment, caregiver reported BHR measured by methacholine challenge.	High maternal anxiety associated with increased risk of childhood asthma (no strong evidence of association with BHR or atopy).	OR 1.64 (1.25–2.17)
GOODWIN [26]	2712	Prospective study: children (boys only), 15 yr follow-up.	Questionnaire assessing various mental health problems, reported by child, caregiver and teacher.	Asthma reported on Finnish national military register.	Moderate depressive problems in childhood associated with increased incidence of asthma. Severe depressive problems in childhood associated with increased incidence of asthma.	OR 2.9 (1.7–5.0) OR 3.5 (1.7–6.5)
STERNTHAL [9]	2228	Longitudinal study: children aged 0–9 yrs at enrolment.	Exposure to community violence (ETV survey) questionnaire, caregiver reported.	Physician-diagnosed asthma, symptoms or medication use, caregiver reported.	Exposure to high levels of community violence associated with increased risk of asthma.	OR 1.56 (1.12–2.18)
LIETZEN [10]	16881	Prospective study: adults with 2 yr follow-up.	Questionnaire assessing stressful life events.	Incident cases of asthma using national drug/treatment registry.	Several stressful life events associated with increased risk of asthma incidence.	OR 1.96 (1.22–3.13)
SUGLIA [11]	2013	Prospective study: children assessed at 36 months.	Questionnaire assessing intimate partner violence and housing quality, assessment of housing quality.	Physician-diagnosed asthma and asthma within 12 months, caregiver reported.	Intimate partner violence associated with increased risk of asthma. Poor housing associated with increased risk of asthma.	OR 1.8 (1–3.5) OR 1.5 (1.1–2)

TABLE 1 Continued

First author [ref.]	Sample size n	Study design	Definition of stress	Definition of respiratory outcome	Variable associated with asthma/respiratory outcome	Adjusted OR/RR/HR (95% CI)
WRIGHT [12]	2066	Retrospective study: 50–69-yr-old adults.	Harvard trauma questionnaire, war related stressor score.	Physician-diagnosed asthma, self-reported.	High stress exposure associated with increased risk of asthma.	OR 2.3 (1.3–3.9)
SHANKARDASS [15]	2456	Prospective study: children.	Social depravity and crime rate derived from census/FBI records.	Physician-diagnosed asthma, caregiver reported.	Poorly funded schooling associated with increased risk of asthma.	HR 1.71 (1.14–2.58)
					High crime rates associated with increased risk of asthma.	HR 2.02 (1.08–3.02)
LANGE [19]	339 twin pairs	Birth cohort study: follow-up at 3 yrs.	Maternal/paternal stress and PTSD according to DSM-IV, self-reported.	Physician-diagnosed asthma, symptoms and medication, caregiver reported.	Maternal depression associated with increased asthma diagnosis.	OR 1.16 (1–1.36)
					Paternal PTSD associated with increased asthma symptoms.	OR 1.08 (1.03–1.14)
LOERBROKS [20]	3341	Cohort study: working adult population, ~10 yr follow-up.	Questionnaire assessing work-related stress, self-reported.	Physician-diagnosed asthma and symptoms, self-reported.	Work-related stress associated with increased incidence of asthma.	RR 2.3 (1.16–4.54)

DSM: Diagnostic and Statistical Manual of Mental Disorders; GHQ: General Health Questionnaire; ETV: Exposure to Violence; PTSD: post-traumatic stress disorder; COPD: chronic obstructive pulmonary disease; MRC: Medical Research Council; BHR: bronchial hyperresponsiveness; FEV_1: forced expiratory volume in 1 s. The OR/RR/HR represents that of the group with the highest exposure to the stress variable of interest compared to the lowest group.

forced vital capacity (FVC) and FEV_1/FVC. However, the PTSD group was substantially older, included more females, were shorter and had a greater proportion of former/current smokers compared to the reference group (no trauma and no PTSD). Lung function was also significantly lower in the group with exposure to trauma, but the deficits were smaller than those for the PTSD group. However, when the analyses were adjusted for potential confounders, the results looked very different; the largest lung function deficits were observed in the group with trauma exposure (significant for FEV_1 and FEV_1/FVC), and there was a negligible (nonstatistically significant) deficit in those with PTSD. Thus, after controlling for confounding, the lung function and symptom results were highly inconsistent, *i.e.* there were strong associations between PTSD and symptoms but no associations with lung function, whereas exposure to trauma showed a significant association with lung function but little association with symptoms.

These conflicting findings are not easily explained but could, in part, be due to the very small sample size of the PTSD group (n=28). This is particularly inadequate for comparisons involving lung function (as a marker of asthma) since asthma is characterised by variable (or episodic) airway obstruction, and a sizable proportion of asthmatics therefore have normal, or close to normal, lung function most of the time. Also, the authors adjusted the analyses for some unusual ''confounders'' including ''asthma/bronchitis'' and ''medication'' (we assume medication refers to asthma medication) which, given their functional relationship with lung function, may have been inappropriate and may have affected the precision and validity of the analyses. In particular, asthma may be an intermediate variable in the causal pathway between stress and lung function in which case it is inappropriate to adjust for it. Also, it is feasible that ''panic attacks'' and ''negative emotional states'' (two other variables that the analyses were adjusted for) were highly associated with PTSD and/or trauma which may have led to multicollinearity, once again potentially resulting in invalid risk estimates. Finally, several studies have shown differential effects of emotional stress on respiratory health between males and females [24, 34]. Therefore, rather than treating sex as a confounder, it might have been better to conduct analyses stratified by sex, although given the low number of subjects in the PTSD group (and low proportion of males) this would not have been possible for all subgroups. The authors provide no indication as to whether these issues were considered when the multiple regression model was developed, and it is therefore not clear whether or not they play a role in explaining the surprising and inconsistent results. If we assume that population size, statistical problems and effect modification by sex in the multivariate analyses were not significant issues then what else could have explained these mixed results? As indicated previously, stress may alter symptom perception, but this would only be a plausible explanation for the findings if symptom perception was different for those with PTSD and those with trauma, with the PTSD group over-reporting symptoms. Differential effects of PTSD and trauma on self asthma management may have also played a role, with better medication adherence for the PTSD group resulting in improved lung function. To fully explain the conflicting results, both phenomena would have had to take place. However, in the absence of data on these specific issues, these potential explanations remain speculative.

To our knowledge there are only three other population-based studies assessing the relationship between psychosocial factors and lung function. In a cross-sectional study of 5,486 patients, GOODWIN *et al.* [35] found a consistent inverse relationship between various mental health problems and obstructive or restrictive lung function assessed by spirometry. A prospective

study of 3,885 middle-aged adults by PEMBROKE *et al.* [24] showed that psychological distress (PD; assessed by questionnaire) was associated with respiratory symptoms such as breathlessness and bronchitis, as well as reduced FEV1, but these effects were only seen in females. In males, PD was associated with an increased risk of bacterial infection but was not associated with other respiratory symptoms or lung function. A recent cross-sectional study (nested in a longitudinal study) in 2,443 young adults by HAYATBAKHSH *et al.* [34] found an increased risk of asthma symptoms and asthma medication in individuals suffering from neurological disorders (including PTSD), but no association with lung function and anxiety, panic or PTSD was found. However, a significant inverse association was shown between (12 months and lifetime) major depression and FEV1 and forced expiratory flow at 25–75% of FVC, but only in males. These studies, in addition to the study by SPITZER *et al.* [33], suggest some evidence of associations with lung function but the results are inconsistent. Therefore, it remains uncertain whether the respiratory symptoms associated with psychosocial factors are due to airway obstruction or other factors not directly related to asthma (or other respiratory conditions such as COPD).

As mentioned previously, the uncertainty about the association between stress and asthma is further complicated by the relative lack of data regarding the underlying mechanisms. SPITZER *et al.* [33] suggest that the lung function changes observed in the traumatised group may be due to inflammation. This assumption (few studies on stress and asthma have collected data on airway inflammation to date) is largely driven by the general consensus that asthma is an inflammatory disease. In addition, there is some, but limited, evidence suggesting that stress (through altered regulation of the hypothalamic-pituitary-adrenal axis and sympathetic-adrenomedullary nervous system) may have immunomodulatory effects involving an atopy-, or Th2-, biased response favouring allergic outcomes [36, 37]. If airway inflammation is indeed the main mechanism through which stress causes asthma, as has been suggested, then it would be expected that stress would also be associated with the exhaled nitric oxide fraction (F_{ENO}) which has been increasingly recognised as an objective measure of airway inflammation in (atopic) asthmatics. However, the few studies that have been conducted on stress and F_{ENO} in small groups of asthmatics and nonasthmatics experimentally exposed to stress also showed mixed results. In particular, some studies showed an (inconsistent) stress-associated increase in F_{ENO} in asthmatics [38–40] and nonasthmatics [40], whereas another study found a stress-associated decrease in F_{ENO} in nonasthmatics and no change of F_{ENO} in asthmatics [41]. In addition to neuroimmunomodulatory effects, it is plausible that direct neurogenic mechanisms may underlie at least part of the association between stress and asthma [42], but these mechanisms have rarely been studied.

Where to from here? Further prospective and cross sectional studies are needed to clarify the relationship between stress, respiratory disease and objective parameters of respiratory function. In addition to collecting valid data on psychosocial factors and potential confounders including general aspects of lifestyle [43], these studies would ideally involve repeated spirometry, atopy testing and objective measures of both airway inflammation and neurogenic mechanisms, and could provide the scientific underpinning of future intervention studies. Of course stress is only one of a range of potential causal exposures for asthma and intervention of stress, therefore, will not prevent all cases of asthma [44]. However, it is a feasible candidate for intervention, which has the added benefit of potentially reducing other stress-related conditions including cardiovascular disease, diabetes, hypertension and obesity, as well as being of importance to public health in itself, a view shared with the classic authoritative scholars such as Hippocrates and Maimonides.

SUPPORT STATEMENT

The Centre for Public Health Research is supported by a Programme Grant from the Health Research Council of New Zealand.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Adams F. The Genuine Works of Hippocrates. London, The Sydenham Society, 1849.
2 Rosner F. Moses Maimonides' treatise on asthma. *Thorax* 1981; 36: 245–251.
3 Salter HH. On Asthma: Its Pathology and Treatment. London, John Churchill and Sons, 1860.
4 Osler W. The Principles and Practice of Medicine. New York, D. Appleton and Company, 1892.
5 Goodwin RD, Fischer ME, Goldberg J. A twin study of post-traumatic stress disorder symptoms and asthma. *Am J Respir Crit Care Med* 2007; 176: 983–987.
6 Spitzer C, Barnow S, Volzke H, *et al.* Trauma, posttraumatic stress disorder, and physical illness: findings from the general population. *Psychosom Med* 2009; 71: 1012–1017.
7 Katon W, Lozano P, Russo J, *et al.* The prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared with controls. *J Adolesc Health* 2007; 41: 455–463.
8 Scott KM, Von Korff M, Ormel J, *et al.* Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiatry* 2007; 29: 123–133.
9 Sternthal MJ, Jun HJ, Earls F, *et al.* Community violence and urban childhood asthma: a multilevel analysis. *Eur Respir J* 2010; 36: 1400–1409.
10 Lietzén R, Virtanen P, Kivimaki M, *et al.* Stressful life events and the onset of asthma. *Eur Respir J* 2010 [Epub ahead of print, DOI: 10.1183/09031936.00164609].
11 Suglia SF, Duarte CS, Sandel MT, *et al.* Social and environmental stressors in the home and childhood asthma. *J Epidemiol Community Health* 2010; 64: 636–642.
12 Wright RJ, Fay ME, Suglia SF, *et al.* War-related stressors are associated with asthma risk among older Kuwaitis following the 1990 Iraqi invasion and occupation. *J Epidemiol Community Health* 2010; 64: 630–635.
13 Loerbroks A, Apfelbacher CJ, Thayer JF, *et al.* Neuroticism, extraversion, stressful life events and asthma: a cohort study of middle-aged adults. *Allergy* 2009; 64: 1444–1450.
14 Subramanian SV, Kennedy MH. Perception of neighbourhood safety and reported childhood lifetime asthma in the United States (U.S.): a study based on a national survey. *PloS One* 2009; 4: e6091.
15 Shankardass K, Jerrett M, Milam J, *et al.* Social environment and asthma: associations with crime and No Child Left Behind programmes. *J Epidemiol Community Health* 2010 [Epub ahead of print DOI: 10.1136/jech.2009.102806].
16 Arif AA. The association between symptomatic asthma and neurobehavioral comorbidities among children. *J Asthma* 2010; 47: 792–796.
17 Chittleborough CR, Winefield H, Gill TK, *et al.* Age differences in associations between psychological distress and chronic conditions. *Int J Public Health* 2011; 56: 71–80.

18 Cookson H, Granell R, Joinson C, *et al.* Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol* 2009; 123: 847–853 e811.

19 Lange NE, Bunyavanich S, Silberg JL, *et al.* Parental psychosocial stress and asthma morbidity in Puerto Rican twins. *J Allergy Clin Immunol* 2010 [Epub ahead of print, DOI: 10.1016/j.jaci.2010.11.010].

20 Loerbroks A, Gadinger MC, Bosch JA, *et al.* Work-related stress, inability to relax after work and risk of adult asthma: a population-based cohort study. *Allergy* 2010; 65: 1298–1305.

21 Weiser EB. The prevalence of anxiety disorders among adults with asthma: a meta-analytic review. *J Clin Psychol Med Settings* 2007; 14: 297–307.

22 Huovinen E, Kaprio J, Koskenvuo M. Asthma in relation to personality traits, life satisfaction, and stress: a prospective study among 11,000 adults. *Allergy* 2001; 56: 971–977.

23 Hasler G, Gergen PJ, Kleinbaum DG, *et al.* Asthma and panic in young adults: a 20-year prospective community study. *Am J Respir Crit Care Med* 2005; 171: 1224–1230.

24 Pembroke TP, Rasul F, Hart CL, *et al.* Psychological distress and chronic obstructive pulmonary disease in the Renfrew and Paisley (MIDSPAN) study. *J Epidemiol Community Health* 2006; 60: 789–792.

25 Thorn J, Bjorkelund C, Bengtsson C, *et al.* Low socio-economic status, smoking, mental stress and obesity predict obstructive symptoms in women, but only smoking also predicts subsequent experience of poor health. *Int J Med Sci* 2007; 4: 7–12.

26 Goodwin RD, Sourander A, Duarte CS, *et al.* Do mental health problems in childhood predict chronic physical conditions among males in early adulthood? Evidence from a community-based prospective study. *Psychol Med* 2009; 39: 301–311.

27 Jonas BS, Wagener DK, Lando JF, *et al.* Symptoms of anxiety and depression as risk factors for development of asthma. *J Appl Biobehav Res* 1999; 4: 91–110.

28 Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. *Psychosom Med* 2008; 70: 102–116.

29 Pekkanen J, Pearce N. Defining asthma in epidemiological studies. *Eur Respir J* 1999; 14: 951–957.

30 Janssens T, Verleden G, De Peuter S, *et al.* Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. *Clin Psychol Rev* 2009; 29: 317–327.

31 Chen E, Hermann C, Rodgers D, *et al.* Symptom perception in childhood asthma: the role of anxiety and asthma severity. *Health Psychol* 2006; 25: 389–395.

32 Cluley S, Cochrane GM. Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids. *Respir Med* 2001; 95: 37–39.

33 Spitzer C, Koch B, Grabe HJ, *et al.* Association of airflow limitation with trauma exposure and post-traumatic stress disorder. *Eur Respir J* 2011; 37: 1068–1075.

34 Hayatbakhsh MR, Najman JM, Clavarino A, *et al.* Association of psychiatric disorders, asthma and lung function in early adulthood. *J Asthma* 2010; 47: 786–791.

35 Goodwin RD, Chuang S, Simuro N, *et al.* Association between lung function and mental health problems among adults in the United States: findings from the First National Health and Nutrition Examination Survey. *Am J Epidemiol* 2007; 165: 383–388.

36 Wright RJ. Stress and atopic disorders. *J Allergy Clin Immunol* 2005; 116: 1301–1306.

37 Haczku A, Panettieri RA Jr. Social stress and asthma: the role of corticosteroid insensitivity. *J Allergy Clin Immunol* 2010; 125: 550–558.

38 Kullowatz A, Rosenfield D, Dahme B, *et al.* Stress effects on lung function in asthma are mediated by changes in airway inflammation. *Psychosom Med* 2008; 70: 468–475.

39 Chen E, Strunk RC, Bacharier LB, *et al.* Socioeconomic status associated with exhaled nitric oxide responses to acute stress in children with asthma. *Brain Behav Immunity* 2010; 24: 444–450.

40 Ritz T, Ayala ES, Trueba AF, *et al.* Acute stress-induced increases in exhaled nitric oxide in asthma and their association with endogenous cortisol. *Am J Respir Crit Care Med* 2010; 183: 26–30.

41 Hoglund CO, Axen J, Kemi C, *et al.* Changes in immune regulation in response to examination stress in atopic and healthy individuals. *Clin Exp Allergy* 2006; 36: 982–992.

42 Ritz T, Kullowatz A, Goldman MD, *et al.* Airway response to emotional stimuli in asthma: the role of the cholinergic pathway. *J Appl Physiol* 2010; 108: 1542–1549.

43 Davey Smith GD., Ben-Shlomo Y., Lynch J. Life course approaches to inequalities in coronary heart disease. *In*: Stansfeld SA, Marmot MG, eds. Stress and the Heart: Psychosocial Pathways to Coronary Heart Disease. London, BMJ Books, 2002; pp. 20–49.

44 Douwes J, Brooks C, Pearce N. Stress and asthma: Hippocrates revisited. *J Epidemiol Community Health* 2010; 64: 561–562.