Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Perceived stress and risk of adult-onset asthma and other atopic disorders: a longitudinal cohort study

N. H. Rod[1], T. S. Kristensen[2], P. Lange[3,4], E. Prescott[4,5] & F. Diderichsen[1]

[1]Department of Public Health, University of Copenhagen; [2]Task-Consult, Copenhagen; [3]Pulmonary Section, Hvidovre University Hospital, Hvidovre, Denmark; [4]The Copenhagen City Heart Study, Bispebjerg University Hospital; [5]Department of Cardiology, Bispebjerg University Hospital, Copenhagen, Denmark

To cite this article: Rod NH, Kristensen TS, Lange P, Prescott E, Diderichsen F. Perceived stress and risk of adult-onset asthma and other atopic disorders: a longitudinal cohort study. *Allergy* 2012; **67**: 1408–1414.

Keywords
asthma; cohort studies; dermatitis; psychological stress; rhinitis.

Correspondence
Naja Hulvej Rod, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, PO box 2099, 1014 Copenhagen K, Denmark.
Tel: (+45) 3532 6735
Fax: (+45) 3535 1181
E-mail: nahuro@sund.ku.dk

Accepted for publication 01 July 2012

DOI:10.1111/j.1398-9995.2012.02882.x.

Edited by: Stephan Weidinger

Abstract

Background: Psychological stress can affect airway inflammatory response to irritants and allergens, but the importance of stress in the etiology of adult-onset respiratory and dermatologic allergic disorders remains unclear. We aim to address the relationship between perceived stress and the risk of adult-onset asthma, allergic rhinitis, atopic dermatitis, and asthma/bronchitis medication.

Methods: Participants (n = 9785) from the Copenhagen City Heart Study, Denmark, free of atopic disorders at baseline in 1981–1983 were asked questions on stress intensity and frequency. They were followed for first-time asthma hospitalization in nationwide registers until 2010, with < 0.1% loss to follow-up. Objective measures of lung function allowed for thorough adjustment for confounding and prevented ambiguity between diagnosis of asthma and chronic obstructive lung disease. Daily intake of asthma/bronchitis medication and incidence of asthma, allergic rhinitis, and atopic dermatitis were assessed by self-report after 10 years of follow-up in 5648 persons.

Results: Perceived stress was associated with atopic disorders in a dose-dependent manner ($P_{trend} < 0.001$). High *vs* low stress was associated with higher risk of self-reported asthma incidence (OR = 2.32; 95% CI: 1.47–3.65), daily intake of asthma/bronchitis medication (OR = 2.26; 95% CI: 1.42–3.58), first-time asthma hospitalization (HR = 2.01; 95% CI: 1.41–2.86), allergic rhinitis (OR = 1.64; 95% CI: 0.99–2.72), and atopic dermatitis (OR = 1.75; 95% CI: 1.11–2.77). The associations were similar for smokers and nonsmokers.

Conclusions: Stress is strongly associated with asthma incidence and hospitalization, use of asthma medication as well as with allergic rhinitis and atopic dermatitis in adults.

There is a rising burden of illness from asthma worldwide, and although most people develop asthma during childhood, adult-onset asthma is rather prevalent (1). Asthma is a chronic inflammatory disease of the airways, and it is well known that stress has the potential to affect the severity of asthma (2). In experimental studies, stress has been shown to operate by accentuating the airway inflammatory response to irritants, allergens, and infections and, in doing so, increases the frequency, duration, and severity of the person's symptoms (3).

How stress affects those with asthma is relatively well documented (2), while sound prospective studies on the relationship between stress and incidence of asthma and other atopic disorders such as rhinitis and dermatitis are still few and the results are conflicting. A recent study from the UK reported an association between several psychosocial factors and asthma hospital admissions, especially among patients with existing asthma (4). Another longitudinal study found a broken life partnership, but not unemployment and death of a close person, to be associated with self-reported incident asthma in 4010 middle-aged Germans (5). Neuroticism has been conceptualized as a stress-related personality trait and was found to also be associated with higher risk of asthma in this population. Contrary to these results, Huovinen and colleagues found no effect of daily stress on incidence of

self-reported asthma among 11 000 younger adults (18 to 45 years) in Finland (6).

We aim to address the relationship between perceived stress and the risk of developing adult-onset asthma, allergic rhinitis, atopic dermatitis as well as first-time hospitalization with asthma after careful adjustment for sociodemographic factors, parental asthma, and lung function at baseline in a cohort study of more than 9000 men and women free of asthma and allergic rhinitis at baseline. Smoking is a potent risk factor affecting asthma morbidity (7), stress may accentuate the inflammatory response to smoking. In order to address this hypothesis, we also aim to evaluate the combined effect of stress and smoking on asthma incidence and hospitalizations.

Methods

Study population

The Copenhagen City Heart Study is a longitudinal study initiated in 1976 including 19 698 men and women. In 1981–1983, the study population was re-invited and supplemented with 500 men and women 20–25 years of age in order to cover a broader age sample. A physical examination was performed, and the participants were asked to fill in a questionnaire. Stress was only assessed at the second wave, which is therefore used as baseline for the present study. All participants gave informed consent. A detailed description of the Copenhagen City Heart Study has previously been published (8). The 12 698 women and men who participated in the second wave constituted a response proportion of 70%, and the vast majority of the participants were Caucasians. Participants who had been hospitalized with asthma from 1977 to baseline ($n = 44$), with self-reported asthma ($n = 373$) or allergic rhinitis at baseline ($n = 2226$), or with missing information on stress or other covariates ($n = 270$) were excluded, leaving 9785 individuals for the analysis of asthma hospitalization. All surviving participants ($n = 10\,012$) were invited to a third wave of the study in 1991–1993 and 7270 men and women participated, which constitute a response proportion of 73%. Participants who had been hospitalized with asthma prior to baseline ($n = 8$), with self-reported asthma ($n = 168$) or allergic rhinitis at baseline ($n = 1342$), or with missing information on stress or other covariates ($n = 104$) were excluded, leaving 3104 women and 2544 men for the longitudinal analyses of self-reported incidence of asthma and allergic rhinitis. We were not able to exclude individuals with atopic dermatitis at baseline because of the lack of information on this variable, so we were only able to address the prevalence of atopic dermatitis at follow-up.

Perceived stress

The study participants were asked about stress in terms of intensity and frequency at baseline in 1981–1983. In the questionnaire, stress was exemplified as the sensation of tension, nervousness, impatience, anxiety, or sleeplessness and no time frame was specified. To assess *stress intensity*, the participants were asked 'Do you feel stressed?' and the response categories were as follows: (0) no, (1) light, (2) moderate, or (3) high. To assess *stress frequency*, the participants were asked 'How often do you feel stressed?' and the response categories were as follows: (0) never/hardly ever, (1) monthly, (2) weekly, or (3) daily. In order to combine the two dimensions of stress, the two questions were added and combined into a seven-point stress score ranging from 0 (indicating low stress) to 6 (indicating high daily stress).

Asthma and other allergic diseases

At the third wave of the study in 1991–1993, the participants were asked to report whether they suffered from asthma based on the question: 'Do you suffer from asthma?' They were also asked to answer the following question on allergic reactions: 'Do foods, medicine, grass, flowers, animals, or other things make you suffer from asthma, hay fever, or eczema?' This question was used to define allergic asthma, allergic rhinitis, or atopic dermatitis. Finally, they were asked whether they currently had a daily intake of asthma/bronchitis medication. Information on asthma hospital admission was obtained from the Danish Hospital Registry, which has consistently used codes from the International Classification of Diseases (ICD), version 8 and, from 1994, version 10. Hospital admissions were defined as asthma related if the following codes were assigned at discharge: ICD-8 code 493; ICD-10 code J45. The hospital registry is updated until August 8, 2010. The vital status of the study population was followed in the Central Death Registry. The participants were followed until date of first asthma hospital admission, death, emigration, or end of follow-up. Less than 0.1% were lost to follow-up owing to emigration.

Covariates

Other covariates included sex, age (continuous), education (<8 years, 8–11 years, or 12 or more years), marital status (married, unmarried, divorced/separated, widowed), parental asthma (one or both parents had asthma), and lung function at baseline (<50% of predicted FEV_1, 50–80% of predicted FEV1, >80% of predicted FEV_1). Lung function was assessed from objective measurements of FEV1 by spirometry in accordance with standards from the American Thoracic Society and the European Respiratory Society (9). Lung function was expressed as percentage of the predicted value based on age, gender, and height. The regression of predicted FEV_1 is based on lifelong nonsmokers in the Copenhagen City Heart Study (women: FEV_1 (ml) = −1431 − 28.5 * age (years) + 34.5 * height (cm); men: FEV_1 (ml) = −3763 − 35.2 * age (years) + 52.9 * height (cm)). The analyses were also adjusted for tobacco smoking (never-smoker; ex-smoker; smoker of 1–14 g/day, 15–24 g/day, and more than 24 g/day), alcohol intake (<1, 1–7, 8–14, 15–21, 22 + drinks/week), physical activity in leisure time (sedentary or very light activity; 2–4 h of light activity per week; more than 4 h of light activity or 2–4 h of high level activity; and competitional level or more than 4 h of hard level activity per week), and body mass index (continuous).

Statistical analyses

First, the associations between stress and risk of adult-onset asthma, allergic rhinitis, and atopic dermatitis over 10 years of follow-up were estimated in a logistic regression model among those without asthma or allergic rhinitis at baseline. Potential confounders were identified according to the methods of Directed Acyclic Graphs (10) and they included sex, age, education, parental asthma, and baseline lung function. Health behaviors may be intermediates of the relationship between stress and atopic disorders, but they may also affect the stress level at baseline. Thus, we adjusted for tobacco smoking, alcohol intake, physical activity, and body mass index in a separate model. Secondly, we evaluated the association between stress and first-time asthma hospital admission by means of Cox proportional hazards models. By including age as the time variable, the estimates were soundly adjusted for age. Adjustment for confounding from other covariates was made as described earlier. Initially, all analyses were performed separately for men and women, but as the associations were similar in men and women, the analyses were combined to gain statistical power. A Wald test was used to test for effect modification by sex. Latent baseline symptoms of atopic disorders may have affected the participants' stress reporting, and we therefore performed additional analyses where we excluded individuals with a hospital admission for asthma within the first 2 years after baseline. Asthma and chronic obstructive lung disease (COPD) may be hard to distinguish, and in order to address this concern, we performed several sensitivity analyses: (i) We excluded all individuals ($n = 463$) with COPD at baseline, (ii) we addressed the associations in never-smokers, and (iii) we excluded all asthma cases at follow-up, which according to spirometry measures also had COPD (defined as $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ of predicted FEV_1). Finally, in order to address the joint effects of smoking and stress on risk of incident asthma and asthma hospitalization, we created a composite variable with six levels combining information on current smoking (yes/no) and stress (low, medium, high). The reference category was nonsmokers with low stress.

Results

Stress and asthma

The mean age at baseline was 57 years; ranging from 21 to 98 years. Nine percent of the women and six percent of the men reported high levels of stress. Baseline characteristics of the population are shown in Table 1. During 10 years of follow-up, 252 of the 5648 eligible men and women developed asthma. Of these, 108 were reported by the participant as being cases of allergic asthma. Perceived stress was associated with both total asthma and allergic asthma in a clear exposure-response manner ($P_{trend} < 0.001$) (Table 2). High stress was associated with more than twice the risk of asthma in general (OR = 2.32; 95% CI: 1.47–3.65) and more than three times the risk of allergic asthma (3.60; 1.95–6.63). Perceived stress was also associated with daily intake of asthma/bronchitis medication at follow-up in a dose–response fashion, with high vs. low stress being associated with twice the risk of daily intake of medication (OR = 2.26; 95% CI: 1.42–3.58). Asthma hospitalizations were registered among the 9785 participants free of asthma or allergic rhinitis at baseline. During 29 years of follow-up, 315 persons were hospitalized with asthma. A clear dose–response association was found for the relationship between stress and asthma hospitalization ($P_{trend} < 0.001$), and high stress was associated with twice the risk of asthma hospitalization during follow-up (HR = 2.01; 95% CI: 1.41–2.86). The risk estimates attenuated slightly after adjustment for health behavior, which indicates that part of the observed associations may be mediated by a behavioral pathway. Excluding individuals who were hospitalized with asthma within the first 2 years of follow-up had virtually no effect on the risk estimates, with high vs. low stress being associated with a HR of 1.99 (95% CI: 1.39–2.84) for asthma hospitalization. Exclusion of individuals with COPD at baseline made the associations slightly stronger, with, for example, high stress being associated with a more than three times higher risk of self-reported asthma incidence (OR = 3.19; 95% CI: 1.93–5.27). Restricting the analyses to lifelong never-smokers severely reduced the study sample to 1287 individuals and 27 cases of incident asthma, but the risk estimate remained almost unchanged (high vs. low stress: OR = 2.36; 96% CI: 0.59–9.40). Of the 252 incident asthma cases, 135 also had underlying COPD according to objective spirometric measures at follow-up. Excluding these cases to prevent ambiguity between asthma and COPD reduced the number of incident asthma cases and resulted in slightly stronger risk estimates, with high stress being associated with an OR of 3.88 (95% CI: 2.17–6.93) for incident asthma compared to low stress.

Stress, smoking, and asthma

Perceived stress was associated with self-reported asthma incidence and asthma hospitalization in a dose–response manner among both smokers and nonsmokers (Figs 1 and 2). For asthma incidence, the dose–response relationship appeared strongest among nonsmokers, but the test for interaction was not statistically significant ($P = 0.29$).

Stress and allergic rhinitis/atopic dermatitis

During 10 years of follow-up, 251 participants developed allergic rhinitis and 294 reported atopic dermatitis. Perceived stress was associated with allergic rhinitis in a dose–response manner ($P_{trend} = 0.002$), although the risk estimates were not as pronounced as for asthma (Table 2). Medium (OR = 1.62; 95% CI: 1.26–2.09) stress and high (1.75; 1.11–2.77) stress were also associated with atopic dermatitis in a dose–response manner ($P_{trend} < 0.001$).

Discussion

In this longitudinal study of more than 9000 men and women without asthma or allergic rhinitis at baseline, we observed a

Table 1 Baseline characteristics of 9785 Danish women and men who participated in the Copenhagen City Heart Study in 1981–1983 according to the level of perceived stress

		Stress		
	Total population (n = 9785)	Low (n = 4952)	Medium (n = 4112)	High (n = 721)
Age at baseline (year); mean ± SD	56 ± 12	57 ± 12	54 ± 12	57 ± 11
Women, %	52	47	57	63
Education < 8 years, %	46	48	42	53
Married, %	64	65	64	52
Parental asthma, %	8	7	9	11
FEV_1 <80% of predicted, %	40	39	38	48
Current smoker, %	59	57	61	66
Physically inactive, %	17	15	16	32
Alcohol above sensible drinking limits†, %	13	12	13	17
Overweight, %	49	52	46	44

†At the time of the study, the Danish recommended that sensible drinking limits were 14 drinks/week for women and 21 drinks/week for men.

Table 2 Relative risks and 95% confidence intervals for incident atopic disorders as well as asthma hospitalization according to perceived stress level among participants in the Copenhagen City Heart Study

	Stress			
	Low	Medium	High	P_{trend}
Asthma (study population, *n* = 5648)				
Cases, *n*	101	119	32	
Age- and sex-adjusted odds ratio (OR)	1 (ref)	1.38 (1.05; 1.82)	2.70 (1.78; 4.10)	<0.001
Multiple-adjusted* OR	1 (ref)	1.45 (1.08; 1.94)	2.32 (1.47; 3.65)	<0.001
OR further adjusted for health behavior†	1 (ref)	1.43 (1.07; 1.92)	2.10 (1.32; 3.34)	0.001
Allergic asthma (study population, *n* = 5648)				
Cases, *n*	33	57	18	
Age- and sex-adjusted odds ratio (OR)	1 (ref)	1.86 (1.20; 2.88)	4.33 (2.40; 7.80)	<0.001
Multiple-adjusted* OR	1 (ref)	1.93 (1.23; 3.01)	3.60 (1.95; 6.63)	<0.001
OR further adjusted for health behaviors†	1 (ref)	1.95 (1.25; 3.05)	3.38 (1.81; 6.31)	<0.001
Daily intake of asthma/bronchitis medication (study population, *n* = 5648)				
Cases, *n*	107	124	32	
Age- and sex-adjusted odds ratio (OR)	1 (ref)	1.40 (1.07; 1.83)	2.55 (1.68; 3.87)	<0.001
Multiple-adjusted* OR	1 (ref)	1.48 (1.11; 1.98)	2.26 (1.42; 3.58)	<0.001
OR further adjusted for health behaviors†	1 (ref)	1.45 (1.08; 1.95)	2.17 (1.35; 3.47)	<0.001
Asthma hospitalization (study population, *n* = 9785)				
Cases, *n*	132	141	42	
Age- and sex-adjusted hazard ratio (HR)	1 (ref)	1.27 (1.00; 1.61)	2.25 (1.59; 3.20)	<0.001
Multiple-adjusted‡ HR	1 (ref)	1.29 (1.01; 1.64)	2.01 (1.41; 2.86)	<0.001
HR further adjusted for health behaviors†	1 (ref)	1.23 (0.97; 1.57)	1.79 (1.25; 2.56)	0.002
Allergic rhinitis (hay fever) (study population, *n* = 5648)				
Cases, *n*	93	138	20	
Age- and sex-adjusted odds ratio (OR)	1 (ref)	1.57 (1.20; 2.06)	1.72 (1.04; 2.82)	0.001
Multiple-adjusted* OR	1 (ref)	1.55 (1.18; 2.03)	1.64 (0.99; 2.72)	0.002
OR further adjusted for health behaviors†	1 (ref)	1.64 (1.25; 2.16)	1.82 (1.09; 3.03)	<0.001
Atopic dermatitis (eczema) (study population, *n* = 5648)				
Cases, *n*	106	163	25	
Age- and sex-adjusted odds ratio (OR)	1 (ref)	1.64 (1.28; 2.12)	1.80 (1.14; 2.83)	<0.001
Multiple-adjusted* OR	1 (ref)	1.62 (1.26; 2.09)	1.75 (1.11; 2.77)	<0.001
OR further adjusted for health behaviors†	1 (ref)	1.64 (1.27; 2.12)	1.70 (1.07; 2.69)	<0.001

*Adjusted for sex, age, educational level, marital status, baseline lung function, and parental asthma.
†Health behaviors: smoking, alcohol consumption, physical activity in leisure time, and body mass index.
‡Adjusted for sex, age, educational level, marital status, and baseline lung function.

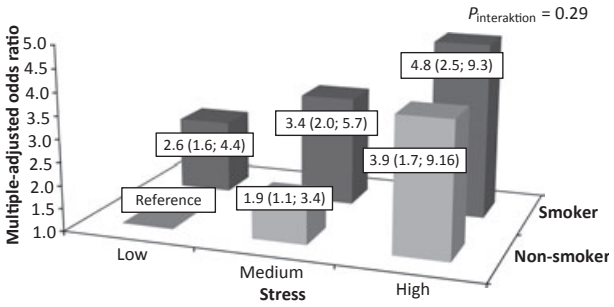

Figure 1 Self-reported asthma incidence.

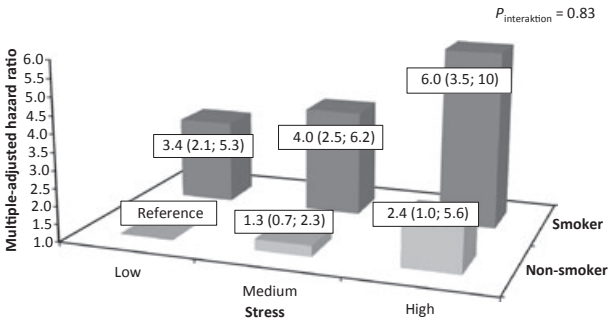

Figure 2 Asthma hospitalization.

clear dose–response relationship between stress and self-reported incidence of asthma, daily use of asthma/bronchitis medication, allergic rhinitis, and prevalence of atopic dermatitis as well as first-time asthma hospitalization after careful adjustment for sociodemographic factors, parental asthma, and lung function at baseline. Biologic hypersensitivity to environmental stimuli is a central feature of atopic disorders (11), and we hypothesized that stress would accentuate the inflammatory response to smoking. This hypothesis was not supported in the present study, where we found similar relationships between stress and asthma in smokers and non-smokers, which suggests that stress is an independent risk factor for asthma.

Only three prospective studies have, to our knowledge, previously addressed this relationship in adults (4–6). The methods applied have been quite diverging, and the results are conflicting. Wainwright et al. (4) found psychosocial factors (current mood disorders, adverse circumstances in childhood, negative life events in adulthood, and negative perceived support from a close confidant) to be associated with higher rates of asthma hospitalization over a 7-year follow-up period. However, individuals with prevalent asthma at baseline were included in the analysis, which precluded a distinction between asthma incidence and progression. In a Finnish study, Houvinen et al. (6) demonstrated a link between a high extroversion score and self-reported adult-onset asthma, but contrary to our findings, found no associations for subjective stress or life satisfaction. The stress measure applied in the Finnish study was based on four self-reported statements of stress in daily activities, and due to the way the scale was constructed, there were only few individuals in the reference category of no stress, which preclude direct comparison with the results of the present study. Loerbroks et al. showed an association between a broken life partnership and self-reported incident asthma, but found no link to unemployment or death of a close person (5). The majority of these studies have focused on external stressors such as major life events or loss of a partner, but the same stressor can produce considerable variability in people's emotional, behavioral and physiologic stress responses, and it is therefore essential to also consider the subjective perception as we have done in the present study.

Stress may affect the risk of asthma through various mechanisms, including alterations in airway structure or function and immune deregulation, psychological changes in perception of breathlessness, and adherence to treatment plans (2). Chronic stress can activate the neuroendocrine and sympathetic nervous system and through cortisol and catecholamine secretion exert an influence on the immune system (11,12). This may lead to a Th1/Th2 imbalance, which ultimately affects cytokine expression and favors an 'allergic' inflammatory response. Poor asthma control and poor compliance with treatment plans have been associated with a range of psychosocial problems (13–15), and one explanation for our findings with hospitalization may be that stressed individuals find it more difficult to manage their asthma and therefore are at higher risk of asthma hospitalization and fatal asthma (16). However, the relationship between psychosocial factors and asthma fatality is also unclear, and a systematic review of psychological factors associated with near fatal and fatal asthma identified only seven smaller case–control studies with conflicting results (16).

Strengths and weaknesses

To our knowledge, this is the first prospective population study to address the relationship between stress and both respiratory and dermatological allergic disorders. Linkage of civil registry numbers to a hospital registry with nationwide coverage further enabled the identification of virtually all first-time cases of asthma hospitalization and allowed for nearly complete long-term follow-up. Information on sociodemographic status, parental asthma, and objective measures of lung function allowed for thorough adjustment for confounding as well as prevented ambiguity between diagnosis of asthma and COPD.

Only two questions on stress intensity and frequency were used to assess perceived stress, which may lead to concern about misclassification. Perceived stress has previously been found to be highly predictive of morbidity and mortality in the same cohort, (17–19) and in a recent study, two similar single-item measures on stress were found to be reliable at measuring stress with a validity similar to three longer multi-item measures (20). This may provide some assurance that the two-item measurements used in the present study provided a reasonable measure of stress.

Information on incident asthma, allergic rhinitis, and atopic dermatitis was obtained by self-report, and personality traits may affect the reporting of both stress and atopic disorders and thereby create a spurious association between the two. To address this problem, we also obtained information on asthma hospitalization from the hospital discharge registry, which we expect to be less biased by personality, and the fact that our results for self-reported incidence of asthma and asthma hospitalization are comparable is reassuring. Asthma can be difficult to distinguish from COPD in older people, because both disorders have similar manifestations despite potentially different causes and underlying abnormalities (1). We had information on both incident asthma and objective measures of lung function, which provided a unique opportunity to distinguish the two, and the relationship between stress and asthma incidence observed in the present study is unlikely to be a result of indistinctness in diagnosis.

Undiagnosed asthma and reduced lung function are likely to affect the perception of stress making reversed causation a concern even in a prospective study. We carefully adjusted our analyses for baseline lung function as well as excluded the first 2 years of follow-up in the hospitalization analyses, and our results were quite robust to such procedures.

A range of genetic and environmental factors affect the maturation of the immune system during childhood and thereby set the stage for the inflammatory processes and altered reactivity to stimuli later in life (11). Although we aimed to address adult-onset atopic disorders by carefully excluding people with existing atopic disorders at baseline or with a history of asthma hospitalization, we are not able to fully distinguish between the role played by stress in the onset of these disorders and the exacerbation of existing atopic disorders.

In conclusion, we found perceived stress to be strongly associated with asthma incidence and hospitalization, use of asthma medication as well as with allergic rhinitis and atopic dermatitis in adults. In an era of declining asthma mortality occurring in younger adults, mortality remains high in older adults, who continue to be underdiagnosed and undertreated for their asthma (1). Stress may interfere with several physiologic pathways, and these results emphasize that stress is important in the etiology of asthma and other atopic diseases. Including an assessment of psychosocial factors in the identification of high-risk patients could allow healthcare professionals to intervene earlier and thereby prevent onset and exacerbation of asthma and other atopic disorders.

Acknowledgements

We thank the staff and the participants of the Copenhagen City Heart Study.

Authors' contributions

Naja Hulvej Rod contributed to the conception and design of the study, the analysis and interpretation of data, and the drafting of the article. Tage S. Kristensen, Peter Lange, Eva Prescott, and Finn Diderichsen contributed to the conception and design of the study and to critically revise the article. All authors have read and approved submission of the manuscript.

Funding

This work was supported by the Danish Medical Research Council [09-062115 to N.H.R.]. The Copenhagen City Heart Study is supported by funds from the Danish Heart Foundation and the Lundbeck Foundation.

Conflicts of interests

There are no conflicts of interests.

Ethical approval

The Danish ethics committee for the City of Copenhagen and Frederiksberg approved the study (# 01-144/01). All participants gave written informed consent.

References

1. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010;**376**:803–813.
2. Vig RS, Forsythe P, Vliagoftis H. The role of stress in asthma: insight from studies on the effect of acute and chronic stressors in models of airway inflammation. *Ann N Y Acad Sci* 2006;**1088**:65–77.
3. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun* 2007;**21**:993–999.
4. Wainwright NW, Surtees PG, Wareham NJ, Harrison BD. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. *Allergy* 2007;**62**:554–560.
5. Loerbroks A, Apfelbacher CJ, Thayer JF, Debling D, Sturmer T. Neuroticism, extraversion, stressful life events and asthma: a cohort study of middle-aged adults. *Allergy* 2009;**64**:1444–1450.
6. 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.
7. Stapleton M, Howard-Thompson A, George C, Hoover RM, Self TH. Smoking and asthma. *J Am Board Fam Med* 2011;**24**: 313–322.
8. Appleyard M, Hansen AT, Schnohr P, Jensen G, Nyboe J. The Copenhagen City Heart Study. A book of tables with data from the first examination (1976–78) and a five year follow-up (1981–83). *Scand J Soc Med* 1989;**170**(Suppl 41):1–160.
9. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995;**8**:1398–1420.
10. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;**10**:37–48.
11. Wright RJ. Stress and atopic disorders. *J Allergy Clin Immunol* 2005;**116**:1301–1306.
12. Montoro J, Mullol J, Jauregui I, Davila I, Ferrer M, Bartra J et al. Stress and allergy. *J Investig Allergol Clin Immunol* 2009;**19**:40–47.
13. Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. *Eur Respir J* 1995;**8**:899–904.

14. Put C, Van den Bergh O, Demedts M, Verleden G. A study of the relationship among self-reported noncompliance, symptomatology, and psychological variables in patients with asthma. *J Asthma* 2000;**37**:503–510.
15. Lavoie KL, Boudreau M, Plourde A, Campbell TS, Bacon SL. Association between generalized anxiety disorder and asthma morbidity. *Psychosom Med* 2011;**73**:504–513.
16. Alvarez GG, Fitzgerald JM. A systematic review of the psychological risk factors associated with near fatal asthma or fatal asthma. *Respiration* 2007;**74**:228–236.
17. Nielsen NR, Zhang ZF, Kristensen TS, Netterstrom B, Schnohr P, Gronbaek M. Self reported stress and risk of breast cancer: prospective cohort study. *BMJ* 2005;**331**:548.
18. Nielsen NR, Kristensen TS, Schnohr P, Gronbaek M. Perceived stress and cause-specific mortality among men and women: results from a prospective cohort study. *Am J Epidemiol* 2008;**168**:481–491.
19. Nielsen NR, Kristensen TS, Prescott E, Larsen KS, Schnohr P, Gronbaek M. Perceived Stress and Risk of Ischemic Heart Disease: causation or Bias? *Epidemiology* 2006;**17**: 391–397.
20. Littman AJ, White E, Satia JA, Bowen DJ, Kristal AR. Reliability and validity of 2 single-item measures of psychosocial stress. *Epidemiology* 2006;**17**:398–403.