Eur Respir J 2008; 32: 1548–1554
DOI: 10.1183/09031936.00026808
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Predicting worsening asthma control following the common cold

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ABSTRACT: The asthmatic response to the common cold is highly variable, and early characteristics that predict worsening of asthma control following a cold have not been identified.

In this prospective multicentric cohort study of 413 adult subjects with asthma, the mini-Asthma Control Questionnaire (mini-ACQ) was used to quantify changes in asthma control and the Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21) to measure cold severity. Univariate and multivariable models were used to examine demographic, physiological, serological and cold-related characteristics for their relationship to changes in asthma control following a cold.

Clinically significant worsening of asthma control was observed following a cold (mean$\pm$SD increase in mini-ACQ score of 0.69$\pm$0.93). Univariate analysis demonstrated that season, centre location, cold duration and cold severity measurements were all associated with a change in asthma control. Multivariable analysis of the covariates available within the first 2 days of cold onset revealed that the day 2 and cumulative sum of day 1 and 2 WURSS-21 scores were significant predictors of the subsequent changes in asthma control.

In asthmatic subjects, cold severity within the first 2 days can be used to predict subsequent changes in asthma control. This information may help clinicians prevent deterioration in asthma control following a cold.

KEYWORDS: Asthma, asthma control, common cold

Respiratory tract infections (including the common cold) have been associated with increased asthma symptoms, exacerbations and hospitalisations [1–4]. Recent prospective longitudinal cohort studies in asthmatic adults have also documented an association between respiratory tract infection and worsening asthma symptoms, decline in lung function and asthma exacerbations [5–9]. For each of these end-points, there was a highly variable clinical response to respiratory tract infection. In the controlled research setting of an experimental rhinoviral infection, asthmatic subjects also demonstrated a variable clinical, pathological and physiological response [10–18]. Despite documentation of an acute upper respiratory infection, asthma symptoms ranged from none to severe. Although these studies observed a highly variable post-cold clinical course, none attempted to identify patient or cold episode characteristics that predict a subsequent change in asthma control. Given the current emphasis on measuring asthma control in the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines [2], improved understanding of the effect of a cold on asthma control is needed.

The Post-cold Asthma Control and Exacerbation (PAX) study was designed to identify early characteristics that predict subsequent worsening of asthma control following a cold. This was a multicentric prospective cohort study in adult subjects with mild-to-moderate persistent asthma aimed at defining the prospective incidence of natural colds in asthmatics and identifying early predictors of the changes in asthma control following a cold. It was postulated that patient

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Received:
February 20 2008
Accepted after revision:
August 11 2008

SUPPORT STATEMENT
This study was supported by grants U10-HL74227, U10-HL74231, U10-HL074204, U10-HL74212, U10-HL74073, U10-HL074206, U10-HL074208, U10-HL74225, U10-HL74218, M01-RR00036 and M01-RR07122 from the National Heart, Lung, and Blood Institute (Bethesda, MD, USA).

STATEMENT OF INTEREST
Statements of interest for J.V. Fahy, M. Kraft, and S.J. Szefler can be found at www.erj.ersjournals.com/misc/statements.shtml

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

This article has supplementary material accessible from www.erj.ersjournals.com

and cold episode characteristics would predict a subsequent worsening of asthma control. In order to examine this hypothesis, use was made of the Asthma Control Questionnaire (ACQ) without lung function, referred to as the mini-ACQ [19], to quantify the cold-induced change in asthma control and multivariable modelling to identify unique predictors of the change in asthma control following the onset of a cold.

MATERIAL AND METHODS

Details of material and methods are provided in the online supplementary material.

Study design

The PAX study was a multicentric prospective cohort study that recruited subjects with mild-to-moderate persistent asthma between January 2005 and April 2006. This study recruited subjects that had been screened for the Long-Acting Beta Agonist Response by Genotype (LARGE) study performed by the National Institutes of Health Asthma Clinical Research Network. At study entry, informed consent was obtained, and this was followed by acquisition of demographic information, completion of questionnaires, spirometry, serum collection and administration of the entry mini-ACQ [19]. At the onset of a self-identified cold, the subject notified the study coordinator so that the mini-ACQ scores could be obtained 7 and 14 days after cold onset. Since asthma control and mini-ACQ score may fluctuate over time, and it was planned to follow subjects for >1 yr, mini-ACQ scores were acquired periodically (every ~8 weeks) to serve as a recent pre-cold mini-ACQ score for comparison with subsequent post-cold mini-ACQ scores. The mini-ACQ was used to quantify asthma control, with the minimal important difference (MID) being a change of 0.5 (figs. S1 and S2 of online supplementary material) [19–22]. The Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21) questionnaire was used to quantify severity of cold symptoms and functional impairment, with the MID being a change of 9.48 (fig. S3 of online supplementary material) [23, 24]. The PAX cold questionnaire was used to assess a subject's prior cold history and consisted of four questions related to previous annual cold frequency, severity of colds, frequency of cold-induced asthma symptoms and severity of cold-induced asthma symptoms (fig. S4 of online supplementary material). Each centre's Institutional Review Board approved the protocol.

Statistical analysis

In order to compare WURSS-21 scores by day, an independent-sample unpaired t-test was used. The pre-cold and day 7 and 14 post-cold mini-ACQ scores were compared using repeated-measures ANOVA. Covariates associated with the change between pre-cold and day 7 post-cold mini-ACQ score were identified using an independent or paired t-test, repeated-measures ANOVA and Pearson's correlation. For all comparisons, a p-value of <0.05 was considered significant. The covariates with an association ($p<0.05$) with a change in asthma control that could be obtained within the first 2 days of cold onset were then analysed using generalised estimating equations [25]. Additional details regarding the statistical analysis are included in the online supplementary material.

RESULTS

Characteristics of the cold cohort

The entire PAX study population comprised 413 subjects with mild-to-moderate persistent asthma. Of these 413 subjects, 134 (32.4%) had a least one self-reported cold and constituted the cold cohort. The baseline demographic and clinical characteristics of the cold cohort are shown in table 1. The cold cohort was indistinguishable from those that did not have a cold (the non-cold cohort) in terms of sex, race or ethnicity, age, centre location of enrolment, pre-bronchodilator lung function, serum immunoglobulin (Ig) E concentrations, atopic status and prior tobacco use. Compared to the non-cold cohort, the cold cohort exhibited a lower initial mini-ACQ score (mean±SD 1.04±0.77 *versus* 1.22±0.79; p=0.04), indicating that the cold cohort showed slightly better asthma control at study entry.

Further characterisation of the 134 subjects in the cold cohort demonstrated that 89 (66.4%) subjects had only one cold and 45 (33.6%) had multiple colds (table 2). In order to assess the relationship between prior cold episodes and asthma symptoms, the PAX cold questionnaire was administered. Subjects recalled a history of 2.51 colds every year (questionnaire range 1–8), that their colds were of ''moderate'' severity, that colds ''sometimes'' to ''usually'' made their asthma symptoms worse and that their asthma was of ''moderate'' severity when a cold worsened their asthma.

TABLE 1 Demographic characteristics of cold cohort

Subjects n	134
Females	93 (69.4)
Race or ethnicity[#]	
White, non-Hispanic	100 (74.6)
Black, non-Hispanic	19 (14.2)
Hispanic	8 (6.0)
Other	7 (5.2)
Age yrs	38.7±11.7
Subjects at centre[¶]	
Boston, MA	25 (18.7)
Denver, CO	18 (13.4)
Madison, WI	29 (21.6)
San Diego, CA	11 (8.2)
San Francisco, CA	17 (12.7)
Saint Louis, MO	16 (11.9)
Winston-Salem, NC	18 (13.4)
Pre-bronchodilator FEV_1	
L	2.69±0.73
% pred	80.0±14.5
Total serum IgE IU·mL^{-1}	99.6 (115)[+]
Atopic[§]	56 (96.6)
Prior tobacco use[#]	26 (19.4)
Entry mini-ACQ score[f]	1.04±0.77

Data are presented as mean± SD or n (%), unless otherwise indicated. FEV_1: forced expiratory volume in one second; % pred: % predicted; Ig: immunoglobulin; ACQ: Asthma Control Questionnaire. [#]: self-reported; [¶]: all USA; [+]: geometric mean (percentage coefficient of variation), n=132; [§]: n=58; [f]: scores can range from 0 (no symptoms) to 6 (severe symptoms), n=125.

Incidence of cold episodes

For all 413 subjects in the PAX study, there were a total of 211 cold episodes over a total of 149.4 subject-yrs of follow-up. The overall incidence of colds per subject-year of follow-up for the entire study population was 1.41 (range 1.11 (Winston-Salem, NC)–1.85 (Madison, WI)). In order to determine the incidence of cold episodes by season, 4-month intervals were chosen such that the November to February interval would correspond to a typical cold season. Approximately half (44%) of the 211 cold episodes occurred during the winter season, when the cold incidence was 2.05 colds·subject-yr^{-1} (table 3). The mean time from study entry to onset of a cold was 4 months, and the duration of cold was ~1 week (mean±SD 7.2±4.4 days).

Measurement of cold severity

The WURSS-21, an illness-specific quality-of-life instrument, was used to measure severity of cold symptoms (range 0–140, with higher scores indicating more symptoms and functional impairment) [23, 24]. Since asthma subjects may exhibit symptoms that could elevate the WURSS-21 score independent of a cold, WURSS-21 scores were compared between asthmatics with and without colds. Compared to asthmatics without a cold, those with a cold demonstrated a significant increase in their daily WURSS-21 scores to day 13 (fig. 1a). Furthermore, the magnitude of this increase was greater than the MID of the WURSS-21 (9.48). The subjects with a cold also showed a significantly higher peak and cumulative sum of days 1–2, days 1–4 and days 1–7 WURSS-21 scores (fig. 1b). Compared to baseline rescue salbutamol use (0.57±0.94 puffs·day^{-1}), there was a significant increase on days 1–7 following cold onset, with the highest mean daily use occurring 4 days after the onset of the cold (2.02±2.56 puffs·day^{-1}).

Measurement of asthma control following a cold

In order to quantify the change in asthma control following the onset of a cold, use was made of the mini-ACQ, an instrument used to measure asthma control, with higher scores indicating worse asthma control [19–22]. The mean change between the pre-cold mini-ACQ score and the day 7 post-cold mini-ACQ score was 0.69±0.93, representing a change greater than the MID of the mini-ACQ (0.5). Although the day 14 post-cold mini-ACQ score remained significantly increased over the pre-cold mini-ACQ score, the difference was below the MID (0.26±0.84; fig. 2). In a subgroup of cold episodes that were associated with a subsequent asthma exacerbation (n=27), the mean change between pre-cold and both day 7 and 14 post-cold mini-ACQ scores was even more pronounced and remained greater than the MID at both-time points (1.41±1.08 and 1.09±1.26, respectively). For complete analysis of the demographic and cold episode characteristics of the subjects without and with a post-cold exacerbation, see the online supplementary material (Results section and tables S1–S3).

Characteristics that predict changes in asthma control

Demographic, physiological, serological and cold episode characteristics were examined in order to identify characteristics that were associated with a change in asthma control following a cold. Season of cold onset, centre location and duration of cold were associated with a change in asthma control. In addition, peak rescue salbutamol use, cumulative rescue salbutamol use on days 1–4 and 1–7, and all WURSS-21 scores (except for day 1) were associated with a change in asthma control following a cold (table 4). No associations were found with sex, race or ethnicity, age, forced expiratory volume in one second (absolute or percentage predicted), IgE concentration, atopic status, prior tobacco use, previous cold frequency, severity of previous colds, frequency of cold-induced asthma symptoms, severity of cold-induced asthma symptoms, day 1 rescue salbutamol use, day 2 rescue salbutamol use, cumulative rescue salbutamol use on days 1–2 or concurrent treatment (inhaled corticosteroids with or without long-acting β-agonists) regimens ($p>0.10$).

TABLE 2 Characteristics of the cold cohort

Subjects n	134
Reported colds per subject	
1	89 (66.4)
2	24 (17.9)
3	13 (9.7)
4	6 (4.5)
5	1 (0.7)
6	1 (0.7)
PAX cold questionnaire responses#	
Colds per year	2.51±1.55
Severity of previous colds¶	3.05±0.76
Frequency of cold-induced asthma symptoms+	3.64±1.10
Severity of cold-induced asthma symptoms§	3.01±0.87

Data are presented as mean±SD or n (%), unless otherwise indicated. PAX: Post-cold Asthma Control and Exacerbation. #: n=76; ¶: scores can range from 1 (extremely mild) to 6 (extremely severe); +: scores can range from 1 (never) to 5 (always); §: scores can range from 1 (extremely mild) to 6 (extremely severe).

Since the present goal was to identify early characteristics that predict a change in post-cold asthma control, the covariates in the multivariable models were limited to those that could be collected during the first 48 h of a cold: season of onset, centre location, day 1 WURSS-21 score, day 2 WURSS-21 score, and sum of days 1–2 WURSS-21 score. Season of onset and centre location were collapsed into fewer categories (season: March–October *versus* November–February; centre location: Eastern *versus* Central/Mountain *versus* Pacific time zone). Accordingly, three multivariable models were generated for day 1, day 2 and the sum of days 1–2 WURSS-21 scores, each also including season of onset and centre location. The day 1 WURSS-21 score, season of onset and centre location covariates were nonsignificant predictors of a change in asthma control ($p>0.05$). The day 2 WURSS-21 score was a significant predictor of a change in the day 7 post-cold mini-ACQ score ($p=0.0009$; estimate=0.012; SEM 0.004; 95% confidence interval (CI) 0.005–0.019), indicating that, for every 1-point increase in day 2 WURSS-21 score, there is a predicted 0.01-point increase in the pre-cold to day 7 post-cold change in mini-ACQ score. The sum of days 1–2 WURSS-21 score was also a significant predictor ($p=0.009$; estimate=0.005; SEM 0.002; 95% CI 0.001–0.009), indicating that, for every 1-point increase in the sum of days 1–2 WURSS-21 score, there is a predicted 0.005-point increase in the pre-cold to day 7 post-cold change in mini-ACQ score.

The aim of the present study was to select the best early cold characteristics for predicting a change in mini-ACQ score

TABLE 3 Incidence of cold episodes

	Episodes n (%)	Incidence colds·subject-yr^{-1}
Total	211	1.41
Centre[#]		
Boston, MA	39 (18.5)	1.30
Denver, CO	31 (14.7)	1.48
Madison, WI	50 (23.7)	1.85
San Diego, CA	16 (7.6)	1.13
San Francisco, CA	28 (13.3)	1.47
Saint Louis, MO	23 (10.9)	1.40
Winston-Salem, NC	24 (11.4)	1.11
Season		
November–February	93 (44.1)	2.05
March–June	61 (28.9)	1.15
July–October	57 (27.0)	1.12

[#]: all USA.

using season of onset, centre location, day 1 WURSS-21 score, day 2 WURSS-21 score and sum of days 1–2 WURSS-21 score. Therefore, a stepwise approach was used, and, after creating the marginal models, only day 2 and sum of days 1–2 WURSS-21 scores were significant predictors ($p=0.0009$ and 0.0038, respectively). Given the high correlation between the day 2 and sum of days 1–2 WURSS-21 scores, both were not included in the same model. The quasi-likelihood under the independence model criterion (QIC_u) for both the day 2 and sum of days 1–2 models were 53.0, indicating that both models fit the data equally well. A correlation structure that makes no assumptions about the relationship between pairs of observations from the same participant was selected for both models using the QIC statistic. Again, both models performed equally. It is concluded that the day 2 ($p=0.0003$; estimate=0.0129; 95% CI 0.0059–0.0198) and the sum of days 1–2 WURSS-21 scores ($p=0.0030$; estimate=0.0061; 95% CI 0.0021–0.0101) were early cold characteristics that predicted changes in asthma control.

DISCUSSION

The results of the present multicentric prospective cohort study indicate that the severity of a cold measured within the first 2 days following cold-onset is a unique predictor of subsequent worsening of asthma control. It was identified that the day 2 and cumulative sum of days 1–2 WURSS-21 scores predicted post-cold worsening of asthma control. The WURSS-21 score is the cumulative sum of 20 Likert scale answers that can be obtained from the asthma subject relatively quickly. Although it is proposed that both WURSS-21 scores could be used in the future, the day 2 WURSS-21 score may be more practical since it requires only one collection time-point. The present multivariate modelling indicated that a day 2 WURSS-21 score of 50 predicted a 0.5-point increase in mini-ACQ score. Since a change of 0.5 is the MID of the mini-ACQ, asthma subjects with a day 2 WURSS-21 score of >50 are at increased risk of a clinically significant worsening of their asthma control.

To the current authors' knowledge, the present study represents the largest prospective cohort study of colds in adult asthmatics, and is the first multicentric study performed.

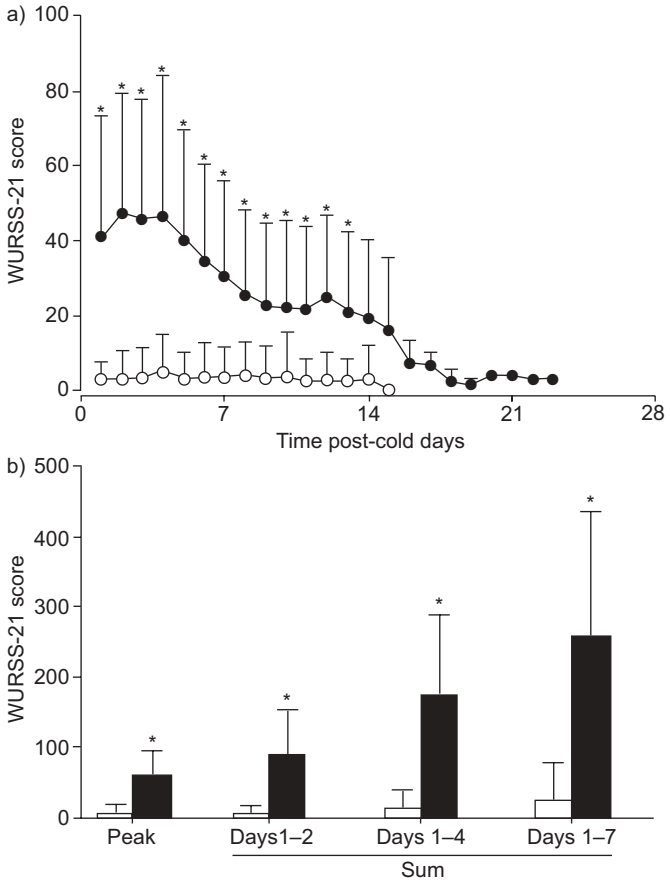

FIGURE 1. Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21) scores for asthmatics with and without colds: a) daily scores (●: with cold (n=44, 31, 9 and 1 on day 1, 7, 14 and 23, respectively); ○: without cold (n=26, 26, 16 and 0 on day 1, 7, 14 and 23, respectively)); and b) peak and cumulative scores (■: with cold (n=44); □: without cold (n=26)). Day 1 indicates the day of cold onset. Data are presented as mean±SD. Asthmatics with a cold demonstrated an increased WURSS-21 score. *: $p<0.05$ (independent-groups t-test).

The seven centres enrolled 413 asthmatics and accrued a total of 149.3 subject-yrs of follow-up. The overall cold incidence per subject-year of follow-up was 1.4, which is similar to previous prospective reports (range 1.2–6.7) [5–9, 26]. The variability in these rates probably reflects different geographical locations and season of follow-up, as well as different criteria for cold identification. In order to avoid over-reporting of cold episodes, the present subjects were specifically instructed not to report a cold if they were only experiencing asthma or allergy symptoms. In order to avoid under-reporting of colds, it was not required that the subject meet any additional criteria other than replying ''yes'' to the cold question, ''Do you have a cold today?''. Even though the study coordinators regularly queried the subjects regarding cold episodes, cold episodes may have been under-reported due to incomplete diary information. Given the multicentric nature of the present study, large sample size, long follow-up times that spanned all seasons, and efforts to avoid under- and over-reporting, the present authors feel that the incidence of approximately one and a half prospectively identified colds per year is accurate.

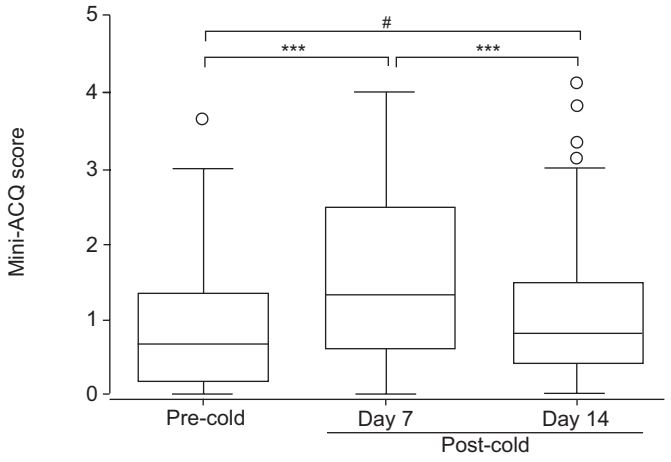

FIGURE 2. Pre-cold and day 7 and 14 post-cold mini-Asthma Control Questionnaire (mini-ACQ) scores for the cohort of cold subjects with complete mini-ACQ data (n=128). Boxes represent median and interquartile range; vertical bars represent the 95% confidence interval (○: outlier; mean±SD scores were 0.83±0.74, 1.51±0.98 and 1.09±0.87, respectively). Asthmatics with a cold demonstrate worsening asthma control. ***: p<0.001; #: p=0.001 (repeated-measures ANOVA).

Since the present study is the first to identify predictors of a change in asthma control following a naturally occurring cold, direct comparison with the literature is not possible. Three experimental rhinoviral inoculation studies attempted to identify characteristics of asthmatics that were associated with a more severe post-viral course and two found no distinguishing factors [12, 16]. In the third study, asthmatic subjects with a high pre-inoculation IgE concentration (>124 IU·mL^{-1}) showed more cold-induced lower respiratory tract symptoms [18]. This study was limited by a small sample size (n=6 and 10 in the high and low IgE cohorts, respectively) and *post-hoc* dichotomisation of individuals according to a relatively arbitrary IgE concentration. No association between IgE concentration and change in asthma control was identified in the present univariate analysis (p=0.83). IgE concentrations were measured at study entry, an average of 4 months prior to cold onset. Accordingly, the possibility cannot be excluded that IgE concentrations measured closer to this cold onset might predict changes in asthma control. However, IgE concentrations are relatively stable over this time frame [27, 28], and thus it is unlikely that additional measurements would identify IgE concentrations as a significant predictor of a change in asthma control following a cold.

The clinical responsiveness of the mini-ACQ for measuring changes in asthma control has been validated in asthmatics with and without stable disease [19, 21]. Compared with the pre-cold mini-ACQ score, the increase in the day 7 post-cold mini-ACQ score was significant and greater than the MID. This clinically significant worsening of asthma control was transient since the increase in the day 14 post-cold mini-ACQ score was less than the MID. This temporal change in asthma control corresponds to the temporal change in asthma symptoms, lung function and airway inflammatory parameters found in previous reports following a natural cold or experimental rhinoviral infection [10–16, 18, 29]. The change in mini-ACQ score following a cold was greater in the cohort with a post-cold asthma exacerbation, and the magnitude of this increase was greater than the MID. Collectively, these data suggest that the mini-ACQ is responsive to changes in asthma control following the onset of a cold and support its use as an end-point in future studies.

TABLE 4 Characteristics of colds associated with a change in asthma control[#]

	p-value
Characteristics of current colds	
Season of onset[¶]	0.05
Centre[¶]	0.005
Duration of cold[+]	<0.001
Rescue salbutamol use after cold onset[§]	
Peak	0.001
Sum days 1–4	0.029
Sum days 1–7	0.004
WURSS-21 assessment of current cold[ƒ]	
Day 1	0.0571
Day 2	<0.0009
Peak	<0.0001
Sum days 1–2	0.0066
Sum days 1–4	0.0009
Sum days 1–7	<0.0001

WURSS-21: Wisconsin Upper Respiratory Symptom Survey-21. [#]: change between pre-cold and day 7 post-cold mini-Asthma Control Questionnaire score; [¶]: repeated-measures ANOVA (n=143); [+]: Pearson's correlation (n=127); [§]: Pearson's correlation (n=67); [ƒ]: generalised estimating equation parameter estimates (n=51).

Cold severity in asthmatics was measured using the WURSS-21, a survey that has been validated in 151 subjects [24]. Compared to the WURSS-21 scores in this previous report, the WURSS-21 scores of the present cohort of asthmatics rose and fell in an identical fashion; however, the day 1 and peak WURSS-21 scores appeared to be ~20% lower and the dispersion was approximately two times greater. This may be related to the present smaller sample size or the inclusion of subjects with less severe colds, since less stringent cold identification criteria were purposely employed. Alternatively, the validation study WURSS-21 scores may be somewhat overestimated if, as stated by the authors, their colds were longer and more severe compared to those in previous studies [24]. To support the use of the WURSS-21 in asthmatics, it was demonstrated that the WURSS-21 scores of asthmatics changed significantly following a self-reported cold, and the WURSS-21 scores in asthmatics without colds were very low and displayed minimal day-to-day variability. Accordingly, the present authors feel that the WURSS-21 can serve as a valuable tool for the measurement of cold severity in asthmatics.

There are limitations of the present study regarding selection criteria, study design and availability of data. The current study excluded subjects with severe disease, a significant smoking history, use of high-dose inhaled corticosteroids or a history of life-threatening asthma. Therefore, the present

results cannot be generalised to asthmatics with these conditions. The PAX study occurred within the ongoing LARGE parent trial, in which asthmatic subjects receiving inhaled corticosteroids were randomised to either placebo or long-acting β-agonists; hence a confounding treatment effect may exist. The PAX cold questionnaire and WURSS-21 data were incomplete due to missing data and the introduction of these questionnaires to the study after some of the cold episodes. External validation of the identified predictors could not be performed because the authors are unaware of any existing data set that includes the required predictors and outcome variables. Finally, microbiological specimens were not collected during the cold episodes and so it is not possible to determine the role of viral or bacterial respiratory tract infections on post-cold asthma control.

In conclusion, it was identified that the day 2 and cumulative sum of days 1–2 Wisconsin Upper Respiratory Symptom Survey-21 scores could predict a post-cold worsening of asthma control. These cold severity measurements may provide an easy-to-use tool for providing important prognostic information to the clinician. Thus clinicians may want to include an assessment of cold severity together with a measure of asthma control and adjust therapy according to the National Asthma Education and Prevention Program guidelines. Furthermore, utilisation of these predictors will aid in the identification of patients at high risk of subsequent worsening of asthma control and may thus be used to develop stratification criteria for clinical or interventional studies designed to modify asthma control following a cold.

ACKNOWLEDGEMENTS

M.J. Walter, M. Castro, M. Reno, T.P. Ramkumar (Washington University School of Medicine, Saint Louis, MO, USA); S.J. Kunselman, V.M. Chinchilli, T.J. Craig (Pennsylvania State University College of Medicine, Hershey, PA, USA); P.C. Avila (Northwestern University Feinberg School of Medicine, Chicago, IL, USA); H.A. Boushey, J.V. Fahy, S.C. Lazarus (University of California at San Francisco, San Francisco, CA, USA); B.T. Ameredes, W.J. Calhoun (University of Texas Medical Branch at Galveston, Galveston, TX, USA); E.R. Bleecker, S.P. Peters (Wake Forest University School of Medicine, Winston-Salem, NC, USA); R.M. Cherniack, R.J. Martin, E.R. Sutherland, S.J. Szefler (National Jewish Medical and Research Center, Denver, CO, USA); L.C. Denlinger, N.N. Jarjour, R.F. Lemanske Jr, C.A. Sorkness (University of Wisconsin School of Medicine, Madison, WI, USA); E. Israel, M.E. Wechsler (Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA); M. Kraft (Duke University School of Medicine, Durham, NC, USA); J.W. Ramsdell, S.I. Wasserman (University of California at San Diego, San Diego, CA, USA).

The authors would like to thank all of the subjects, clinical coordinators and administrators at each centre for their dedication and effort in completing the present study: M.E. Scheipeter, S. DeMartino, E. Bender and J. Kiviat (Washington University School of Medicine, Saint Louis, MO, USA); R. Zimmerman, K. Bixler and K. Sheaffer (Pennsylvania State University College of Medicine, Hershey, PA, USA); P. Cadbury (University of California at San Francisco, San Francisco, CA, USA); W. Kahn, S.M. Trahan, C. Wilmoth, L. Imboden, J. Krings, K. Calloway and B. Hmieleski (Wake Forest University School of Medicine, Winston-Salem, NC, USA); M. Gill (National Jewish Medical and Research Center, Denver, CO, USA); J. Matthews, B. Miller and A. Sexton (University of Wisconsin School of Medicine, Madison, WI, USA); and S. Bunga and G. Marigowda (Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA).

REFERENCES

1 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. www.ginasthma.org/Guidelineitem.asp??l1=2&l2=1&intId=60 Date last updated: 19 December 2007. Date last accessed: 13 February 2008.
2 National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf Date last updated: 28 August 2007. Date last accessed: 13 February 2008.
3 Lambert HP, Stern H. Infective factors in exacerbations of bronchitis and asthma. *BMJ* 1972; 3: 323–327.
4 Minor TE, Dick EC, DeMeo AN, Ouellette JJ, Cohen M, Reed CE. Viruses as precipitants of asthmatic attacks in children. *JAMA* 1974; 227: 292–298.
5 Atmar RL, Guy E, Guntupalli KK, *et al.* Respiratory tract viral infections in inner-city asthmatic adults. *Arch Intern Med* 1998; 158: 2453–2459.
6 Beasley R, Coleman ED, Hermon Y, Holst PE, O'Donnell TV, Tobias M. Viral respiratory tract infection and exacerbations of asthma in adult patients. *Thorax* 1988; 43: 679–683.
7 Corne JM, Marshall C, Smith S, *et al.* Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002; 359: 831–834.
8 Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ* 1993; 307: 982–986.
9 Hudgel DW, Langston L Jr, Selner JC, McIntosh K. Viral and bacterial infections in adults with chronic asthma. *Am Rev Respir Dis* 1979; 120: 393–397.
10 Bardin PG, Fraenkel DJ, Sanderson G, van Schalkwyk EM, Holgate ST, Johnston SL. Peak expiratory flow changes during experimental rhinovirus infection. *Eur Respir J* 2000; 16: 980–985.
11 Cheung D, Dick EC, Timmers MC, de Klerk EP, Spaan WJ, Sterk PJ. Rhinovirus inhalation causes long-lasting excessive airway narrowing in response to methacholine in asthmatic subjects *in vivo*. *Am J Respir Crit Care Med* 1995; 152: 1490–1496.
12 Fleming HE, Little FF, Schnurr D, *et al.* Rhinovirus-16 colds in healthy and in asthmatic subjects: similar changes in upper and lower airways. *Am J Respir Crit Care Med* 1999; 160: 100–108.
13 Fraenkel DJ, Bardin PG, Sanderson G, Lampe F, Johnston SL, Holgate ST. Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. *Am J Respir Crit Care Med* 1995; 151: 879–886.

14 Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. *Am J Respir Crit Care Med* 2000; 162: 2226–2231.

15 Grunberg K, Sharon RF, Sont JK, *et al.* Rhinovirus-induced airway inflammation in asthma: effect of treatment with inhaled corticosteroids before and during experimental infection. *Am J Respir Crit Care Med* 2001; 164: 1816–1822.

16 Halperin SA, Eggleston PA, Beasley P, *et al.* Exacerbations of asthma in adults during experimental rhinovirus infection. *Am Rev Respir Dis* 1985; 132: 976–980.

17 Mosser AG, Vrtis R, Burchell L, *et al.* Quantitative and qualitative analysis of rhinovirus infection in bronchial tissues. *Am J Respir Crit Care Med* 2005; 171: 645–651.

18 Zambrano JC, Carper HT, Rakes GP, *et al.* Experimental rhinovirus challenges in adults with mild asthma: response to infection in relation to IgE. *J Allergy Clin Immunol* 2003; 111: 1008–1016.

19 Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue β_2-agonist use? *Respir Med* 2001; 95: 319–323.

20 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; 14: 902–907.

21 Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; 99: 553–558.

22 Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying ''well-controlled'' and ''not well-controlled'' asthma using the Asthma Control Questionnaire. *Respir Med* 2006; 100: 616–621.

23 Barrett B, Locken K, Maberry R, *et al.* The Wisconsin Upper Respiratory Symptom Survey (WURSS): a new research instrument for assessing the common cold. *J Fam Pract* 2002; 51: 265–273.

24 Barrett B, Brown R, Mundt M, *et al.* The Wisconsin Upper Respiratory Symptom Survey is responsive, reliable, and valid. *J Clin Epidemiol* 2005; 58: 609–617.

25 Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics* 2001; 57: 120–125.

26 Tarlo S, Broder I, Spence L. A prospective study of respiratory infection in adult asthmatics and their normal spouses. *Clin Allergy* 1979; 9: 293–301.

27 Boulet LP, Chapman KR, Cote J, *et al.* Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997; 155: 1835–1840.

28 Fahy JV, Fleming HE, Wong HH, *et al.* The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155: 1828–1834.

29 Pizzichini MM, Pizzichini E, Efthimiadis A, *et al.* Asthma and natural colds. Inflammatory indices in induced sputum: a feasibility study. *Am J Respir Crit Care Med* 1998; 158: 1178–1184.