

The Asthma Disease Activity Score: A discriminating, responsive measure predicts future asthma attacks

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Background: Classifying asthma severity or activity has evolved, but there are no published weighted composite measures of asthma disease activity that account for the relative importance of the many individual clinical variables that are widely used.

Objectives: We sought to develop a weighted and responsive measure of asthma disease activity.

Methods: Discriminant and multiple regression analyses based on 2 previously conducted clinical trials were used to develop the Asthma Disease Activity Score (ADAS-6).

Results: The ADAS-6 demonstrated content validity because its components assess different manifestations of asthma:

FEV₁ (percent predicted), Asthma Quality of Life Questionnaire–Symptom domain, rescue β -agonist use, nocturnal awakenings, peak expiratory flow diurnal variability,

and rescue β -agonist use diurnal variability. The ADAS-6 demonstrated cross-sectional and longitudinal validity. It was discriminating: it distinguished levels of disease activity and response to different treatment intensities ($P < .0001$). Similar results were obtained with an independent clinical trial. The ADAS-6 was highly responsive to treatment effects, with a standardized effect size exceeding that of other widely used outcome measures. Using ADAS-6 as the primary end point in the montelukast pivotal trials would have significantly reduced the sample size needed to detect a comparable change in outcome. Furthermore, increments in the ADAS-6 predicted the risk of future asthma attacks. A simplified Asthma Disease Activity Score 4-variable version (ADAS-4) demonstrated similar measurement properties.

Conclusions: The ADAS-6 and ADAS-4 are novel, weighted, and responsive measures of asthma disease activity. Use of these measures in clinical trials might better separate treatment effects, predict future asthma attacks, and substantially reduce sample size. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Asthma, activity, exacerbations, asthma-specific quality of life, regression, validity

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Outcome measures that are commonly used in clinical trials include single measures, such as FEV₁ and the daytime symptom score, as well as composite measures (eg, the Asthma Control Questionnaire (ACQ) score,¹ the Asthma Control Test score,² and others). The principal advantage of composite measures is that they capture multiple aspects of asthma disease severity, control, or both, thereby collectively strengthening the content validity of the outcome measure. Although most composite measures have been validated for relevant disease populations, existing measures assign equal weights to each component variable.³ For example, FEV₁ and daytime symptoms receive equal weighting in the ACQ. However, there is no empiric justification for why single-outcome measures should be considered equivalent in distinguishing different burdens of disease, predicting future loss of control, or judging the relative effectiveness of different therapeutic interventions. This problem is not restricted to clinical pulmonary diseases, of course, and has been addressed in other fields through the development of weighted composite outcome measures. For example, the disease activity score (DAS) for rheumatoid arthritis (RA)⁴ has gained widespread use in clinical trials.

There are significant challenges to developing weighted similar composite measures of efficacy outcomes in asthma. First, existing single-outcome measures correlate poorly with each other,⁵ which questions their convergent validity (ie, overlap between measurements that presumably measure a similar clinical construct).

Abbreviations used

ACQ:	Asthma Control Questionnaire
ADAS-6:	Asthma Disease Activity Score 6-variable version
ADAS-4:	Asthma Disease Activity Score 4-variable version
AQLQ:	Asthma Quality of Life Questionnaire
DA:	Discriminant analysis
DAS:	Disease activity score
DSS:	Daytime Symptom Score
MR:	Multiple regression
PEF:	Peak expiratory flow
RA:	Rheumatoid arthritis

Second, like other diseases, such as RA, asthma is clinically heterogeneous. Clinical manifestations among patients might best be captured by different sets of outcome measures. This poses obvious challenges in clinical trials when groups of asthmatic patients with different endotypes or phenotypes^{6,7} are likely to be included in the same clinical trial.

Finally, unlike some organs, such as the skin, in which clinical disease manifestations (eg, erythema and edema) can be readily perceived and objectively quantified, the lung is largely inaccessible except through invasive measures, necessitating the use of surrogate and indirect measures of tissue pathology.

We recently reported a statistical reanalysis of data from the pivotal trials of montelukast^{8,9} to determine which outcome measures best distinguished different levels of disease activity.¹⁰ The results of this prior work provided a framework on which to base the development of a weighted composite score of asthma activity. The purpose of the present analysis is to use the prior results to develop the Asthma Disease Activity Score.

METHODS

Clinical trial database

We created a dataset by pooling the data from 2 large, phase III pivotal studies of montelukast. Full reports of both clinical trials used in this analysis have been published previously.^{8,9} Both consisted of a 2-week, single-blind placebo run-in period; a 12-week, double-blind active treatment period; and a 3-week, double-blind placebo washout period. In both studies otherwise healthy nonsmoking men and women 15 years of age or older with at least a 1-year history of asthma who met prespecified criteria regarding lung function, reversibility, and asthma symptoms were eligible; qualifying patients were randomized to receive montelukast (both studies), beclomethasone (1 study⁸), or placebo (both studies) during the active treatment periods. Summary statistics of the combined population have been published previously.¹⁰

Outcome measures

In both studies FEV₁ was measured at each visit during the baseline period and 12-week active treatment period (ie, weeks 3, 6, 9, and 12); asthma-specific quality of life (AQLQ) was assessed at baseline (week 0), week 3, and week 12. Rescue β -agonist use, daytime symptom score, and peak expiratory flow (PEF; morning and evening) were derived from patients' entries on daily diary cards. Oral corticosteroid rescue medication was initiated for worsening asthma. The following additional outcome measures were used: asthma attack (an unscheduled visit to a doctor's office, emergency department, or hospital or treatment with oral, intravenous, or intramuscular corticosteroids for worsening asthma), days with an asthma exacerbation, asthma-free days, and oral corticosteroid rescue. These additional outcome measures were also derived from patients' entries on the daily diary card during the treatment period and were not evaluated at baseline because they were measured on treatment only. Definitions for these and other outcome measures are provided in Table E1 in this article's Online Repository at www.jacionline.org.

Defining disease activity

Analogous to the DAS for RA,¹¹ we defined asthma disease activity based on patients' manifestations of asthma, regardless of the level of treatment intensity. In addition, we specifically avoided the terms asthma disease severity or control to avoid conflating our definitions with these related concepts. Subjects were characterized as having high or low disease activity based on cutoffs derived from the guidelines established by the Global Initiative for Asthma¹² and the Expert Panel Report 3 from the National Heart, Lung, and Blood Institute.^{10,13} In brief, this classification included high and low cutoffs for the following variables: daytime symptom score, nocturnal awakenings, average rescue β -agonist use, AQLQ-Activity domain, FEV₁ (percent predicted), and asthma attacks (similar to severe asthma exacerbations, as defined by the American Thoracic Society/European Respiratory Society Statement on asthma control and exacerbations).¹⁴ Classification of high disease activity required a subject to meet any of the individual lower-limit criteria (eg, FEV₁ <60% of predicted value or ≥ 4 puffs/d of rescue β -agonist use), whereas classification of low disease activity required a subject to meet all of the upper-limit criteria (eg, FEV₁ $\geq 80\%$ of predicted value and ≤ 1 puff/d of rescue β -agonist use).

Statistical methods

Using the combined trial database described above, we previously performed principal components analysis, a type of multivariate analysis related to factor analysis that reveals the internal structure of the data that best explains the variance in the data, and discriminant analysis (DA). DA resulted in the derivation of a discriminant function, a latent continuous measure of disease activity.¹⁰ We used the discriminant function, a linear function consisting of 6 factors, as the dependent variable and 13 variables (see Table E1) as the independent variables in a stepwise, forward, multiple regression (MR) analysis. The output of the MR (β coefficients) was used to derive the Asthma Disease Activity Score 6-variable version (ADAS-6). A correction constant was added to the ADAS-6, such that an asymptomatic subject would score close to 0. The correction constant was derived by assuming the asymptomatic patient's β -agonist use, nocturnal awakening, and diurnal variability of PEF rate and β -agonist use were all 0, the AQLQ symptom domain was 7, and percent predicted FEV₁ was 120%. The ADAS-6 contains 2 derived outcome variables: diurnal variability of PEF and diurnal variability of rescue β -agonist use. Both calculations require diary data that must be entered twice daily, which add to subject and site burden; in addition, these data are obviously not obtainable from the many clinical trials that collect diary data on a daily basis only. Therefore we developed a simplified version of the ADAS-6, the Asthma Disease Activity Score 4-variable version (ADAS-4), by repeating the DA and MR but excluding these 2 derived variables. All data were analyzed with SAS version 9.1 software (SAS Institute, Cary, NC).

RESULTS

Correlations between outcome measures within and between individual asthmatic subjects

Summary statistics of the combined database have been published previously.¹⁰ We determined the extent to which 21 individual outcome measures of asthma (see Table E1) correlated with one another. Individual outcome measures at baseline demonstrated either no correlation or a modest degree of correlation at best. Correlation coefficients were greatest between outcome measures that reflected similar constructs (eg, between different domains of the AQLQ [0.56-0.74] or between FEV₁ [percent predicted] and morning/evening PEF [0.37-0.41]). For outcome variables that were less clearly related, correlation coefficients ranged from less than 0.1 between FEV₁ (percent predicted) and individual domains of the AQLQ to 0.55 between nocturnal asthma score and rescue β -agonist use. Even after treatment, the extent of correlation was low between different outcome measures within the same subjects or between the same outcome

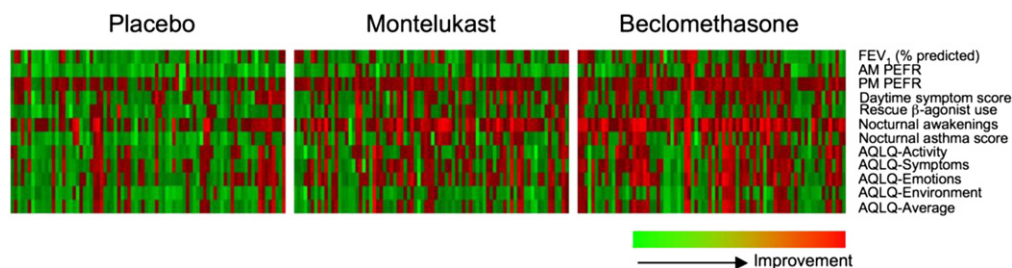


FIG 1. Heat map of selected outcomes in the combined dataset. Patients were selected at random ($n = 80$ per group). Each column represents a single patient, and each row represents change from baseline in the indicated outcomes. Data were subjected to a row-normalized heat map-generating algorithm (adapted from King et al¹⁵). Note the marked interindividual and intraindividual variability in the change from baseline in each outcome. AM PEF, Morning PEF rate; PM PEF, evening PEF rate.

measures across subjects within the same treatment groups (Fig 1).¹⁵ These poor correlations illustrate the limitations of relying on any single asthma outcome measure to capture the multiple clinical manifestations of asthma. Furthermore, these findings provide empiric support to develop a weighted composite measure of disease activity.

Development of a weighted Asthma Disease Activity Score

We adopted an approach used in the development of the DAS for RA.¹¹ This is based on a sequential statistical analysis of clinical trial data, beginning with factor analysis or principal components analysis, development of classification rules to characterize high and low disease activity, and DA to develop a continuous measure of disease activity.¹⁰ We used the output of DA in a forward-selection stepwise MR. Many variables contributed minimally to the MR model, even though they were statistically significant. We selected variables with partial R^2 values of greater than 0.01 to construct the ADAS-6, which resulted in identification of 6 variables that contributed significantly to the model (see Table E2 in this article's Online Repository at www.jacionline.org). The 6 variables thus identified were rescue β-agonist use, FEV₁ percent predicted, AQLQ-Symptom domain, PEF diurnal variability, rescue β-agonist diurnal variability, and nocturnal awakenings. The ADAS-6 was calculated based on these 6 variables by using the regression model as follows:

$$\text{ADAS-6} = 4.6534 + 0.1118(\text{Rescue } \beta\text{-agonist puffs/day}) - 0.0236(\text{FEV}_1 \text{ \% predicted}) - 0.2602(\text{AQLQ-Symptom domain}) + 4.3633(\text{Diurnal variability in PEF}) + 0.5765(\text{Diurnal variability in rescue } \beta\text{-agonist use}) + 0.1226(\text{Night-time awakenings}).$$

Each of the 6 variables contributed in a relatively balanced fashion to the MR model (see Table E2). For example, the relative contribution toward the composite score was greatest for FEV₁ (standardized coefficient of -0.299) and least for PEF diurnal variability (standardized coefficient of 0.241). As applied to the clinical trial database, the ADAS-6 ranged from approximately 0 to 8, with 0 representing essentially an absence of clinical manifestations of asthma and 8 representing the highest level of disease activity. Correlations among the 6 variables comprising the ADAS-6 and the ADAS-6 itself were primarily moderate to strong; rescue β-agonist use had the strongest correlation ($r = 0.81$) with the ADAS-6 (see Table E3 in this article's Online Repository at www.jacionline.org), although it

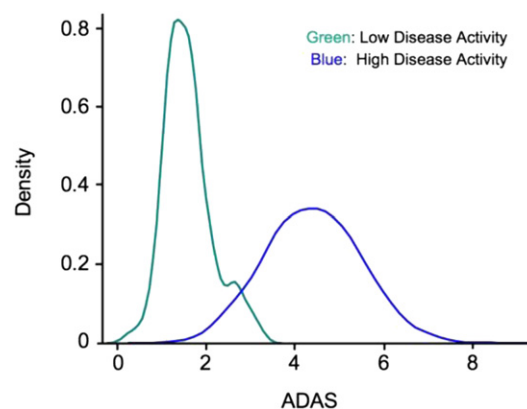


FIG 2. Density plots of ADAS-6 values at week 12 in patients classified as having high or low disease activity ($n = 1293$).

did not contribute disproportionately to the composite score (compare standardized coefficients are shown in Table E2). The distribution of ADAS-6 values at the end of 12 weeks of treatment in those patients with high and low degrees of disease activity can be depicted as density plots in Fig 2. This degree of separation between high and low disease activity is comparable with what was observed for subjects with RA who were also categorized as having high and low disease activity by using the DAS.⁴ The distribution of ADAS-6 in those patients with high disease activity was wider than that of patients with low disease activity. Because the inclusion criteria prevented patients with low disease activity from entering the trial, the narrow distribution of patients with low disease activity at the end of 12 weeks of therapy is most likely explained by an appreciable response to therapy. In contrast, patients with a high level of disease activity at 12 weeks represented a large proportion of patients receiving placebo, as well as a mixture of nonresponders and partial responders to active therapy.

Psychometric properties of the ADAS-6 in this sample

Content validity is established when a measurement is shown to reflect multiple aspects of the content that is being measured. The ADAS-6 comprised 6 variables, each of which captures different aspects of clinical asthma, and is consistent with this requirement of content validity. Furthermore, the ADAS-6 exhibited a moderate degree of internal consistency among its individual

TABLE I. ADAS-6 values and various outcome measures in subjects with different levels of overall disease activity at week 12

End point	Disease activity	Mean	SD	T values (mean difference/SE)*		
				Moderate vs low	Moderate vs high	High vs low
ADAS-6	Low	1.6	0.5	10.2	−28.9	25.5
	Moderate	2.7	0.8			
	High	4.4	1.1			
ADAS-4	Low	1.5	0.4	8.5	−32.7	25.5
	Moderate	2.3	0.5			
	High	4.0	1.1			
FEV ₁ (L)	Low	3.2	0.8	−5.2	12.0	−11.4
	Moderate	2.8	0.7			
	High	2.3	0.8			
Rescue β-agonist use (puffs/d)	Low	0.3	0.3	3.9	−26.9	17.8
	Moderate	1.5	1.1			
	High	5.6	3.5			
Nighttime awakenings (nights/wk)	Low	0.2	0.3	3.2	−26.0	16.6
	Moderate	1.0	1.2			
	High	4.2	2.7			
AQLQ	Low	5.3	0.6	−5.8	15.2	−13.8
	Moderate	4.6	0.9			
	High	3.8	1.1			
Daytime symptom score	Low	0.6	0.5	8.3	−17.8	17.6
	Moderate	1.4	0.9			
	High	2.3	0.9			

*The greater the absolute value of the T values, the more discriminating the end point.

components (Cronbach $\alpha = 0.73$), indicating that individual items are not redundantly measuring a single construct (otherwise Cronbach α would be ≥ 0.9).

Convergent validity is determined by examining the extent of overlap between 2 or more measures of presumably the same construct. This type of validity is met when the measure in question correlates with other measures of the same construct cross-sectionally, longitudinally, or both. The extent of correlation of the ADAS-6 with outcome variables that are not themselves components of the ADAS-6 was significant for all correlations ($P < .01$); these correlations (positive or negative) ranged from 0.32 for asthma exacerbations to -0.73 for asthma-free days (see Table E4 in this article's Online Repository at www.jacionline.org). These correlations are consistent with the ADAS-6 demonstrating cross-sectional validity. The ADAS-6 also demonstrated longitudinal validity because correlations were significant between change in the ADAS-6 and change in other outcome variables after treatment (see Table E4).

The ADAS-6 was highly discriminating because it distinguished between subjects with different levels of disease activity (Table I) and in response to therapies of different potencies (Fig 3 and see Table E5 in this article's Online Repository at www.jacionline.org). Finally, the ADAS-6 demonstrated predictive validity because successive increments in the ADAS-6 predicted the risk of future asthma attacks (Fig 4). Its predictive

validity was greater than that of other commonly used outcome measures (Table II).

Comparative statistical power of the ADAS-6

A major limitation in designing clinical trials in asthma is that many existing outcome measures are relatively insensitive to change, lack sufficient precision to limit the sample size, or both. One way to capture the inherent power of an outcome measure is to determine its effect size or standardized response mean. As applied to the combined database, the ADAS-6 exhibited greater standardized response means than many existing outcome measures (Table III), including FEV₁, which is the most common primary outcome measure used in clinical asthma trials. All else being equal, using the ADAS-6 as an outcome measure would have required the fewest number of subjects to have detected the responses that were observed in these trials, assuming equivalent power.

ADAS-4 compared with the full 6-variable ADAS-6

We developed a simplified version of the ADAS, the ADAS-4, that excludes variables requiring twice-daily diary entries (the diurnal variation of the PEF and β-agonist use). DA of the ADAS-4 demonstrated nearly the same canonical correlation and correct classification rate as the original ADAS-6 (0.68 vs 0.69 and 97.4% vs 98.3%, respectively). After MR, the resultant ADAS-4 was calculated as follows: ADAS-4 = 5.7497 + 0.1611(Rescue β-agonist puffs/day) − 0.0307(FEV₁ % predicted) − 0.2951(AQLQ-Symptom domain) + 0.0858(Nighttime awakenings).

Standardized coefficients for components of the ADAS-4 indicated that rescue β-agonist use contributed most to the model and nocturnal awakenings the least; the standardized coefficients for rescue β-agonist use, FEV₁ (percent predicted), AQLQ-Symptom domain, and nocturnal awakenings were 0.43, -0.39 , -0.26 , and 0.18, respectively. The internal consistency of the ADAS-4, as determined by using the Cronbach α value at 0.76, was similar to that of the ADAS-6 ($\alpha = 0.73$). Similar to the ADAS-6, the ADAS-4 demonstrated cross-sectional and longitudinal validity (see Table E6 in this article's Online Repository at www.jacionline.org), and it was nearly as discriminating as the ADAS-6, although the ADAS-6 was slightly more discriminating, as measured by differences between levels of disease activity (Table I) and treatment groups (compare Tables E5 and E7 in this article's Online Repository at www.jacionline.org). As assessed by treatment differences in relation to SE, these differences were greater in 4 of 6 comparisons. When applied to an independent dataset, these differences were apparent in 5 of 6 comparisons (data not shown). The ADAS-4 also demonstrated predictive validity (Table II), and its statistical power was similar to that of the ADAS-6.

Further criterion validity of the ADAS-6 and ADAS-4

Criterion validity is comprised of concurrent validity (the degree to which the measure correlates with other measures of the same construct that are measured at the same time) and predictive validity. Both the ADAS-6 and the ADAS-4 demonstrated predictive validity (Fig 4 and Table II), and both correlated with multiple asthma outcome measures both cross-sectionally and

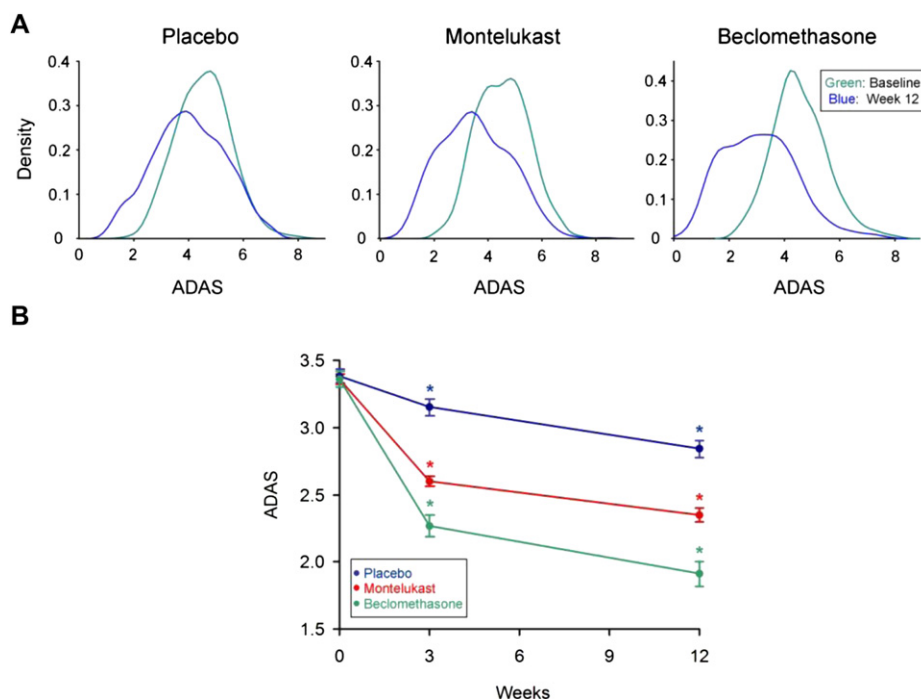


FIG 3. ADAS-6 as a function of time and treatment group. **A**, Density plots of ADAS-6 values in patients at baseline and week 12. Patients were randomized to the indicated treatment group ($n = 1576$). **B**, Patients were randomized to indicated treatment, and ADAS-6 values were determined for baseline (week 0) and weeks 3 and 12. Data represent means $\pm$ SEMs ($n = 1576$). * $P < .0001$, montelukast vs placebo, montelukast vs beclomethasone, and beclomethasone vs placebo.

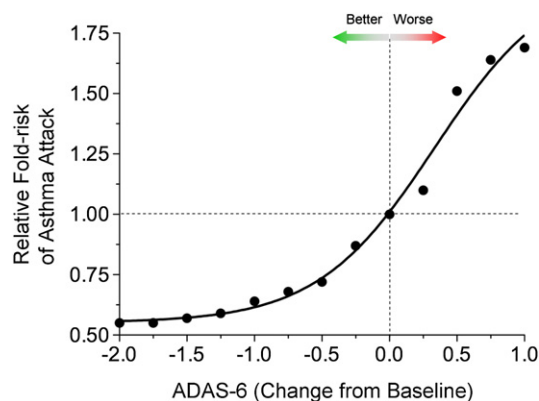


FIG 4. Relative risk of having an asthma attack as a function of change in ADAS value. The week 3 ADAS-6 value, calculated as the change from baseline, is plotted against the risk of having an asthma attack between weeks 3 and 12. The risk of an asthma attack was calculated as a percentage of the average risk of having an asthma attack in those subjects whose change from baseline in ADAS-6 value was 0 (indicated by the dashed lines).

longitudinally (see Table E4). To provide further concurrent validation, we determined the correlation of the ADAS-6 and ADAS-4 with the investigator's and patient's global evaluation of change. These outcome measures attempt to capture in a single overall assessment by the investigator or the patient how the patient felt at the end compared with the beginning of the study. The ADAS-6 and ADAS-4 both correlated with these outcome measures to a greater extent than other single-outcome measures (Table IV), which is consistent with a more accurate estimate of

the investigator's assessment or the patient's self-assessment at the end of the study.

Measurement properties of the ADAS-6 and ADAS-4 using an independent dataset

To further validate the ADAS-6 and ADAS-4, we calculated these outcome variables using single-outcome measures from an independent dataset (MF/F P04334),¹⁶ which consisted of a population of patients with slightly milder asthma who participated in a placebo-controlled randomized clinical trial of formoterol, mometasone, or the combination. The mean FEV₁ at baseline in this population ($n = 606$) was 72% of predicted value compared with a mean of 65.9% of predicted value for the original dataset. The pattern of correlations between subjects' outcome variables and components of the ADAS-6 was generally similar to that of the original dataset, with some values lower (eg, -0.12 for the correlation between FEV₁ percent predicted and rescue β -agonist use vs -0.32 for the same correlation in the original dataset) and some higher (eg, 0.26 for the correlation between nocturnal awakenings and diurnal variability in rescue β -agonist use vs -0.04 for the same correlation in the original dataset; see Table E8 in this article's Online Repository at www.jacionline.org). Similar to the original dataset, when tested against the P04334 dataset, the ADAS-6 demonstrated cross-sectional and longitudinal validity (see Table E9 in this article's Online Repository at www.jacionline.org) and was highly discriminating (see Table E10 in this article's Online Repository at www.jacionline.org). In addition, the ADAS-6 demonstrated predictive validity when applied to the P04334 dataset: the response in the ADAS-6 at week 3 predicted the risk of subsequent asthma attacks (manuscript in

TABLE II. Predictive validity: estimated odds ratio of an asthma attack between weeks 3 and 12 given 1 SD unit of change at week 3

Change in outcome variable (1 SD) at week 3	Estimated odds ratio	Lower bound of 95% CI	Upper bound of 95% CI
ADAS-6	2.05	1.67	2.52
ADAS-4	2.07	1.71	2.52
FEV ₁ (L)	1.67	1.40	2.00
Rescue β -agonist use (puffs/d)	1.57	1.31	1.89
Nighttime awakenings (nights/wk)	1.41	1.18	1.69
AQLQ score	1.36	1.14	1.63
Daytime symptom score	1.66	1.39	1.99

TABLE III. Comparative power of the ADAS-6 and various other efficacy outcome measures using data derived from the montelukast pivotal trials

End point	Montelukast			Beclomethasone		
	Mean difference*	SRM	NNS†	Mean difference*	SRM	NNS†
ADAS-6	-0.49	0.44	83	-0.94	0.77	28
ADAS-4	-0.41	0.47	73	-0.90	0.72	32
FEV ₁ (L)	0.18	0.42	90	0.21	0.43	86
Rescue β -agonist use (puffs/d)	-1.09	0.38	110	-1.98	0.61	44
AQLQ score	0.29	0.27	217	0.61	0.49	67
Nighttime Awakening (nights/wk)	-0.69	0.27	217	-1.74	0.64	40
Daytime symptom score	-0.16	0.17	545	-0.43	0.46	76

SRM, Placebo-subtracted standardized response mean.

*From baseline.

†The number needed to study (NNS) represents the number of patients required to detect the responses obtained in the combined database, assuming a 2-sided *P* value of less than .05 and 80% power.

preparation). Similar results were obtained by using the ADAS-4 when applied to the P04334 database, although as was the case in the original database, the ADAS-6 was somewhat more discriminating than the ADAS-4 in detecting small treatment differences (data not shown).

DISCUSSION

This study describes the derivation of 2 weighted composite outcome measures for asthma disease activity, the ADAS, a 6-variable version, and the ADAS-4, a simplified version. Both measures demonstrated content validity because they captured multiple manifestations of asthma with appropriately moderate internal consistency and were more discriminating than existing single-outcome measures. Both measures demonstrated cross-sectional, longitudinal, and predictive validity by using both the original dataset of the combined montelukast pivotal trials and an independent dataset.

An obvious question that arises from this analysis is whether a weighted composite measure of asthma activity is needed, given

the multiple single-outcome measures available, as well as unweighted composite measures, such as the ACQ and the Asthma Control Test, which have gained widespread use. The chief benefit of unweighted composite measures, in addition to capturing multiple aspects of asthma control, is their simplicity. We would argue that because the ADAS-6 and ADAS-4 were derived based on a maximal separation between the attributes of asthmatic patients that would be considered to have very mild and very severe disease manifestations, their value lies in the ability to detect small changes in the clinical status of asthmatic patients. When applied to a population of asthmatic patients, the ADAS-6 and ADAS-4 demonstrated a high degree of sensitivity to change and a relatively low degree of variation, which translates to an increased standard response mean (ie, a placebo-corrected effect size) and a more responsive outcome measure for use in clinical trials. We anticipate that powering a study based on the ADAS-6 or ADAS-4 would result in fewer patients needed to demonstrate a significant effect. Furthermore, because the ADAS-6 and ADAS-4 are weighted, it is anticipated that they might capture multiple aspects of asthma in a single tool with appreciable accuracy. Therefore we would predict that the ADAS-6 and ADAS-4 would be particularly good at separating responses to different drugs of varying potencies or different doses of the same drug; they also might be better at predicting future loss of asthma control across the population. Indeed, the ADAS-6 and ADAS-4 were highly discriminating and predictive when applied to an independent database.

Another anticipated benefit of the ADAS-6 and ADAS-4 is that they can serve as the basis of a responder analysis. For example, in clinical trials of RA, the DAS is used to determine whether a given patient has undergone a clinical remission; a score of less than 2.6 for the 28-joint count version of the DAS is considered indicative of a remission.¹⁷ Because the DAS for RA is reported on a continuous scale, its inherent power is greater than, for example, a noncontinuous dichotomous measure, such as the ACR20. This precision might not be as important in very large phase III trials, which tend to be highly powered because of their large sample sizes, but might be very useful in smaller proof-of-concept trials in which cost and time to complete the trials are critical.

There are limitations to the current study. The first is that the combined database used for the statistical analysis that led to the development of the ADAS-6 and ADAS-4 consisted of asthmatic patients recruited for 2 large, multicenter clinical trials. Their attributes might be different from those of subjects recruited in other trials, and therefore the ADAS-6 and ADAS-4 might not perform similarly in other asthmatic populations. However, both the ADAS-6 and ADAS-4 performed similarly in another independent population (the P04334 dataset),¹⁶ supporting the applicability of the ADAS-6 and ADAS-4 to different asthmatic populations. Similar to the case for the ACQ and AQLQ, we would expect that application of the ADAS/ADAS-4 to the pediatric age group would require further development based on parameters derived from pediatric asthma trials.

Another potential criticism is that the ADAS-6 is difficult to calculate and includes the need for diary data entries twice daily. Anticipating this difficulty, the ADAS-4 was developed; however, even this simplified version requires use of a calculator or computer to derive the score. For this reason, although these measures might not be routinely adopted in the clinic, they are relatively easy to obtain during a routine analysis of clinical trial data.

TABLE IV. Concurrent validity: Pearson correlation coefficients of outcome variables at week 12 and the investigator's and patient's global evaluation of change

Outcome variable	Investigator's global evaluation	95% CI	Patient's global evaluation	95% CI
ADAS-6	0.48	0.43 to 0.52	0.43	0.39 to 0.48
ADAS-4	0.46	0.42 to 0.50	0.42	0.38 to 0.46
FEV ₁ (L)	−0.26	−0.31 to −0.21	−0.17	−0.22 to −0.12
Rescue β -agonist use (puffs/d)	0.32	0.28 to 0.37	0.33	0.28 to 0.38
Nighttime awakenings (nights/wk)	0.32	0.28 to 0.37	0.31	0.26 to 0.36
AQLQ score	−0.39	−0.43 to −0.34	−0.40	−0.44 to −0.35
Daytime symptom score	0.34	0.29 to 0.39	0.32	0.28 to 0.37

Finally, it is anticipated that because of the unique mechanism of action of some drugs that primarily reduce the risk of asthma exacerbations,¹⁸⁻²⁰ the ADAS-6 and ADAS-4 might not be as sensitive to clinical changes because of use of these drugs compared with “broader-spectrum” drugs for asthma. Although the ADAS-6 and ADAS-4 were derived by using a DA that included asthma exacerbations and attacks,¹⁰ we excluded these end points from the MR model. The reason for their exclusion is that because of their infrequent occurrence, even in patients with uncontrolled asthma, the recall period for such variables would have been far longer than that of other variables in the composite score, potentially confounding the day-to-day changes in the outcome variables that are currently captured very well in the ADAS. For this reason, the ADAS-6 and ADAS-4, as well as other composite scores, are meant to complement, rather than replace, traditional exacerbation outcome variables in the assessment of asthma drugs.

The decision as to which of the 2 scores to use largely depends on the availability of once- or twice-daily diary data. Because the ADAS-6 contains 2 additional variables, it is not surprising that its discriminating ability exceeds that of the ADAS-4. Although the level of statistical significance for both scores was extremely high when applied to comparisons between treatment groups ($P < .0001$ in all cases), this was partly driven by the large samples sizes. We have found that by using smaller sample sizes, differences in treatment effects clearly favored the ADAS-6 over the ADAS-4 (data not shown). However, both composite measures performed far better than existing single-outcome measures (Table III).

In conclusion, we have developed the ADAS-6 and ADAS-4 as weighted composite measures of asthma disease activity. Both tools demonstrate multiple aspects of validity, and both are highly sensitive to change. We predict that they will be better able than existing outcome measures to detect small changes in the clinical status of asthmatic patients, which might translate to smaller and more efficient clinical trial designs. Future work will include additional validation of these measures in prospective randomized clinical trials.

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Clinical implications: Use of this novel, weighted, and highly responsive measure of asthma disease activity might better differentiate levels of disease burden and help identify populations of responders to asthma therapy.

REFERENCES

- 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;14:902-7.
- Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
- Cloutier MM, Schatz M, Castro M, Clark N, Kelly HW, Mangione-Smith R, et al. Asthma outcomes: composite scores of asthma control. *J Allergy Clin Immunol* 2012;129(suppl):S24-33.
- van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996;39:34-40.
- Zhang J, Yu C, Holgate ST, Reiss TF. Variability and lack of predictive ability of asthma end-points in clinical trials. *Eur Respir J* 2002;20:1102-9.
- Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008;372:1107-19.
- Lotvall J, Akdis CA, Bacharier LB, Björner L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-60.
- Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Wei LX, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med* 1999;130:487-95.
- Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. *Arch Intern Med* 1998;158:1213-20.
- Greenberg S, Liu N, Kaur A, Lakshminarayanan M, Zhou Y, Nelsen LM, et al. Airway obstruction liability helps distinguish levels of disease activity in asthma. *Respir Med* 2012;106:500-7.
- van der Heijde DM, 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;49:916-20.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2008.
- EPR. Expert panel report: guidelines for the diagnosis and management of asthma (EPR 3-2007). Bethesda: US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program; 2007. NIH publication no. 08-5846.
- Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
- King JY, Ferrara R, Tabibiazar R, Spin JM, Chen MM, Kuchinsky A, et al. Pathway analysis of coronary atherosclerosis. *Physiol Genomics* 2005;23:103-18.
- Nathan RA, Nolte H, Pearlman DS. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. *Allergy Asthma Proc* 2010;31:269-79.
- Fransen J, Creemers MC, van Riel PL. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology (Oxford)* 2004;43:1252-5.
- Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90.
- Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001;108:E36.
- Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-61.

TABLE E1. Efficacy outcome variables used in this study

Variable	Description or definition	Inclusion in MR model
AQLQ-Activity domain	Juniper Asthma Quality of Life Questionnaire–Activity Domain	+
AQLQ-Symptom domain	Juniper Asthma Quality of Life Questionnaire–Symptom domain	+
AQLQ-Emotions domain	Juniper Asthma Quality of Life Questionnaire–Emotions domain	+
AQLQ-Environment domain	Juniper Asthma Quality of Life Questionnaire–Environment domain	+
DSS-Asthma symptom component	Based on a 0- to 6-point scale, the average of answers to the questions: “How often did you experience asthma symptoms today?” and “How much did your asthma symptoms bother you today?”	
DSS-Activity component	Based on a 0- to 6-point scale, the average of answers to the questions: “How much activity could you do today?” and “How often did your asthma affect your activities today?”	
Nocturnal awakenings (nights/wk)	The number of nights/week (between consecutive visits) that a patient awakened with asthma was determined by dividing the number of nights a patient awakened with asthma (positive responses of once, more than once, and awake “all night”) by the total number of nights (all responses) and then multiplying by 7 (standardized to a 7-day period).	+
Nocturnal symptom score	The responses (no, once, more than once, and awake “all night”) were assigned numeric values (0, 1, 2, and 3, respectively). The average score for the visit was determined by averaging the daily scores over all days between consecutive visits.	+
Total daily β -agonist use	Number of puffs/day of rescue albuterol (salbutamol) use	+
Asthma-free day (%)	Any 1 day when all of the following criteria were met: no asthma attacks, no rescue medication (corticosteroids, cromolyn [oral, inhaled, and nebulized], epinephrine, nebulized salbutamol, and bronchodilators other than inhaled salbutamol), no nocturnal awakenings, and use of ≤ 2 puffs of β -agonist.	
Morning PEF (L/min)	PEF rate obtained on arising in the morning	+
FEV ₁ (L)	Forced expiratory volume in 1 second	+
Evening PEF (L/min)	PEF rate obtained just before bedtime	+
FEV ₁ (percent predicted)	Percent predicted forced expiratory volume in 1 second	+
Diurnal variability of PEF	Average over 3 weeks of daily determinations: $\frac{ AM - PM\ PEF }{Average\ of\ AM\ and\ PM\ PEF}$	+
Asthma attacks	Unscheduled asthma care visit in an office, emergency department, or hospital setting or systemic corticosteroid rescue for worsening asthma	
Corticosteroid rescue	Use of a corticosteroid (oral, intravenous, or intramuscular) to relieve an asthma attack	
Asthma exacerbations	Any of the following: decrease in morning PEF of $>20\%$ from baseline, morning PEF of <180 L/min, an increase from baseline in β -agonist use of $>70\%$ (and a minimum increase of ≥ 2 puffs), an increase of $>50\%$ from baseline in daytime symptom score, awake “all night” on the overnight diary, or the occurrence of an asthma attack	
Daily variability of activity component of the DSS	Average over 3 weeks of daily determinations of activity component of the DSS: $\frac{ DSS\ at\ day\ t - DSS\ at\ day\ (t-1) }{Average\ of\ DSS\ at\ day\ t\ and\ day\ (t-1)}$	
Daily variability of symptom component of the DSS	Average over 3 weeks of daily determinations of symptom component of the DSS: $\frac{ DSS\ at\ day\ t - DSS\ at\ day\ (t-1) }{Average\ of\ DSS\ at\ day\ t\ and\ day\ (t-1)}$	
Diurnal variability of β -agonist use	Average over 3 weeks of daily determinations: $\frac{ AM - PM\ rescue\ \beta - agonist\ use }{Average\ of\ AM\ and\ PM\ rescue\ \beta - agonist\ use}$	+

AM, Morning; PM, evening.

TABLE E2. Output of MR for ADAS-6

Step	Variable entered	Partial R^2 *	Model R^2 †	Regression coefficients‡	Standardized coefficients (β)§
1	Rescue β-agonist use	0.562	0.562	0.1118	0.297
2	FEV ₁ (% predicted)	0.170	0.732	−0.0236	−0.299
3	AQLQ-Symptom domain	0.074	0.807	−0.2602	−0.233
4	PEF diurnal variability	0.059	0.866	4.3633	0.241
5	Rescue β-agonist use diurnal variability	0.046	0.911	0.5765	0.268
6	Nocturnal awakenings	0.039	0.951	0.1226	0.253
7	FEV ₁ (L)	0.005	0.956		
8	AQLQ-Emotions domain	0.002	0.958		
9	Nocturnal asthma score	0.001	0.959		
10	AQLQ-Activity domain	0.001	0.960		
11	Morning PEF	<0.001	0.960		

*Partial R^2 values measure the marginal contribution of the variable entered at step k when the previous k-1 variables are already included in the model.

†The model R^2 value at step k is the total R^2 value with k variables included in the model.

‡Coefficients from the regression using the 6 measurements selected from the stepwise forward MR analysis.

§Regression coefficients were derived by using independent variables expressed in normalized units. This facilitates a direct comparison of regression coefficients for each independent variable, which simplifies estimating the extent to which each independent variable contributes to the model.

TABLE E3. Pearson correlations between individual components of the ADAS-6

	ADAS	Rescue β -agonist use	FEV ₁ (% predicted)	AQLQ-Symptom domain	PEF VarD	Rescue β -agonist use VarD	Nocturnal awakenings
ADAS	1.00	0.81	−0.60	−0.71	0.56	0.42	0.70
Rescue β -agonist use	0.81	1.00	−0.32	−0.57	0.31	0.21	0.64
FEV ₁ (% predicted)	−0.60	−0.32	1.00	0.27	−0.27	−0.09	−0.28
AQLQ-Symptom domain	−0.71	−0.57	0.27	1.00	−0.25	−0.11	−0.56
PEF VarD	0.56	0.31	−0.27	−0.25	1.00	0.15	0.26
Rescue β -agonist use VarD	0.42	0.21	−0.09	−0.11	0.15	1.00	−0.04
Nocturnal awakenings	0.70	0.64	−0.28	−0.56	0.26	−0.04	1.00

PEF VarD, Diurnal variability of PEF; Rescue β -agonist use VarD, Diurnal variability of rescue β -agonist use.

TABLE E4. Correlations between selected outcome variables and ADAS-6 values: cross-sectional and longitudinal validity

Outcome variable	ADAS-6 (week 12)*	ΔADAS-6 (change from baseline)†
FEV ₁ (L)	−0.44	−0.55
FEV ₁ (% predicted)	−0.60	−0.58
Morning PEF	−0.42	−0.49
Evening PEF	−0.29	−0.37
Rescue β-agonist use	0.81	0.72
Daytime symptom score	0.62	0.63
Nocturnal awakenings	0.70	0.63
Nocturnal asthma score	0.69	0.62
AQLQ-Symptoms domain	−0.71	−0.75
AQLQ-Activity domain	−0.52	−0.59
AQLQ-Emotions domain	−0.54	−0.57
AQLQ-Environment domain	−0.45	−0.47
PEF rate diurnal variability	0.56	0.47
Rescue β-agonist use diurnal variability	0.42	0.38
Asthma-free days	−0.73	—‡
Asthma exacerbations	0.32	—‡

*Correlations were determined between indicated variables and ADAS-6 values at week 12, when the primary outcome was measured. All correlations are significant ($P < .01$).

†Correlations were determined between the change from baseline in the indicated variables at week 12 and the change from baseline in the ADAS-6 value (ΔADAS) at week 12, when the primary outcome was measured. All correlations are significant ($P < .01$).

‡These variables were captured only during treatment but not at baseline, and therefore change from baseline could not be assessed.

TABLE E5. Pairwise comparisons of ADAS-6 values (change from baseline) by treatment groups

Pairwise comparisons	Difference	SE	Difference/SE	<i>P</i> value
Week 3				
Montelukast vs placebo	−0.55	0.06	−9.77	<.0001
Beclomethasone vs placebo	−0.87	0.07	−11.69	<.0001
Beclomethasone vs montelukast	−0.31	0.07	−4.54	<.0001
Week 12				
Montelukast vs placebo	−0.49	0.07	−7.06	<.0001
Beclomethasone vs placebo	−0.94	0.09	−10.35	<.0001
Beclomethasone vs montelukast	−0.45	0.08	−5.33	<.0001

TABLE E6. Correlations between selected outcome variables and ADAS-4 values: cross-sectional and longitudinal validity

Outcome variable (week 12 or change from baseline)*†	ADAS-4 (week 12)*	ΔADAS-4 (change from baseline)†
FEV ₁ (L)	−0.52	−0.38
FEV ₁ (% predicted)	−0.67	−0.68
Morning PEF	−0.43	−0.30
Evening PEF	−0.36	−0.27
Rescue β-agonist use	0.86	0.84
Daytime symptom score	0.61	0.41
Nocturnal awakenings	0.74	0.72
Nocturnal asthma score	0.76	0.46
AQLQ-Symptoms domain	−0.75	−0.81
AQLQ-Activity domain	−0.57	−0.38
AQLQ-Emotions domain	−0.58	−0.37
AQLQ-Environment domain	−0.49	−0.28
Asthma-free days‡	−0.70	—
Asthma exacerbations‡	0.33	—

*Correlations were determined between indicated variables and ADAS-6 values at week 12, when the primary outcome was measured. All correlations are significant ($P < .01$).

†Correlations were determined between the change from baseline in the indicated variables at week 12 and the change from baseline in the ADAS-6 value (ΔADAS) at week 12, when the primary outcome was measured. All correlations are significant ($P < .01$).

‡These variables were not captured at baseline, and therefore change from baseline could not be assessed.

TABLE E7. Pairwise comparisons of ADAS-4 values (change from baseline) by treatment groups

Pairwise comparisons	Difference	SE	Difference/SE	<i>P</i> value
Week 3				
Montelukast vs placebo	−0.55	0.05	−10.39	<.0001
Beclomethasone vs placebo	−0.81	0.07	−11.47	<.0001
Beclomethasone vs montelukast	−0.27	0.07	−4.03	<.0001
Week 12				
Montelukast vs placebo	−0.49	0.06	−7.74	<.0001
Beclomethasone vs placebo	−0.86	0.09	−10.13	<.0001
Beclomethasone vs montelukast	−0.37	0.08	−4.71	<.0001

TABLE E8. Pearson correlations between individual components of the ADAS-6 obtained from the P04334 database*

	ADAS	Rescue β -agonist use	FEV ₁ (% predicted)	AQLQ-Symptom domain	PEF VarD	Rescue β -agonist use VarD	Nocturnal awakenings
ADAS	1.00	0.70	−0.52	−0.62	0.56	0.48	0.65
Rescue β -agonist use	0.70	1.00	−0.12	−0.27	0.26	0.16	0.43
FEV ₁ (% predicted)	−0.52	−0.12	1.00	0.17	−0.19	−0.14	−0.13
AQLQ-Symptom domain	−0.62	−0.27	0.17	1.00	−0.19	−0.28	−0.42
PEF VarD	0.56	0.26	−0.19	−0.19	1.00	0.13	0.22
Rescue β -agonist use VarD	0.48	0.16	−0.14	−0.28	0.13	1.00	0.26
Nocturnal awakenings	0.65	0.43	−0.13	−0.42	0.22	0.26	1.00

PEF VarD, Diurnal variability of PEF; Rescue β -agonist use VarD, Diurnal variability of rescue β -agonist use.

*From Nathan et al.¹⁶ Correlations are based on data obtained at week 12.

TABLE E9. Correlations between selected outcome variables and the ADAS-6: a comparison of the cross-sectional and longitudinal validity of the ADAS-6 between the original database and the P04334 database

Outcome variable (primary end point or change from baseline)*†	Original database‡		P04334 database§	
	ADAS-6*	ΔADAS-6†	ADAS-6*	ΔADAS-6†
Rescue β-agonist use	0.78	0.74	0.70	0.61
FEV ₁ (% predicted)	−0.59	−0.61	−0.52	−0.46
AQLQ-Symptoms domain	−0.69	−0.78	−0.62	−0.57
Nocturnal awakenings	0.68	0.68	0.65	0.55
PEF rate diurnal variability	0.59	0.51	0.56	0.49
Rescue β-agonist use diurnal variability	0.29	0.36	0.48	0.49
AQLQ-Activity domain	−0.50	−0.37	−0.48	−0.37
AQLQ-Emotions domain	−0.54	−0.36	−0.51	−0.39
AQLQ-Environment domain	−0.43	−0.29	−0.41	−0.32
Daytime symptom score	0.60	0.39	0.42	0.39
Nocturnal asthma score	0.68	0.39	0.45	0.35
FEV ₁ (L)	−0.44	−0.33	−0.36	−0.43
Morning PEF rate	−0.41	−0.32	−0.36	−0.42
Evening PEF rate	−0.28	−0.23	−0.36	−0.35
Asthma-free days	−0.73			
Asthma exacerbations	0.32			
ACQ			0.72	0.61

*Correlations were determined between indicated variables and the ADAS-6 at the end of the active treatment periods. All correlations are significant ($P < .01$).

†Correlations were determined between the indicated variables at the end of the active treatment period expressed as change from baseline and the change from baseline in ADAS-6 values at the end of the active treatment period expressed as change from baseline (ΔADAS). All correlations are significant ($P < .01$).

‡From the original combined database.

§From Nathan et al.¹⁶ Correlations are based on data obtained at week 12.

||These variables were not captured at baseline, and therefore change from baseline could not be assessed. These variables were not available from the P04334 study.¹⁵

TABLE E10. Pairwise comparisons of ADAS-6 values (change from baseline) by treatment groups in the P04334 database*

Pairwise comparisons	Difference	SE	Difference/SE	P value
Week 4				
Mometasone/formoterol vs placebo	−0.72	0.09	−7.74	<.0001
Mometasone vs placebo	−0.44	0.09	−4.76	<.0001
Formoterol vs placebo	−0.18	0.09	−1.89	.0590
Mometasone/formoterol vs mometasone	−0.28	0.09	−3.09	.0021
Mometasone/formoterol vs formoterol	−0.55	0.09	−5.88	<.0001
Mometasone vs formoterol	−0.26	0.09	−2.86	.0043
Week 12				
Mometasone/formoterol vs placebo	−0.62	0.09	−6.54	<.0001
Mometasone vs placebo	−0.34	0.09	−3.67	<.0003
Formoterol vs placebo	−0.14	0.10	−1.39	.1637
Mometasone/formoterol vs mometasone	−0.27	0.09	−3.07	.0023
Mometasone/formoterol vs formoterol	−0.48	0.09	−5.06	<.0001
Mometasone vs formoterol	−0.21	0.09	−2.18	.0293
Week 26				
Mometasone/formoterol vs placebo	−0.45	0.11	−4.21	<.0001
Mometasone vs placebo	−0.21	0.11	−1.97	.0488
Formoterol vs placebo	0.06	0.11	0.55	.5858
Mometasone/formoterol vs mometasone	−0.24	0.10	−2.40	.0168
Mometasone/formoterol vs formoterol	−0.51	0.11	−4.80	<.0001
Mometasone vs formoterol	−0.27	0.11	−2.56	.0108

*From Nathan et al.¹⁶