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Validation of the maximum symptom day among children with asthma

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Conflict of Interest Statement

The authors declare no relevant conflicts of interest.

Keywords

Symptom day; MSD; validity; responsiveness; pediatric asthma; urban asthma

Acronyms and Abbreviations

ACT: Asthma Control Test
ANOVA: Analysis of variance
ATAQ-Control: Pediatric Asthma Therapy Assessment Questionnaire, Control Domain
C-ACT: Childhood Asthma Control Test
CASI: Composite Asthma Severity Index
FEV1: Forced expiratory volume in the first second
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LABA: Long-acting beta agonist
LRA: Leukotriene receptor antagonist
MSD: Maximum symptom day
pp: Percent predicted
SABA: Short-acting beta agonist

Capsule Summary

The maximum symptom day, a primary outcome of inner-city asthma research for almost two decades, is a valid measure that consistently relates to asthma control and is predictive of clinically relevant asthma endpoints.

To the Editor –

The maximum symptom day (MSD) is a composite measure of asthma symptomatology that integrates three questions related to daytime and nighttime asthma symptoms. It is the largest value of the number of days in the prior two weeks that a participant reports (1) cough, wheezing, or shortness of breath, (2) slowed activities due to these symptoms, or (3) nocturnal awakening due to these symptoms. Originally defined in the pivotal National Cooperative Inner City Asthma Study, the MSD has been used as a primary endpoint in numerous studies of inner-city asthma (some of which are collected under section C of the Supplemental Material). Surprisingly, since the first publication citing this outcome almost twenty years ago, it has never been validated(1).

The standardization of outcomes is important in conducting comparable and reproducible research. A necessary requirement is the use of outcomes that have been contextually validated. Because this has not performed for the MSD, it was classified as a “emerging” by the 2010 NIH/AHRQ Asthma Outcomes Workshop, where its core use in asthma research was not supported. Additional evidence reviews have criticized outcomes such as the MSD on this basis(2, 3).

Because a large body of research relies on the MSD, its validation is important, not only to support inferences in these past and future studies, but also to address the disparity that arises by the prioritization of, and reliance on, an unvalidated outcome for research within minority populations. The unintended consequence is that the strength of evidence from these studies, which are specifically aimed at understanding and intervening upon asthma within especially vulnerable populations, may be downgraded, stifling development and dissemination of effective interventions.

Our objective was to assess the reliability, validity, responsiveness, and predictive characteristics of the maximum symptom day. We analyzed the Mouse Allergen and Asthma Intervention Trial, a parallel-design randomized clinical trial testing a pest management intervention for allergic asthma(4). 350 participants recruited from Baltimore, Maryland and Boston, Massachusetts were followed every three months for one year (5 encounters). Outcomes recorded at each encounter included the MSD, days of rescue inhaler use in the prior two weeks, unanticipated asthma-related healthcare utilization and oral steroid use in the prior 3 months, and the Childhood Asthma Control Test (C-ACT, ages 5-11), Asthma Control Test (ACT, ages 12-17), and Pediatric Asthma Therapy Assessment Questionnaire-Control Subscale (ATAQ-Control)(5). Pre-bronchodilator spirometry

for FEV_{1pp} and FEV_1/FVC was also performed. Spirometry and ACT/C-ACT were only measured at baseline, 6, and 9 months.

Full details on methodology (section A) and participant characteristics (Table S1) are included in the Supplemental Material. Internal consistency reliability was assessed by Cronbach's α at all visits. These ranged from 0.74-0.82, indicating satisfactory reliability (Table S2). The MSD was equal to all three of its constituent symptom responses in 39.5% of instances and to two of the three responses in 19.1% of instances. Otherwise, the MSD was determined by the global symptoms response in 27.4%, slowed activity in 9.8%, and nocturnal waking in 4.2% of instances. Test-retest reliability was assessed by the intraclass correlation coefficient (ICC) among individuals who had stable control on the ACT/C-ACT. This was 0.57 between the baseline and 6-month visit ($n=111$) and 0.55 between the 6-month and 12-month visit ($n=120$), reflecting moderate test-retest reliability.

Criterion validity was demonstrated by identifying significant Spearman's correlations between MSD and ACT/C-ACT scores, ATAQ-Control scores, and days of rescue inhaler use at all visits (Table 1). Absolute mean correlation with ACT score was 0.71, C-ACT score was 0.52, ATAQ-Control score was 0.53, and rescue inhaler use was 0.62. Low correlations between MSD and spirometric parameters were only evident at 6- and 12-month clinic visits.

Discriminant validity was confirmed by comparing MSD distributions using Wilcoxon rank-sum tests between groups expected to have meaningful differences in asthma symptoms. At all visits, high MSD strongly identified participants who had poor control on ACT/C-ACT and ATAQ-Control scores, an asthma-related acute care visit, corticosteroid need, and rescue inhaler need (Table S3).

Responsiveness was confirmed by two approaches. First, clinical trajectories of asthma control were defined by ACT/C-ACT. Using ANOVA, we found that the MSD distributions differed among these strata; the MSD decreased in those with improved control and increased in those with worsened control (Table S4). Second, change in MSD was significantly correlated to changes in ATAQ-Control score and days of rescue inhaler use between all adjoining visits (Table S5). There were no consistent correlations between change in MSD and change in FEV_{1pp} and FEV_1/FVC .

Predictive validity was confirmed by demonstrating significant associations between MSD and risk of acute healthcare or corticosteroid need in the following 3 months. A one-day increase in MSD was associated with a 4% increase in risk of an acute care encounter (RR 1.04, 95% CI 1.02-1.06; $p<0.01$, Figure 1) and a 3% increase in risk

of oral steroid utilization (RR 1.03, 95% CI 1.01-1.05; $p=0.02$, Figure S1). There was no evidence of non-linearity in the association between MSD and either outcome.

Finally, we performed an exploratory analysis assessing the correlation of spirometry to ACT/C-ACT and ATAQ-Control scores. Similar to the MSD, we found no to low correlations with FEV_{1pp} and FEV_1/FVC (Table S6). No measures were consistently responsive to changes in spirometry (Table S7).

Our results support the maximum symptom day as a valid asthma outcome within minority populations. In this dual-center interventional trial of inner-city asthma, the MSD was a reliable and responsive measure that consistently correlated with markers of asthma control. Increases in MSD were associated with increased risk of subsequent asthma-related acute healthcare utilization and use of corticosteroids, without floor or ceiling effects.

Development of patient-reported outcomes that are contextually meaningful are valuable for understanding the impact of diseases specific to under-represented or disproportionately burdened populations. This is especially true of urban asthma, which is associated with more symptomatic, uncontrolled disease, driven by risk factors that are unique to these environments. However, if such outcomes are not validated, future public health impacts of studies that utilize them are fundamentally weakened. This study addresses this disparity which has existed for the MSD for nearly two decades.

The MSD is simple to collect, easy to understand, and intrinsically meaningful. Community asthma stakeholders endorse symptom outcomes like the MSD as more patient-centered and interpretable(6). The Composite Asthma Severity Index, the only other instrument developed in an inner-city population, includes symptoms with medication parameters, lung function, and exacerbations, necessarily diminishing the importance of symptoms within the overall instrument(7). Additionally, the MSD's moderate correlation to the other patient-reported outcomes in MAAIT suggests that it captures unique information not fully represented by these other measures. The MSD therefore represents a valuable endpoint to be independently determined, especially in trials that do not actively modify participant medications.

There are two opportunities for further study. First, the moderate test-retest reliability at six months may have been influenced by the long time interval, which we note is substantially longer than the four to twelve week spans reported for other asthma questionnaires. Second, provider assessment of asthma control was unavailable from this study, which would be an additionally informative criterion.

It is notable that the MSD, ACT/C-ACT, and ATAQ-Control were all poorly correlated to lung function. This finding is compatible with literature reporting inconsistent relationships between spirometry and symptoms in children, and it underscores its complementary value in pediatric asthma.

In conclusion, the maximum symptom day is a reliable, responsive, and valid measure of asthma symptomatology that is consistently correlated with other measures of asthma control among inner-city populations. Our results strengthen the level of evidence of studies that have utilized this outcome and support its continued use in observational and interventional trials of inner-city asthma.

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TABLE AND FIGURE LEGEND

Table 1. Internal consistency reliability and criterion validity

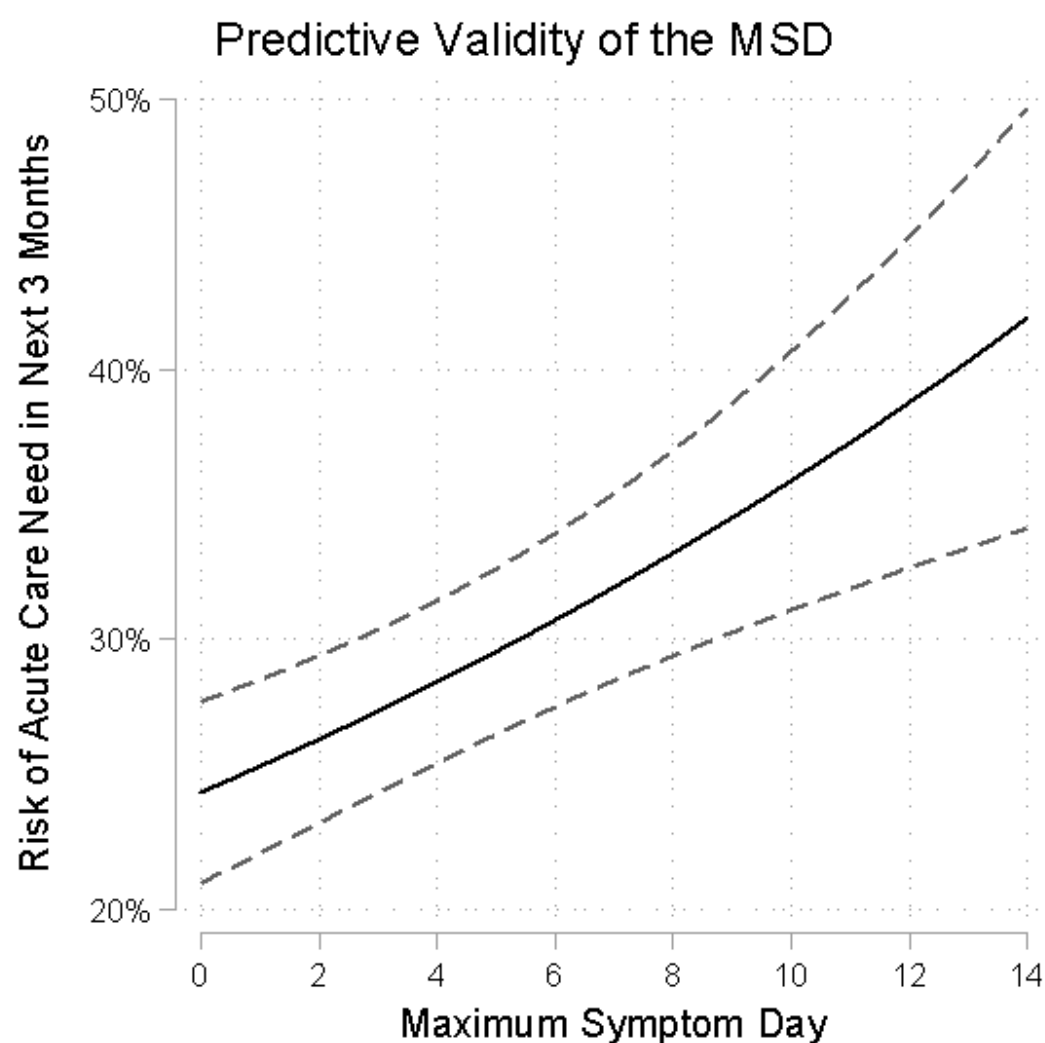
Encounter	Reliability Cronbach's α	Criterion Validity Spearman Correlation Between MSD and Criteria					
		C-ACT	ACT	ATAQ-Control	SABA Days	FEV1pp	FEV1/FVC
Baseline	0.74	-0.51	-0.68	0.35	0.50	-0.13 ^a	-0.11 ^a
3 Month	0.81			0.60	0.64		
6 Month	0.82	-0.57	-0.75	0.56	0.59	-0.20 ^b	-0.23
9 Month	0.74			0.60	0.74		
12 Month	0.82	-0.49	-0.69	0.56	0.64	-0.20 ^b	-0.30
Average	0.79	-0.52	-0.71	0.53	0.62	-0.18	-0.21

All cells are statistically significant at a p-value<0.001 unless noted otherwise.

^a not statistically significant (p-value>0.05)

^b p-value<0.05

Figure 1 Legend. Risk of acute care encounter in subsequent 3 months by maximum symptom days



Supplemental material

Validation of the maximum symptom day among children with asthma

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Section A. Methods

Study Design

The Mouse Allergen and Asthma Intervention Trial (MAAIT) is a parallel-design randomized clinical trial testing an integrated home pest management intervention versus education alone for reduction of asthma symptoms. Participants were aged 5-18, had persistent asthma, and were mouse-sensitized. Recruitment occurred from the metropolitan areas of Baltimore, Maryland and Boston, Massachusetts, between 2010 and 2014. Full details, including the study protocol, have been reported elsewhere(1). Participants were followed every three months for one year, with clinic visits occurring at baseline, 6, and 12 months, and telephone calls occurring at 3 and 9 months. For participants aged 5-11, the caregiver was the primary respondent; for those aged 12-17, the participant was the primary respondent.

Data Collection and Study Instruments

The maximum symptom day (MSD) was recorded at all encounters. This was the largest value of the number of days in the prior two weeks that the participant had (1) cough, wheezing, or shortness of breath; (2) slowed activities due to asthma symptoms; or (3) nocturnal awakening due to cough, wheezing, or shortness of breath(2). The MSD, therefore, ranged from 0-14, with higher numbers indicating worse asthma symptomatology.

The Asthma Control Test (ACT) and Childhood Asthma Control Test (C-ACT) was administered to participants aged 12-17 and 5-11, respectively, at each clinic visit. The ACT is participant-completed and ranges from 5-25, with higher numbers indicating better asthma control(3). The minimally important difference (MID) is 3 points(4). The C-ACT is completed by both the caregiver and participant and ranges from 0-27, with higher numbers indicating better asthma control(5). The minimally important difference is 2 points(6). In both instruments, a score ≤ 19 is reflective of poor control.

The control domain of the Pediatric Asthma Therapy Assessment Questionnaire (ATAQ-Control) was recorded at all encounters(7). The ATAQ-Control ranges from 0-7, with higher numbers indicating worse asthma control, and has been validated in those ages 5-17(8). A score ≥ 4 is reflective of poor control, based on analysis that suggested strong associations between this range and risk of asthma exacerbation. A minimally important difference has not been established for this instrument.

Spirometry was obtained at each clinic visit according to American Thoracic Society standards(9). Pre-bronchodilator FEV₁ and FVC were recorded, from which the ratio of FEV₁/FVC was calculated. Percent predicted values were derived from equations developed by Hankinson and colleagues(10). Consequently, only results for participants older than eight years of age are reported.

Finally, healthcare utilization and rescue inhaler use information were obtained at each encounter. Participants reported whether they had an acute care contact (an unanticipated physician visit, emergency department visit, or hospitalization) for asthma in the prior 3 months, need for an oral corticosteroid in the prior 3 months, and number of days they needed use of a rescue inhaler in the prior 2 weeks.

Analytic Approach

Internal consistency reliability was assessed by Cronbach's α , with satisfactory reliability defined at $\alpha > 0.7$ (11). Test-retest reliability was assessed by the intraclass correlation coefficient (ICC), calculated among those with stable asthma control, defined as individuals who had ACT or C-ACT scores that were within 1 MID of each other at adjoining visits. Two 6-month ICCs were determined, between baseline to 6 months and between 6 to 12 months. Moderate test-retest reliability was defined as an ICC between 0.5 to 0.75(12). We were unable to estimate 3-month ICCs by comparison against ATAQ-Control, as the MID for this instrument has not been determined.

65 Criterion validity was assessed by calculating Spearman correlation coefficients between MSD and ACT
66 score (age 12-17), C-ACT score (age 5-11), ATAQ-Control score, number of days in the last two weeks where a
67 rescue inhaler was needed, pre-bronchodilator FEV1 percent predicted, and pre-bronchodilator FEV₁/FVC ratio.

68 Discriminant validity was assessed by comparing MSD distributions between groups that would be
69 expected to have clinically meaningful differences in asthma symptoms. Participants were separated by (1) presence
70 of poor asthma control as assessed by ACT/C-ACT and (2) ATAQ-Control scores, by (3) having an acute care
71 contact or (4) needing to use oral corticosteroids in the prior 3 months, and by (5) needing to use a rescue inhaler in
72 the prior 2 weeks. MSD distributions between these groups were compared by non-parametric Wilcoxon rank-sum
73 tests.

74 Responsiveness was assessed by comparing change in MSD between encounters with change in other
75 measures of asthma control. Two approaches were used. First, participants were categorized as having improved,
76 stable, or worsened asthma control on the basis of ≥ 1 MID change in ACT/C-ACT score. Change in MSD between
77 these three trajectories were compared by ANOVA. Second, Spearman correlation coefficients were calculated
78 between change in MSD and (1) change in ATAQ-Control score, (2) change in number of days of rescue inhaler use
79 in the prior 2 weeks, (3) change in FEV1 percent predicted, and (4) change in FEV₁/FVC ratio.

80 Predictive validity was assessed by determining the association between MSD and risk of acute care
81 contact and oral corticosteroid use in the following 3 months, based on retrospective report at the subsequent visit.
82 The association was fit by generalized estimating equations to account for the longitudinal nature of the data(13).
83 MSD was parameterized as a continuous term after determining that there was no departure from linearity in its
84 association with the outcomes (no floor or ceiling effects within this cohort). Because the outcomes were common,
85 risk ratios rather than odds ratios were produced(14).

86 Analyses were performed in Stata 13 (StataCorp; College Station, Texas). A two-tailed p-value of 0.05 was
87 used to determine statistical significance. The study was approved by the institutional review boards of the Johns
88 Hopkins University School of Medicine, Boston Children's Hospital, and Columbia University School of Public
89 Health. Written informed consent was obtained from parents and assent was obtained from all participants.
90

Section B. Result Tables

Table S1. Participant characteristics, n=350

Demographic characteristics, no. (%)	
Age (years), mean±SD	9.8±3.2
Male gender	218 (62)
African-American race	278 (79)
Hispanic ethnicity	75 (21)
Annual household income	
<30,000	232 (66)
30,000-50,000	57 (16)
>50,000	31 (9)
Refused or unknown	30 (9)
Asthma medication characteristics, no. (%)	
Use of controller	309 (88)
Treatment step ^a	
SABA only	38 (12)
Low-dose ICS or LRA	61 (19)
Low-dose ICS + LABA, or medium-dose ICS	49 (15)
Medium-dose ICS + LABA	16 (5)
High-dose ICS ± LABA	162 (50)
Asthma characteristics, median (IQR)	
Maximum symptom day	3 (0-7)
Days of rescue inhaler use/2 weeks	3 (1-8)
Asthma control scales	
ACT score	19 (16-22)
C-ACT score	19 (16-21)
ATAQ-Control score	5 (3-6)
Event in prior 3 months, no. (%)	
Acute care need due to asthma	234 (67)
Use of oral corticosteroids	165 (47)
Pre-bronchodilator spirometry, mean±SD ^b	
FEV ₁ percent predicted	88±17
FVC percent predicted	98±15
FEV ₁ /FVC ratio	0.78±0.09

ACT=Asthma Control Test, ATAQ-Control=Pediatric Asthma Therapy Assessment Questionnaire-Control Domain, C-ACT=Childhood Asthma Control Test, ICS=Inhaled corticosteroid, LABA=Long-acting beta agonist, LRA=Leukotriene receptor antagonist, SABA=Short-acting beta agonist

^aBased on the Composite Asthma Severity Index, n=326

^breported for ages ≥8, n=305

Table S2. Internal consistency reliability and criterion validity

Encounter	Reliability Cronbach's α	Criterion Validity Spearman Correlation Between MSD and Criteria (n)					
		C-ACT	ACT	ATAQ- Control	SABA Days	FEV1pp	FEV1/F VC
Baseline	0.74	-0.51	-0.68	0.35	0.50	-0.13 ^a	-0.11 ^a
3 Month	0.81			0.60	0.64		
6 Month	0.82	-0.57	-0.75	0.56	0.59	-0.20 ^b	-0.23
9 Month	0.74			0.60	0.74		
12 Month	0.82	-0.49	-0.69	0.56	0.64	-0.20 ^b	-0.30
Average	0.79	-0.52	-0.71	0.53	0.62	-0.18	-0.21

All cells are statistically significant at a p-value<0.001 unless noted otherwise.

^a not statistically significant (p-value>0.05)

^b p-value<0.05

Table S3. Discriminant validity: Difference in MSD by presence or absence of clinical factors at all visits

Factor	Visit	Absence of Factor		Presence of Factor		p-value
		N	MSD, median (IQR)	N	MSD, median (IQR)	
Poor control on ACT/C-ACT	Baseline	147	1 (0-3)	199	4 (2-10)	<0.001
	6 Mo.	189	0 (0-2)	132	4 (2-7.5)	<0.001
	12 Mo.	193	0 (0-2)	113	4 (2-12)	<0.001
Poor control on ATAQ-Control	Baseline	123	1 (0-3)	277	4 (2-8)	<0.001
	3 Mo.	201	1 (0-3)	142	4 (3-8)	<0.001
	6 Mo.	203	0 (0-2)	121	4 (2-8)	<0.001
	9 Mo.	201	0 (0-3)	125	4 (3-10)	<0.001
	12 Mo.	196	0 (0-3)	110	4 (2-8)	<0.001
Need for acute care in prior 3 months	Baseline	116	2 (0-4)	234	3 (1-8)	<0.001
	3 Mo.	248	2 (0-4)	98	3 (1-7)	<0.001
	6 Mo.	223	1 (0-4)	101	3 (0-7)	<0.001
	9 Mo.	239	2 (0-3)	87	4 (2-14)	<0.001
	12 Mo.	224	1 (0-3)	84	4 (1-8.5)	<0.001
Need for oral steroids in prior 3 months	Baseline	185	2 (0-5)	165	3 (1-8)	0.005
	3 Mo.	264	2 (0-4)	82	3 (1-7)	<0.001
	6 Mo.	246	1 (0-4)	78	3.5 (1-7)	0.005
	9 Mo.	249	2 (0-3)	77	3 (2-7)	0.002
	12 Mo.	254	1 (0-4)	54	4 (1-10)	<0.001
Need for rescue inhaler in prior 2 weeks	Baseline	83	0 (0-3)	267	3 (1-7)	<0.001
	3 Mo.	104	0 (0-2)	240	3 (2-7)	<0.001
	6 Mo.	115	0 (0-2)	209	3 (1-6)	<0.001
	9 Mo.	107	0 (0-0)	77	3 (2-7)	<0.001
	12 Mo.	107	0 (0-1)	54	3 (1-7)	<0.001

Table S4. Comparison of change in MSD across change in asthma control as defined by ACT/C-ACT^a

Comparison	Worsened		No Change		Improved		p-value
	n	ΔMSD	n	ΔMSD	n	ΔMSD	
6 Mo. vs. Baseline	59	2.2±4.2	111	-0.9±3.9	142	-2.6±4.6	<0.001
12 Mo. vs. 6 Mo.	79	1.8±4.7	120	-0.1±3.4	89	-0.8±4.7	<0.001

^a Change in asthma control defined as at least 1 MID between visits, for ACT ≥3, for C-ACT ≥2

Table S5. Responsiveness

Spearman Correlation Between ΔMSD and ΔCriteria Measures				
Comparison	ΔATAQ-Control	ΔSABA Days	ΔFEV1pp	ΔFEV1/FVC
3 Mo. vs. Baseline	0.35	0.23		
6 Mo. vs. 3 Mo.	0.36	0.36		
6 Mo. vs. Baseline			-0.13 ^a	-0.16 ^b
9 Mo. vs. 6 Mo.	0.41	0.32		
12 Mo. vs. 9 Mo.	0.59	0.42		
12 Mo. vs. 6 Mo.			-0.06 ^a	-0.08 ^a

All cells are statistically significant at a p-value<0.001 unless noted otherwise.

^a Not statistically significant (p-value>0.05)^b p=0.03Table S6. Correlation between composite measures of asthma control and spirometry^a

Measure	Visit	FEV1pp	p-value	FEV1/FVC	p-value
ACT	Baseline	0.09	0.44	0.03	0.77
	6 Mo.	0.29	0.01	0.25	0.03
	12 Mo.	0.20	0.07	0.03	0.82
C-ACT	Baseline	0.10	0.26	0.16	0.08
	6 Mo.	0.06	0.55	0.22	0.03
	12 Mo.	0.19	0.06	0.44	<0.01
ATAQ-Control	Baseline	-0.11	0.12	-0.16	0.02
	6 Mo.	-0.09	0.25	-0.11	0.13
	12 Mo.	-0.18	0.02	-0.16	0.04
MSD	Baseline	-0.13	0.07	-0.11	0.12
	6 Mo.	-0.20	0.01	-0.23	<0.01
	12 Mo.	-0.20	0.01	-0.30	<0.01

^a Reported for ages ≥8, maximum symptom day included for comparison, bolded values are statistically significant at p<0.05Table S7. Correlation between change in composite measures of asthma control and change in spirometry^a

Measure	Comparison	ΔFEV1pp	p-value	ΔFEV1/FVC	p-value
ACT	6 Mo. vs. Baseline	0.26	0.03	0.24	0.051
	12 Mo. vs. 6 Mo.	0.10	0.40	0.05	0.70
C-ACT	6 Mo. vs. Baseline	0.12	0.24	0.10	0.30
	12 Mo. vs. 6 Mo.	0.04	0.73	0.09	0.43
ATAQ-Control	6 Mo. vs. Baseline	-0.01	0.89	-0.04	0.60
	12 Mo. vs. 6 Mo.	0.13	0.10	0.00	0.99
MSD	6 Mo. vs. Baseline	-0.13	0.09	-0.16	0.03
	12 Mo. vs. 6 Mo.	-0.06	0.46	-0.08	0.30

^a Maximum symptom day included for comparison, bolded values are statistically significant at p<0.05

124

125 Section C. Studies Utilizing the Maximum Symptom Day126 Included below is a non-comprehensive list of notable studies that have utilized the maximum symptom day as its
127 primary outcome, arranged in alphabetical order of first author.

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