

The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: Systematic review and meta-analysis

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Background: Currently, the cornerstone of asthma management is the achievement and maintenance of optimal asthma control, but the diagnostic performances of the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) have not been evaluated systematically.

Objective: We explored the diagnostic performances of and statistically compared the ACT and ACQ.

Methods: Studies that examined the accuracy of the ACT, ACQ, or both in the assessment of asthma control were found by searching PubMed, CENTRAL, Web of Science, Ovid, and Embase. Summary estimates of sensitivity, specificity, and diagnostic odds ratios for the different levels of asthma control were determined by using bivariate random-effects models and hierarchical summary receiver operating characteristic models. **Results:** Twenty-one studies with 11,141 subjects assessed with the ACT and 12,483 assessed with the ACQ were identified. The ACT had good diagnostic accuracy for assessment of controlled and not well-controlled asthma, and the ACQ (ACQ-7 and ACQ-6) had good diagnostic accuracy for assessment of not well-controlled asthma at prespecified cutoff points. The ACT and ACQ had significant differences in the assessment of controlled and not well-controlled asthma after adjusting for potential factors ($P = .001$ and $P = .015$). For assessment of uncontrolled asthma, the ACT had poor accuracy, with a hierarchical summary receiver operating characteristic area under the curve of 0.69, and the cutoff point for the ACQ has not been established.

Conclusion: The ACT is preferable to the ACQ in clinical practice, and the ACQ requires further cross-validation.

Moreover, neither the ACT nor the ACQ is useful for the assessment of uncontrolled asthma. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Global Initiative for Asthma, National Asthma Education and Prevention Program, Asthma Control Test, Asthma Control Questionnaire, diagnostic performance, meta-analysis

Asthma is a chronic inflammatory disorder of the airways that affects more than 300 million persons worldwide and causes substantial morbidity.¹ The prevalence of asthma and its personal and societal tolls continue to increase despite advances in the understanding of the pathophysiology and the availability of effective therapies. Because there is currently no cure for asthma, the cornerstone of asthma management is the achievement and maintenance of optimal asthma control.

Specific goals are the achievement of the best possible clinical control and reduction in the future risk of adverse outcomes.² Since the 2000s, the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP)³ have defined the term *control* as effective management of the clinical characteristics of the disease, including symptoms, nocturnal awakening, reliever use, activity limitation, and lung function. Poor asthma control can increase the expected future risks of asthma, including exacerbation, accelerated decrease in lung function, and side effects of treatment.¹ On the basis of this definition, GINA and NAEPP established the 3 levels of asthma control (controlled/well controlled, partially controlled/not well controlled, and uncontrolled/very poorly controlled).

Recently, several standardized self-administered questionnaires, such as the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ), have been developed. These questionnaires are simple and easily completed by patients and make it easy for clinical practitioners to assess how effectively asthma symptoms are controlled. The ACT contains 5 questions that are related to the frequency of both asthma symptoms and required rescue medication use during the previous 4 weeks. The scores in the ACT range from 5 (worse control) to 25 (total control).⁴ The ACQ assesses 7 items, which include asking patients to recall their experiences in the previous week and to respond to questions about nighttime waking, symptoms on waking, activity limitations, shortness of breath, wheezing, required use of short-acting β_2 -agonists for rescue, and FEV₁ percent predicted before bronchodilator on a 7-point scale.⁵ All of these items are equally weighted, and the ACQ score is the mean of the 7 items and ranges from 0 (totally controlled) to 6 (severely uncontrolled). Developmental studies have established the cutoff points for controlled asthma (ACT, ≥ 20 points; ACQ, ≤ 0.75 points), not

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Abbreviations used

ACQ:	Asthma Control Questionnaire
ACT:	Asthma Control Test
AUC:	Area under the curve
DOR:	Diagnostic odds ratio
GINA:	Global Initiative for Asthma
HSROC:	Hierarchical summary receiver operating characteristic
NAEPP:	National Asthma Education and Prevention Program
QUADAS-2:	Revised tool for the quality assessment of diagnostic accuracy studies

well-controlled asthma (ACT, ≤ 19 points; ACQ, ≥ 1.5 points), and uncontrolled asthma (ACT, ≤ 15 points).^{4,6,7} Furthermore, the 2 questionnaires have been validated,^{5,6} and the respective minimal clinically important differences of 3 for the ACT and 0.5 for the ACQ have been achieved.^{7,8} Lately, the ACT and ACQ, as 2 asthma control composite score instruments, have been designated core measures for National Institutes of Health–initiated clinical research in adults.⁹

The relationship of the questionnaires to the different degrees of asthma control has been studied by using GINA,¹ NAEPP,³ and other criteria.¹⁰ However, the relationship between current asthma control, as assessed with either the ACT or ACQ, and the future risk of asthma outcomes^{11,12} needs to be systematically characterized. In addition, the diagnostic performances of both questionnaires across different countries, care settings, and ethnicities need to be determined. Furthermore, clinicians urgently need to know which questionnaire is better for assessing asthma control in real-world settings.

METHODS

Search strategy and selection criteria

Electronic databases, including PubMed (1998 to December 2011), CENTRAL (Cochrane Controlled Trials Register, issue 1, 2012), Web of Science (1998 to December 2011), Ovid (1998 to December 2011), and Embase (1998 to December 2011), were searched for relevant articles. Details are provided in the Methods section in this article's Online Repository at www.jacionline.org.

Data extraction

The following details were extracted from each included article: authors, year of publication, study population, settings, race and sex of subjects, age of subjects, sample size, asthma definition, whether lung function was evaluated, asthma severity based on asthma guidelines, inclusion/exclusion criteria, reference standards, diagnostic cutoff points (whether cutoff points were prespecified), whether an interview for asthma control assessment tools was performed on site, real-world design, whether the studies were developmental or cross-validation studies, true- and false-positive results, false- and true-negative results, and methodological quality.

Two reviewers independently assessed the quality of each study and extracted data. Disagreements were resolved by consensus or by consulting a third reviewer (G.W.). If information was not reported adequately, details were requested from the authors. If the authors did not respond to the requests, the “unknown” items were treated as “unclear.” Each reviewer extracted the data to construct a 2×2 table indicating prespecified and nonprespecified cutoff points that were published in each study.

Quality assessment

The methodological quality of the studies was assessed by using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2).¹³

Details of the quality assessment are provided in the Methods section in this article's Online Repository.

Reference standards and prespecified cutoff points

The reference standards used in the developmental studies for the ACT and ACQ were those of the NAEPP and GINA guidelines, which have a high level of agreement ($\kappa > 0.82$).¹⁴ The characteristic domains of the NAEPP, GINA, Brazilian guidelines, ACT, and ACQ that were used in this study to assess asthma control levels are shown in Tables I and E1 (available in this article's Online Repository at www.jacionline.org). On the basis of the developmental studies,^{4,6,7} the prespecified cutoff points for controlled asthma (ACT, 20 points; ACQ, 0.75 points), not well-controlled asthma (ACT, 19 points; ACQ, 1.5 points), and uncontrolled asthma (ACT, 15 points) were established. The nonprespecified cutoff points for asthma control levels were defined as the optimal points at which the best performance was achieved in these studies that did not use the prespecified cutoff points before performing the trials. Therefore the included studies were divided into prespecified and nonprespecified studies.

Statistical analysis

The 2×2 tables were constructed to include true-positive, false-positive, false-negative, and true-negative results for both prespecified and nonprespecified cutoff points. In addition, the ACT or ACQ diagnostic performance data used to assess levels of asthma control were combined quantitatively across the included studies. A random-effects approach of a bivariate model that took into account heterogeneity beyond chance between the studies was used to calculate summary estimates of sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios (DORs).¹⁵⁻¹⁷ Furthermore, a hierarchical summary receiver operating characteristic (HSROC) curve of all the studies was created because this method is better for summarizing the results than a single jointed summary estimate of sensitivity and specificity.¹⁷ Furthermore, this method denoted whether a threshold effect was present in the nonprespecified studies.^{16,18} The HSROC area under the curve (AUC) was used to judge the degree of accuracy of the tests according to established guidelines (excellent, ≥ 0.97 ; very good, 0.93-0.96; good, 0.75-0.92; and poor, 0.50-0.75).¹⁹ Summary estimates were calculated when each group or subgroup included data from at least 4 diagnostic studies. In other cases the median and range (minimum and maximum) were used. The Q-points were detected by graphing the HSROC as a sensitivity versus (1-specificity) plot, where sensitivity equaled specificity. The z statistics of the 2 HSROCs were compared to detect a statistical difference in diagnostic performance between the prespecified and nonprespecified studies or the ACT and ACQ.²⁰ In addition, agreement between the index tests (ACT or ACQ) and the reference standards (GINA or NAEPP) was evaluated by using the κ coefficient. Methods used for the assessment of heterogeneity are provided in the Methods section in this article's Online Repository. Furthermore, a Deeks funnel plot was used to inspect publication bias.²¹

All statistical analyses were performed with Stata version 11.0 software with the module Midas (Stata Corp, College Station, Tex). All statistical tests were 2 sided, with P values of less than .05 denoting statistical significance.

RESULTS

Included studies

Our search strategy initially yielded 1607 citations (Fig 1). Of these, 21 eligible trials that used the ACT ($n = 12$), the ACQ ($n = 6$), or both ($n = 3$) to assess asthma control were included in our study.^{4,6,7,22-39} One was a poster abstract, and 2 were real-world studies.

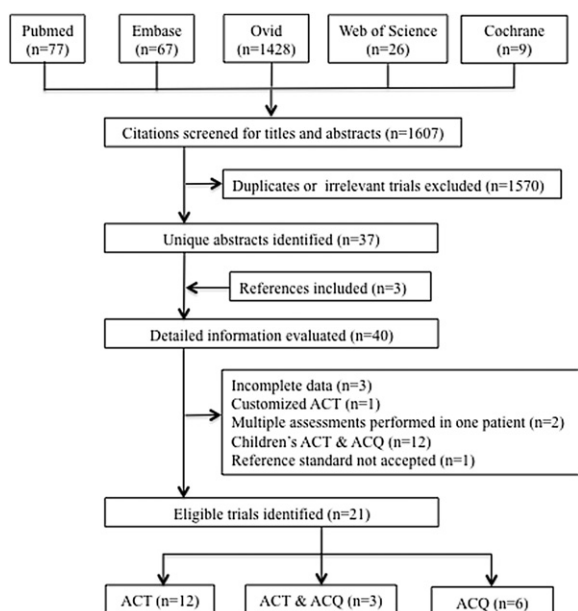
Study characteristics and quality of reporting

Table II and Tables E2 to E5 and Fig E1 (available in this article's Online Repository at www.jacionline.org) show the characteristics and quality of reporting of the included studies. The trials

TABLE I. Domains that are used for assessment of asthma control levels by distinct asthma control tools and guidelines

Domain	ACT	ACQ			NAEPP	Brazilian guideline	GINA
		ACQ-7	ACQ-6	ACQ-5			
Daytime symptoms	X	X	X	X	X	X	X
Nighttime symptoms	X	X	X	X	X	X	X
Activity limitation	X	X	X	X	X	X	X
ED visits or hospitalizations					X		
Exacerbations						X	X
SABA use	X	X	X		X	X	X
Patient self-assessment	X						
FEV ₁ or PEF percent predicted		X			X	X	X

ED, Emergency department; PEF, peak expiratory flow; SABA, short-acting β_2 -agonist.

**FIG 1.** Flowchart of study identification, inclusion, and exclusion.

took place in the United States, the Asia-Pacific region, and Europe over the past decade. There were 11,141 subjects included in ACT assessments and 12,483 in ACQ assessments. The average sample size was 742 (range, 100-3852) for the ACT and 1387 (range, 108-8188) for the ACQ. The subjects from the included studies varied from the primary to tertiary care settings, and 13 studies described asthma severity. Details about the quality of reporting are provided in the Results section in this article's Online Repository at www.jacionline.org.

Reference standards, data synthesis, and meta-analysis

Data about reference standards, thresholds, and prevalence of asthma control are provided in the Results section in this article's Online Repository.

The meta-analyses and comparative analyses in the prespecified and nonprespecified studies were based on the different instruments (ACT and ACQ) and the levels of asthma control (Table III and Table E6 [available in this article's Online Repository at www.jacionline.org]). The summary sensitivity and specificity values at levels of controlled, not well-controlled, and uncontrolled asthma in the prespecified studies for the ACT

were as follows: 0.77 (95% CI, 0.68-0.84) and 0.84 (95% CI, 0.74-0.91), 0.75 (95% CI, 0.63-0.83) and 0.82 (95% CI, 0.76-0.87), and 0.49 (95% CI, 0.42-0.56) and 0.92 (95% CI, 0.86-0.96), respectively. The summary sensitivity and specificity values at the not well-controlled asthma level for the ACQ-7 and ACQ-6 were 0.74 (95% CI, 0.61-0.83) and 0.81 (95% CI, 0.72-0.88) and 0.65 (95% CI, 0.52-0.76) and 0.90 (95% CI, 0.86-0.92), respectively. The other summary sensitivity and specificity values for the ACQ were not pooled for less than 4 studies. The ACQ had an increased sensitivity for assessing controlled asthma, and there was also an increased specificity when ACQ-7 was excluded from assessing not well-controlled asthma. On the whole, the 2 arms for the ACT were balanced across the 3 levels of asthma control (Fig 2). In addition, the positive and negative likelihood ratios were generally all in the range of a small-to-moderate effect, whereas the negative likelihood ratios of the ACQ for not well-controlled asthma and of the ACT for uncontrolled asthma would have a "tiny" effect for influencing posttest probability. In the nonprespecified studies the sensitivity and specificity values for the ACT and ACQ were significantly improved for selection of optimal cutoff points when compared with the prespecified studies (see Table E6).

HSROC curves with AUCs and Q* values, defined by the point where sensitivity equals specificity, and results from the bivariate models for the 2 different methods of assessing levels of asthma control are shown in Fig 3, Table III, and Table E6. In the prespecified studies summary DORs were 17.78 (95% CI, 11.07-28.56), 13.51 (95% CI, 8.49-21.48), and 11.33 (95% CI, 6.50-19.73), and HSROC AUC values were 0.87 ± 0.02 , 0.86 ± 0.02 , and 0.69 ± 0.09 for ACT-mediated assessments of controlled, not well-controlled, and uncontrolled asthma, respectively. For ACQ-7 and ACQ-6 assessment of not well-controlled asthma, the DORs were 12.41 (95% CI, 8.14-18.92) and 15.78 (95% CI, 10.71-23.25), and the HSROC AUC values were 0.85 ± 0.03 and 0.90 ± 0.03 , respectively. When the performance of HSROC AUC was compared between the prespecified and nonprespecified studies, we did not find any statistical differences for ACT assessments of controlled, not well-controlled, and uncontrolled asthma ($P = .448$, $P = .421$, and $P = .082$, respectively). Furthermore, we found no statistically significant differences between the ACT and ACQ (ACQ-7 and ACQ-6) for assessments of not well-controlled asthma ($P = .359$ and $P = .102$, respectively). In addition, Fig 3 shows the HSROC curves and bivariate analyses. As Fig 3 indicates, there were evident overlaps in HSROC curves and in the 95% CIs of bivariate analyses between the ACT and ACQ (ACQ-7 and ACQ-6) in assessment of not well-controlled asthma. We did not perform the head-to-head

TABLE II. Characteristics of the included studies involving the ACT and ACQ that were included in our analyses

Tools	Reference	Setting	No. (% female)
ACT	Nathan et al, 2004 ⁴	Tertiary hospital, United States	471 (NA)
	Schatz et al, 2006 ⁶	Primary care setting, United States	313 (NA)
	Vega et al, 2007 ²²	Multidimensional hospitals, Spain	607 (61.4)
	Zhou et al, 2009 ²⁴	Primary hospital, China	403 (NA)
	Ko et al, 2009 ²⁵	Tertiary hospital, Hong Kong	383 (68.1)
	Thomas et al, 2009 ²⁶	Primary care settings in Europe and the United States	2949 (56.2)
	Roxo et al, 2010 ²⁷	Tertiary hospitals, Brazil	291 (74.2)
	Alvarez-Gutierrez, 2010 ²⁸	Primary care settings, Spain	441 (65.8)
	Grammatopoulou et al, 2011 ²⁹	Tertiary hospital, Greece	100 (79)
	Lai et al, 2011 ³⁰	Tertiary hospitals, Asia	4805 (57.5)
	Ko et al, 2012 ³¹	Tertiary hospital, Hong Kong	379 (68.3)
	Nguyen et al, 2011 ³²	Tertiary hospital, Vietnam	323 (NA)
ACQ	Juniper et al, 2006 ⁷	International primary care settings	1323 (NA)
	Van den Nieuwenhof, 2006 ³³	Primary hospitals, The Netherlands	108 (71.0)
	Leite et al, 2008 ³⁴	Tertiary hospitals, Brazil	278 (75.2)
	Olaguibel et al, 2010 ³⁵	Primary and secondary hospitals, Spain	1363 (60.3)
	Sastre et al, 2010 ³⁶	Primary care settings, Spain	607 (61.4)
	O'Byrne et al, 2010 ²³	International tertiary hospitals	8188 (59.4)
Both ACT and ACQ	Wallenstein et al, 2007 ³⁷	NA, United States	313 (NA)
	Zhou et al, 2007 ³⁸	Tertiary hospitals, China	305 (NA)
	Korn et al, 2011 ³⁹	Tertiary hospitals, Germany	150 (52.0)

ATS, American Thoracic Society; I, intermittent; Mi, mild; Mo, moderate; NA, not applicable; PEF, peak expiratory flow; S, severe.

comparison between the ACT and ACQ because of the limited number of studies ($n = 3$). In our meta-analysis a nonpublication bias was detected by using a Deeks funnel plot asymmetry test in the ACT and ACQ for assessments of different levels of asthma control (data not shown, all $P > .05$).

Subgroup and meta-regression analyses

We found most of the summary estimates had substantial heterogeneity across studies, and therefore it was necessary to perform subgroup and meta-regression analyses (Table IV). Subgroup and meta-regression analyses data (see Tables E7 and E8 in this article's Online Repository at www.jacionline.org) are provided in the Results section in this article's Online Repository.

DISCUSSION

To our knowledge, this is the first study to systematically explore the diagnostic performances of the ACT and ACQ in assessments of levels of asthma control and to provide comparative analyses. Our study suggests that the ACT provided a good diagnostic accuracy for assessments of controlled and not well-controlled asthma and that the ACQ (ACQ-7 and ACQ-6) accurately assessed not well-controlled asthma at prespecified cutoff points. However, the sensitivity and specificity of the ACQ were in a distinct imbalance. Neither the ACT nor the ACQ were useful for assessing uncontrolled asthma because the ACT had a poor accuracy (the HSROC AUC value was 0.69 at the prespecified cutoff point), and the cutoff point for the ACQ has not yet been established. Furthermore, we found statistical differences in the performance of the ACT and ACQ in defining both controlled and not well-controlled asthma after adjusting for potential factors. In addition, we found that some potential factors, such as age, whether lung function was evaluated, asthma

severity, whether an on-site interview was performed, real-world design, risk of bias, and whether the study was developmental or cross-validation, could influence the diagnostic accuracy.

Clinical guidelines are currently based on the scientific evidence of therapeutic interventions. All reference standards used in the present study, such as the NAEPP, GINA, and other local GINA-based guidelines, are generally accepted, and a high level of agreement has previously been achieved when these guidelines are compared. Although our study suggested that DORs calculated with the GINA guidelines are twice what were seen with the NAEPP guidelines in the subgroup analyses, our meta-regression did not show any statistical differences between the guidelines when controlled and uncontrolled asthma ($P = .947$ and $P = .693$, respectively) were assessed. The only difference was seen when not well-controlled asthma ($P = .019$) was assessed. Furthermore, there were no significant differences in HSROC values between the NAEPP and GINA guidelines when the ACT was used to assess not well-controlled asthma ($z = 0.647$, $P = .261$). These comparative results could result from a slight difference in domains between the NAEPP and GINA guidelines (Table I).

The ACT and ACQ are multidimensional, standardized, and validated and the most widely used instruments for assessing clinical control of asthma that score the goals of treatment as continuous variables and provide numeric values to distinguish different levels of control. For the ACT, 5 items were selected from an initial panel of 22 proposed by a group that consisted of 4 primary care physicians and 7 asthma specialists in America.⁴ For the ACQ, the top 5 items were selected from a total of 10 items linked to asthma control that were originally proposed by 100 leaders in the field of asthma research.⁵ The ACT is an easy-to-use questionnaire that has been translated into more than 80 languages, and the ACQ is the most widely used numeric composite control measure in clinical trials.² Both instruments have some

TABLE II. (Continued)

Age (y)	Asthma definition	Lung function	Asthma severity (no.)	Estimates of optimal cutoffs
		FEV ₁ /PEF % predicted	I/Mi/Mo/S	
45.2 ± 18.5	Physician's diagnosis	84.9 (30-140)/NA	87/192/113/48	Area under ROC curve
35.3 ± 15.3		89.0 ± 20.7/NA	83/140/64/22	Area under ROC curve
45.6 ± 17.1	Physician's diagnosis	82.1 ± 20.8/80.6 ± 26.6	0/204/280/123	Area under ROC curve
44.0 ± 13.7	Objective lung function	69.7 ± 19.3/NA	100/79/111/113	Youden index
46.1 ± 13.4	Objective lung function	84.7 ± 20.8/NA	NA	Area under ROC curve
42 ± 17	Physician's diagnosis	NA/NA	NA	Area under ROC curve
45 (32-56)	Physician's diagnosis	NA/NA	80/41/43/126	Correct classification
39 ± 17	GINA	95.1 ± 20.3/NA	45/153/204/39	Youden index
49.9 ± 16.8	GINA	NA/NA	0/58/32/10	Nearest point to upper left corner
>12	Physician's diagnosis	NA/NA	NA	Area under ROC curve
46.1 ± 13.2	Objective lung function	85.2 ± 20.5/81.4 ± 10.8	NA	Area under ROC curve
36 (12-80)	GINA	NA/NA	71/82/90/80	Area under ROC curve
12-80	Objective lung function	NA	NA	NA
34.9 ± 7.5	Physician's diagnosis	NA	NA	NA
46 (17-81)	Physician's diagnosis	65.5 (22-125)/NA	77/39/40/122	NA
38 ± 14	GINA	NA	NA	NA
45.6 ± 17.1	GINA	82.1 ± 20.8/NA	0/235/246/126	Area under ROC curve
40 (11-89)	ATS/objective lung function	72.0 (29-222)	NA	Prespecified
35 ± 15	Physician's diagnosis	NA	83/133/62/23	Area under ROC curve
44.7 ± 14.2	Objective lung function	73.1 ± 24.2/NA	73/51/83/98	Youden index
46	Physician's diagnosis	NA	21/25/31/73	Prespecified

similar items, such as nocturnal awakening, activation limitations, shortness of breath, and short-acting β_2 -agonist use, but they have different durations of scoring periods and scoring systems.

To determine summary performances of asthma control tools and generalization in clinical practice, we divided the included trials into the prespecified and nonprespecified studies, in which the latter studies can lead to an overestimation of test performance. Although cross-validation is widely recommended for prognostic models, investigators rarely consider what proportion of patients should be in the training (developmental) and test (cross-validation) sets.⁴⁰ It is evident that the proportions of validation for the ACQ are very low when compared with the proportions for the ACT, which would overestimate the performance of the ACQ⁴⁰ and weaken generalization for clinical practice. Intriguingly, if the developmental or cross-validation sets were not included as a potential factor in the meta-regression analyses, we did not find any statistical differences in the diagnostic accuracy between the ACT and ACQ for the assessment of controlled and not well-controlled asthma ($P = .962$ and $P = .119$, respectively). In the subgroup analyses there was an increased trend of DORs in the Asian, elderly, tertiary setting, GINA-defined, and moderate-to-severe asthmatic patients when assessed by using the ACT or ACQ. According to our results, the ACQ-7 had the best DORs but an apparently lower specificity among the 3 versions of the ACQ. However, the evaluation of lung function might be important for assessing asthma control. It was interesting that ACT studies that evaluated lung function had decreased DORs when compared with those that did not. One possible explanation for this finding is that NAEPP and GINA guidelines should be changed to exclude lung function evaluation items. Making this change could decrease the DORs.

Although both the ACT and ACQ had a good diagnostic performance in assessing controlled and not well-controlled

asthma, their applicability differs both in clinical research and clinical practice. The ACQ was developed in 1999,⁵ but the prespecified cutoff points were not established until 2006. In a 2006 ACQ developmental study,⁷ cutoff points were determined to differentiate between controlled and not well-controlled asthma and to provide low risks of missing not well-controlled asthma and including controlled asthma. Furthermore, it is difficult to identify the asthma control levels in patients with an ACQ score of between 0.75 and 1.5 points.⁷ Although the 1.0-point level was the cutoff between controlled and not well-controlled asthma in the 2006 developmental study,⁷ this value has not been validated and is therefore not the optimal cutoff point. Therefore it is more suitable for the ACQ to be used in clinical trials. The ACT was specifically designed for use in clinical practice. First, the ACT provides a more simple assessment of control than the ACQ by not requiring lung function evaluation. Therefore it is more useful for clinicians who are seeing a high volume of patients within a limited amount of time in primary settings and also in rural clinics in developing countries, such as China and India. Second, the ACT is a useful tool that allows general practitioners to adjust (step-up or step-down) asthma treatment regimens based on prespecified cutoff points. Third, the ACT is suitable for periodic monitoring of patients with asthma because it can be administered by mail,⁴¹ in pharmacies,⁴² over the Internet,⁴³ and by speech-recognition telephone calls.⁴⁴ Furthermore, both the ACT and the ACQ would be the tools to select subjects with controlled asthma or not well-controlled asthma for special trials. However, clinicians and investigators should understand that the ACT performed poorly when attempting to define uncontrolled asthma. Furthermore, the ACT cannot be used for short-term (<4 weeks) clinical studies. In addition, if the ACT or ACQ were selected as the primary outcomes in clinical research, our meta-regression and

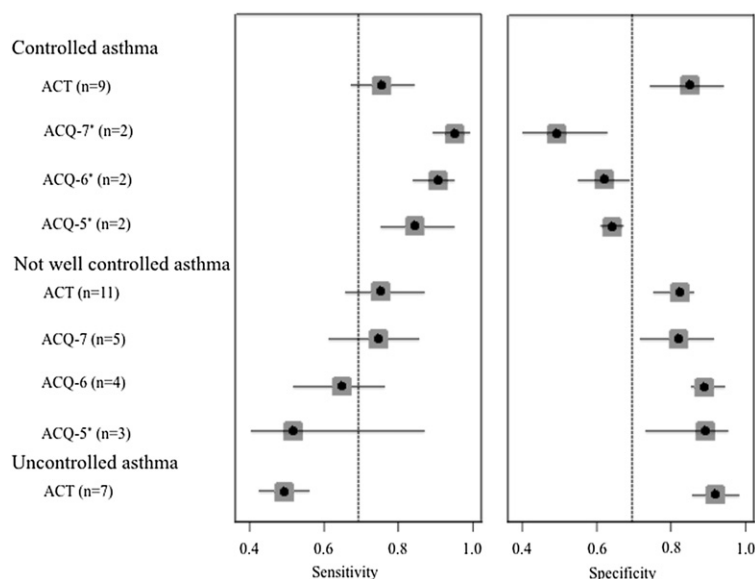
TABLE III. Diagnostic performances of the ACT and ACQ in assessing levels of asthma control in prespecified studies

Level of asthma control	Tool	No.	Sensitivity	Specificity	Positive LR	Negative LR	DOR	AUC
Controlled	ACT	9	0.77 (0.68-0.84)*	0.84 (0.74-0.91)*	4.82 (3.06-7.60)*	0.27 (0.20-0.37)*	17.78 (11.07-28.56)*	0.8707 ± 0.0203
	ACQ							
	ACQ-7	2	0.95 (0.90-0.99)	0.50 (0.36-0.63)	1.98 (1.54-2.42)	0.10 (0.03-0.16)	31.97 (14.99-48.94)	NA
	ACQ-6	2	0.91 (0.85-0.96)	0.62 (0.54-0.69)	2.43 (2.07-2.79)	0.14 (0.07-0.21)	20.70 (13.13-28.27)	NA
Not well controlled	ACQ-5	3	0.86 (0.76-0.94)	0.64 (0.45-0.65)	2.17 (1.71-2.39)	0.22 (0.14-0.36)	10.98 (5.97-12.22)	NA
	ACT	11	0.75 (0.63-0.83)*	0.82 (0.76-0.87)*	4.15 (3.18-5.42)*	0.31 (0.21-0.44)*	13.51 (8.49-21.48)*	0.8636 ± 0.0212
	ACQ							
	ACQ-7	5	0.74 (0.61-0.83)*	0.81 (0.72-0.88)*	4.00 (2.85-5.60)*	0.32 (0.22-0.47)*	12.41 (8.14-18.92)*	0.8510 ± 0.0278
Uncontrolled	ACQ-6	4	0.65 (0.52-0.76)*	0.90 (0.86-0.92)	6.21 (4.96-7.79)	0.39 (0.29-0.54)*	15.78 (10.71-23.25)	0.8991 ± 0.0258
	ACQ-5	3	0.52 (0.35-0.84)	0.89 (0.73-0.95)	4.65 (3.09-6.40)	0.55 (0.22-0.69)	9.33 (8.53-13.97)	NA
	ACT	7	0.49 (0.42-0.56)*	0.92 (0.86-0.96)*	6.22 (3.69-10.47)*	0.55 (0.48-0.62)*	11.33 (6.50-19.73)*	0.6925 ± 0.0867

Pooled estimates are presented as medians (minimums-maximums) if the number of studies was less than 4.

LR, Likelihood ratio; NA, not available.

*Statistical heterogeneity was found.

**FIG 2.** Forest plots of pooled sensitivity and specificity of the ACT and ACQ in prespecified studies. *Median (minimum-maximum) for less than 4 studies.

subgroup analyses would have provided much more information about selection bias, which could have improved the quality of the studies.

Systematic reviews of diagnostic accuracy studies are often characterized by markedly heterogeneous results originating from differences in the design and conduct of the included studies.¹³ Careful assessment of the quality of the included studies is therefore essential. In this study we used QUADAS-2, an updated and revised tool for the quality assessment of diagnostic accuracy studies.¹² In the meta-regression analyses we found evidence that a risk of bias in the design quality of the included studies could contribute to heterogeneity in the accurate performance of the ACT and ACQ-mediated assessments of uncontrolled asthma.

The comparative diagnostic performances of the ACT and ACQ, before adjusting for potential factors, were also visualized with HSROC curves and bivariate analyses (Fig 3). First, there was a cross of HSROC curves between uses of the ACT

and ACQ (ACQ-7 and ACQ-6) for assessment of not well-controlled asthma. Second, we found that there were considerable overlaps in the 95% CIs of summary sensitivity and specificity between uses of ACT and ACQ (ACQ-7 and ACQ-6) for assessments of not well-controlled asthma. However, the 95% CIs of the ACT were much narrower than those of the ACQ (ACQ-7 and ACQ-6), which indicated that the estimation precision for the ACT was much greater than for the ACQ (ACQ-7 and ACQ-6).

Our study has some limitations. First, no clear definitions of asthma control have been provided, and neither the NAEPP nor GINA guidelines are considered reference gold standards for the assessment of asthma control. Second, the diagnostic accuracies between some subgroups were not statistically compared because of the limited number of studies. This was especially true for studies that used the ACQ. Third, the differences in the diagnostic accuracies of the ACT and ACQ mainly originated from indirect comparisons rather than head-to-head comparisons. Fourth, the

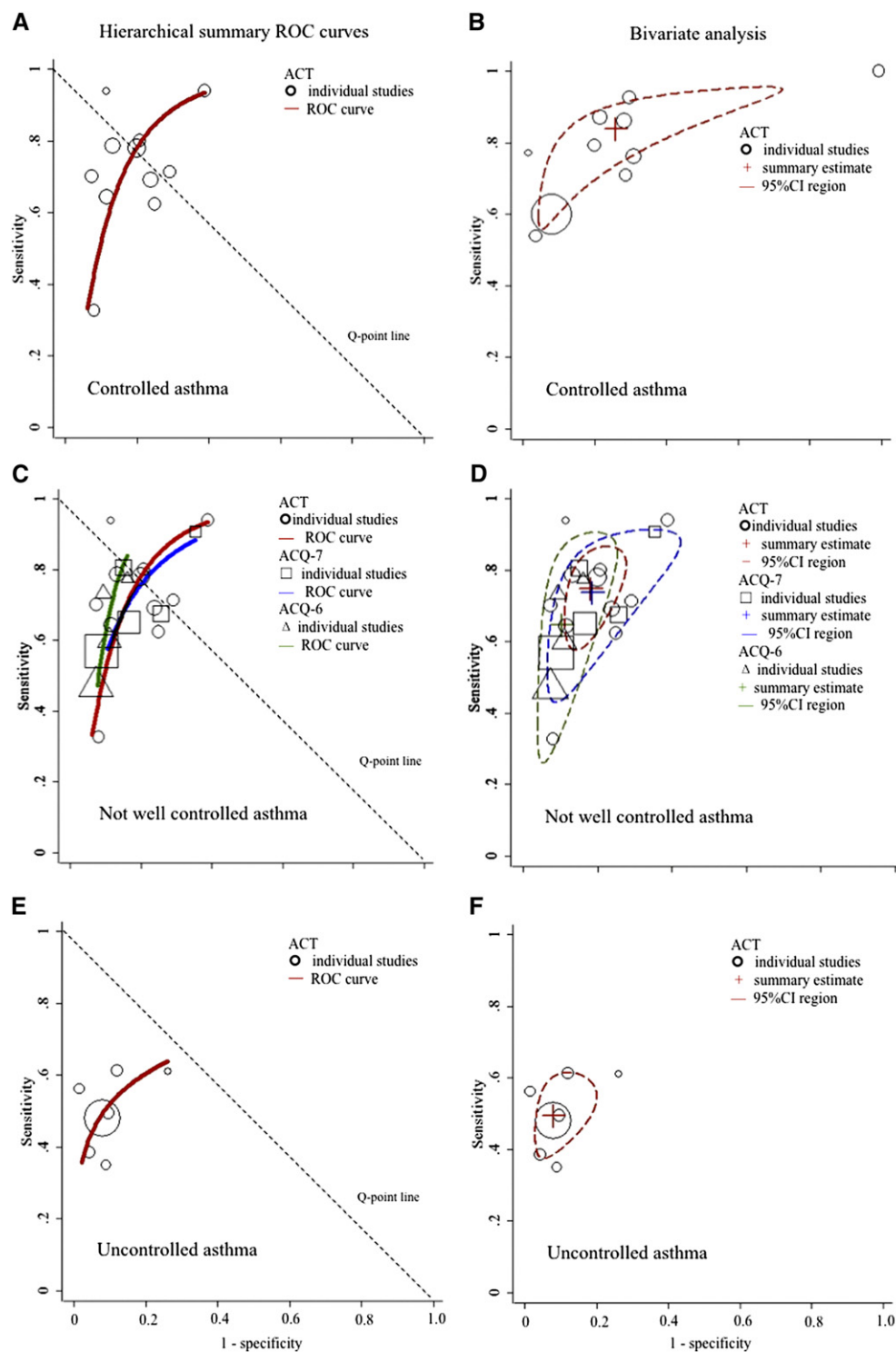


FIG 3. HSROC curves and results of bivariate analyses for tools with 4 or more studies. **A, C, and E,** HSROC curves. **B, D, and F,** Bivariate models. The cross in the bivariate analysis indicates the summary value of sensitivity and 1-specificity, and the ellipse reflects the 95% confidence region around the summary value.

sensitivity and specificity can be overestimated in studies at a high risk of bias in some quality of design domains when compared with real-world settings. Fifth, there was some obvious heterogeneity among included studies that affected our meta-analysis, although meta-regression and subgroup analysis were undertaken in this study. In addition, we did not further explore the

relationship between the accuracy of the ACT and the ACQ with future risk because current asthma control and future risk together represent overall asthma control.

In conclusion, our analyses suggest that the ACT and ACQ (ACQ-7 and ACQ-6) performed well when used to assess controlled and not well-controlled asthma at the prespecified

TABLE IV. Weighted meta-regression analyses for potential sources of heterogeneity

Level of asthma control	Covariates	Coefficient	RDOR (95% CI)	P value
Controlled	Cte	−0.25		.779
	S	−0.30		.097
	Settings	−0.28	0.75 (0.47-1.20)	.214
	Race	−0.87	0.42 (0.14-1.25)	.110
	Age	0.81	2.25 (1.08-4.67)	.033
	Asthma severity	0.99	2.68 (1.39-5.16)	.006
	Whether lung function was evaluated	−1.27	0.28 (0.13-0.61)	.004
	Risk of bias	−0.56	0.57 (0.05-6.39)	.615
	Reference standard	0.15	1.16 (0.01-177.28)	.947
	Prespecified or not	−0.21	0.81 (0.51-1.27)	.319
	Inclusion/exclusion criteria	1.41	4.10 (1.71-9.80)	.004
	Asthma definition	−1.04	0.36 (0.06-2.11)	.228
	Real-world design	2.03	7.58 (1.86-30.78)	.008
	On-site interview	2.12	8.29 (2.51-27.34)	.002
	ACT or ACQ	3.00	20.14 (4.02-100.95)	.001
Not well controlled	Developmental or cross-validation	1.42	4.12 (1.64-10.36)	.005
	Cte	1.92		<.001
	S	−0.04		.405
	Settings	−0.38	0.68 (0.55-0.84)	.001
	Race	−0.04	0.96 (0.68-1.35)	.810
	Age	0.73	2.08 (1.33-3.25)	.003
	Asthma severity	0.31	1.36 (1.12-1.66)	.004
	Whether lung function was evaluated	−1.96	0.14 (0.08-0.26)	<.001
	Risk of bias	0.09	1.10 (0.95-1.26)	.184
	Reference standard	0.44	1.55 (1.08-2.22)	.019
	Prespecified or not	0.13	1.14 (0.90-1.43)	.265
	Inclusion/exclusion criteria	0.98	2.65 (1.59-4.43)	<.001
	Asthma definition	0.12	1.13 (0.43-2.97)	.799
	Real-world study			
	On-site interview	0.43	1.53 (0.95-2.46)	.077
	ACT or ACQ	0.51	1.66 (1.11-2.48)	.015
Uncontrolled	Developmental or cross-validation	1.31	3.70 (2.16-6.33)	<.001
	Cte	1.69		<.001
	S	−0.01		.886
	Settings	0.10	1.10 (0.90-1.34)	.309
	Race	0.23	1.26 (0.85-1.86)	.226
	Age	−0.13	0.88 (0.60-1.29)	.469
	Asthma severity	0.02	1.02 (0.55-1.89)	.935
	Whether lung function was evaluated	−1.37	0.26 (0.11-0.60)	.005
	Risk of bias	0.50	1.64 (1.30-2.07)	.001
	Reference standards	0.13	1.13 (0.57-2.27)	.693
	Prespecified or not	−0.22	0.81 (0.36-1.81)	.557
	Inclusion/exclusion criteria	1.66	5.23 (2.15-12.74)	.002
	Asthma definition	0.03	1.03 (0.42-2.51)	.950
	Real-world study	0.57	1.77 (0.31-10.04)	.475
	On-site interview	NA	NA	NA
	ACT or ACQ	0.31	1.37 (0.93-2.00)	.100
	Developmental or cross-validation	0.09	1.09 (0.35-3.41)	.856

Cte, Constant term in equation; NA, not available; RDOR, DOR ratio; S, indicator of threshold (logit true-positive rate + logit false-positive rate).

cutoff points. However, neither the ACT nor the ACQ was useful for assessing uncontrolled asthma. The ACT, which had an increased DOR ratio compared with the ACQ, is suitable for use in clinical practice because the ACQ also needs further cross-validation. Additional randomized controlled trials, in which the investigators randomize patients with asthma to either the ACT instrument or a sham test with subsequent adjustments of antiasthma therapies, are needed to assess future risk of asthma outcomes in a longitudinal fashion.

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Clinical implications: The ACT is preferable to the ACQ in clinical practice because the ACQ requires further cross-validation. Moreover, neither the ACT nor the ACQ is useful for the assessment of uncontrolled asthma.

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Online Repository Materials

METHODS

Search strategy and selection criteria

We used combinations of the following key words to identify all original articles in which ACT, ACQ or both were used in assessing asthma control: (“asthma control test” or ACT or “asthma control questionnaire” or ACQ) and (asthma or wheeze) and (sensitivity and specificity). The references provided by review articles were also scanned to identify other potentially eligible studies. Asthma was defined as physician-diagnosed asthma (whether confirmed or subject self-reported), by its International Classification of Diseases (ICD-) 9 code, or by asthma fulfilling guidelines such as American Thoracic Society criteria and GINA.^{E1} Trials where multiple assessments using the same instrument were performed in one patient were excluded. There were no limitations on language, year of publication, or publication status. Trials were included if they involved diagnostic tests and adequately reported data for calculations of sensitivity and specificity. After exclusion of duplicates, two reviewers (C.E.J. and Y.L.) reviewed the full text of all papers with titles and abstracts that seemed to fit the criteria for inclusion.

Quality assessment

QUADAS is comprised four domains: patient selection, index test, reference standard, and flow and timing.^{E2} Each domain was assessed for risk of bias, and concerns regarding applicability were also assessed for patient selection, index test and reference standard. Each domain had a set of signaling questions that helped reach the judgments about risk of bias and concerns about applicability. If a study was judged as “low” in all domains related to bias or applicability, then an overall judgment of “low risk of bias” or “low concern regarding applicability” was made for that study. If a study was judged as “high” or “unclear” in one or more domains, then an overall judgment of “at risk of bias” or “concerns regarding applicability” was made. Test accuracy studies that have design deficiencies can produce biased results^{E3}. Therefore, the following characteristics of study design, which encompass some of the more important forms of bias, were evaluated^{E4}: (1) study registration; (2) real-world design; (3) Institutional Review Board (IRB); (3) sample size calculation; (4) prospective data collection; (5) stringent or lenient inclusion/exclusion criteria; and (6) on-site interviews with questionnaires. Studies that had inclusion/exclusion criteria with more than three items were defined as stringent.

Heterogeneity analysis

Heterogeneity was assessed by the Cochran Q method and by the test of inconsistency (I^2). A low *P-value* (< 0.10) suggested the presence of heterogeneity beyond what would be expected by chance, and I^2 ($> 50\%$) was used to quantify the amount of heterogeneity. Subgroup and meta-regression analyses were performed to detect the effects of the different tools for assessing asthma control levels and the effects of potential factors based on characteristics including subjects, disease, and study design. The potential factors were settings, race, age, asthma definition, whether lung function was evaluated, asthma severity, whether an on-site interview was performed, reference standards, inclusion/exclusion criteria (stringent or lenient), whether the studies were pre-specified, real-world design, risk of bias, and whether the studies were developmental or cross-validation.

RESULTS

Study characteristics and quality of reporting

TABLES E2 and E3, and FIG. E1 show the characteristics of quality of reporting in the included studies. All included diagnostic tests were cross-sectional studies. Eighteen of 21 trials were approved by an IRB, and no studies were registered in a public domain service platform. Sample size calculations were applied in only three studies. Subjects that participated in ACT or ACQ assessments were chosen consecutively or at random in five studies. There were two retrospective studies, and a blinding method was used in 14 studies.

The QUADAS-2 results are shown in FIG. E1 and TABLE E3. For risk of bias, most studies did not describe in detail whether a consecutive or random sample of patients was enrolled. In the index test domain, a threshold was applied in all studies. Diagnostic accuracies of ACT and ACQ were tabulated at various cutoff points in most of the studies. Therefore, diagnostic accuracies of ACT and ACQ at pre-specified and non pre-specified cutoff points were calculated. According to the cutoff points that have been established in developmental studies, the included studies were divided into either pre-specified ($n=14$ in ACT and $n=6$ in ACQ) or non pre-specified ($n=14$ in ACT and $n=7$ in ACQ). Assessments of flow and timing identified incomplete data and lost to follow-up in five studies, which resulted in a failure to include all of the recruited patients in the analyses provided by the 2×2 tables. The concerns regarding the three applicability sections were all low risk.

We analyzed the proportion of subjects in the developmental and cross-validation

studies for ACT and ACQ. In the pre-specified studies, the proportions of subjects in the developmental and cross-validation studies for ACT were 8.49% (436/5131), 12.93% (436/5131) and 2.82% (160/5681) for controlled, not well-controlled and uncontrolled asthma. However, these proportions for controlled and not well-controlled asthma were 958.79% (1323/138) and 97.93% (1323/1351) in ACQ-7, 837.34% (1323/158) and 123.64% (1323/1070) in ACQ-6, and 15.63% (1323/8466) and 15.63% (1323/8466) in ACQ-5, respectively.

Reference standards, data synthesis and meta-analysis

The reference standards included NAEPP^{E5} GINA and the Brazilian Consensus on Asthma Management, in which the GINA guidelines were used extensively in 14 of 21 studies (TABLES E4 and E5). According to asthma control levels defined in the reference standards, the patients were divided into three groups: controlled, not well-controlled (partly controlled plus uncontrolled) and uncontrolled asthma. The overall prevalences of controlled, not well-controlled, and uncontrolled patients across countries were 33.3% (12.7-69.5%), 69.6% (30.5-82.0%) and 29.4% (14.9-50.1%), respectively. We found that agreement between the reference standards, and either ACT or ACQ was moderate in most of the studies. In the head-to-head comparison of pre-specified studies between ACT and ACQ for assessing not well-controlled asthma (n=3), the κ statistic between ACQ and the reference standard was slightly increased when compared to ACT and the reference standard (0.42 vs. 0.37 and 0.65 vs. 0.59, respectively). In addition, the κ coefficients for both ACT and ACQ in the non pre-specified and prospective studies were significantly elevated when compared to the pre-specified and retrospective studies because optimal cutoff points were selected in the non pre-specified studies and the prospective studies were high quality. Among the different versions of ACQ, ACQ-7 had the best κ coefficient, which indicated that ACQ-7 and the reference standard had the highest level of agreement.

Subgroup and meta-regression analyses

There were three versions of ACQ (ACQ-7, -6 and -5) used to assess asthma control^{E6}. Therefore, the diagnostic performances of the different ACQ versions were analyzed at different asthma control levels (TABLES IV and E6). We found that the DOR decreased from ACQ-7 to -5 in both pre-specified and non pre-specified studies. When the performance of ACQ-7 and -6 for assessment of not well-controlled asthma,

was compared, we did not find any statistical differences in HSROC AUC ($Z=1.27$, $P=0.102$). Other quantitative comparisons between the different versions were not performed because we did not perform pool summary estimates for a limited number of studies ($n<4$).

Subgroup analyses were performed for both ACT and ACQ. The covariates included real-world design, race, settings, age, asthma definition, whether lung function was evaluated, asthma severity, inclusion/exclusion criteria (stringent or lenient), whether an on-site interview was performed and reference standards (GINA or NAEPP) (TABLES E7 and E8). A greater than 50% difference in DOR was found in ACT between the two subgroups in asthma definition, whether lung function was evaluated, asthma severity, and reference standards in controlled asthma; asthma definition, whether lung function was evaluated, and asthma severity in not well-controlled asthma; and race, whether lung function was evaluated, and asthma severity in uncontrolled asthma. When comparing the difference between subgroups by using the Z statistic for ACT, we found that there were statistical differences in asthma definition ($Z=4.16$, $P<0.001$) and whether lung function was evaluated ($Z=1.96$, $P=0.025$) for assessment of controlled asthma; and in age ($Z=2.58$, $P=0.005$), asthma definition ($Z=3.34$, $P<0.001$), and inclusion/exclusion criteria ($Z=1.81$, $P=0.035$) for assessment of not well-controlled asthma. For ACQ, we found a greater than 50% difference in DOR in asthma definition, inclusion/exclusion criteria, and whether an on-site interview was performed in controlled asthma; and in race, age, asthma severity, reference standards and whether an on-site interview was performed in not well-controlled asthma.

Possible sources of heterogeneity across all studies were explored using meta-regression analyses with the following covariates as predictor variables: real-world design, race, clinical settings, age, asthma definition, whether lung function was evaluated, asthma severity, inclusion/exclusion criteria (stringent or lenient), reference standards (GINA or NAEPP), whether an on-site interview was performed, whether the studies were pre-specified studies, whether the studies were developmental or cross-validation, risk of bias, and different tools (ACT or ACQ) (TABLE IV). The meta-regression analyses demonstrated that age (RDOR=2.25 [1.08, 4.67], $P=0.033$), inclusion/exclusion criteria (RDOR=4.10 [1.71, 9.80], $P=0.017$), asthma severity (RDOR=2.68 [1.39, 5.16], $P=0.006$), whether lung function was evaluated (RDOR=0.28 [0.13, 0.61], $P=0.004$), real-world design (RDOR=7.58 [1.86, 30.78],

135 $P=0.008$), whether an on-site interview was performed (RDOR=8.29 [2.51, 27.34],
136 $P=0.002$), different tools (RDOR=20.14 [4.02, 100.95], $P=0.001$), and whether the
137 study was developmental or cross-validation (RDOR=4.12 [1.64, 10.36], $P=0.005$)
138 proved to be statistically significant for the assessment of controlled asthma. In
139 addition, setting (RDOR=0.68 [0.55, 0.84], $P=0.001$), age (RDOR=2.08 [1.33, 3.25],
140 $P=0.003$), asthma severity (RDOR=1.36 [1.12, 1.66], $P=0.004$), whether lung
141 function was evaluated (RDOR=0.14 [0.08, 0.26], $P<0.001$), reference standards
142 (RDOR=1.55 [1.08, 2.22], $P=0.019$), inclusion/exclusion criteria (stringent or lenient)
143 (RDOR=2.65 [1.59, 4.43], $P<0.001$), different tools (RDOR=1.66 [1.11, 2.48],
144 $P=0.015$), and whether the study was developmental or cross-validation (RDOR=3.70
145 [2.16, 6.33], $P<0.001$) proved to be statistically significant for assessment of not well-
146 controlled asthma. Finally, whether lung function was evaluated (RDOR=0.26 [0.11,
147 0.60], $P=0.005$), inclusion/exclusion criteria (RDOR=5.23 [2.15, 12.74], $P=0.002$)
148 and risk of bias (RDOR=1.64 [1.30, 2.07], $P=0.001$) significantly contributed to the
149 heterogeneity in assessment of uncontrolled asthma.

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167 TABLE E1. Defining levels of asthma control with GINA, Brazilian guideline, NAEPP, ACT and ACQ.

Levels of asthma control	ACT score	ACQ score	NAEPP	GINA/Brazilian guideline
Controlled	≥20	≤0.75	Daytime symptoms (2 days or less/week); Interference with normal activity (none); Nighttime awakening (≤2/month); Short-acting beta2-agonist use for symptom control (≤2 days/week); lung function (normal); Exacerbations (0-1/year)	Daytime symptoms (twice or less/week); Limitation of activity (none); Nocturnal symptoms/awakening (none); Need for reliever/rescue treatment (twice or less/week); lung function (normal); Exacerbations (none)
Partly controlled/not well-controlled	16-19	≥1.5	Daytime symptoms (≥2 days /week); Interference with normal activity (some); Nighttime awakening (1-3/week); Short-acting beta2-agonist use for symptom control (>2 days/week); lung function (60-80% predicted/personal best); Exacerbations (≥2/year)	Daytime symptoms (more than twice/week); Limitation of activity (any); Nocturnal symptoms/awakening (any); Need for reliever/rescue treatment (>2/week); lung function (<80%% predicted or personal best if known); Exacerbations (any)
Uncontrolled	≤15	NA	Daytime symptoms (throughout the day); Interference with normal activity (extremely limited); Nighttime awakening (≥4/week); Short-acting beta2-agonist use for symptom control (several times/day); lung function (<60% predicted/personal best); Exacerbations (≥2/year)	Three or more features of partly controlled asthma.

168 ACQ=asthma control questionnaire; ACT=asthma control test; GINA=the the Global Initiative for asthma; NAEPP=National Asthma Education and Prevention Program.

169

TABLE E2. Quality assessment of included studies that used ACT and ACQ.

Tools	Reference	Study registration	IRB	Cross-sectional design	Multi-center	Consecutive/random	Prospective	Blinding	Sample size calculation	Inclusion/exclusion criteria	On-site interview	Real-world design
ACT	Nathan 2004	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Lenient	Yes	No
	Schatz2006	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Stringent	Yes	No
	Vega 2007	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Lenient	Yes	No
	Zhou 2009	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Stringent	Yes	No
	Ko 2009	No	Yes	Yes	No	Unclear	Yes	Yes	No	Stringent	Yes	No
	Thomas 2009	No	Yes	Yes	Yes	Consecutive	Yes	Unclear	No	Lenient	Yes	Yes
	Roxo 2010	No	Yes	Yes	Yes	Consecutive	Yes	Yes	No	Lenient	Yes	No
	Álvarez-Gutiérrez 2010	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Stringent	Yes	No
	Grammatopoulou 2011	No	Yes	Yes	No	Unclear	Yes	Yes	No	Stringent	Yes	No
	Lai 2011	No	No	Yes	Yes	Random	Yes	Unclear	Yes	Lenient	Yes	No
	Ko 2011	No	Yes	Yes	No	Unclear	Yes	Yes	No	Stringent	Yes	No
	Nguyen 2011	No	Unclear	Yes	No	Unclear	Yes	Unclear	Yes	Stringent	Yes	No
ACQ	Juniper 2006	No	Yes	Yes	Yes	Unclear	No	Unclear	No	Stringent	No	No
	van den Nieuwenhof 2006	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Lenient	No	No
	Leite 2008	No	Yes	Yes	Yes	Consecutive	Yes	Yes	No	Lenient	Yes	No
	Olaguibel 2010	No	Unclear	Yes	Yes	Unclear	Yes	Unclear	No	Stringent	Yes	No
	Sastre 2010	No	Yes	Yes	Yes	Unclear	No	Unclear	No	Lenient	No	No
	O'Byrne 2010	No	Yes	Yes	Yes	Unclear	No	Yes	No	Stringent	No	No
Both ACT & ACQ	Wallenstein2007	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Lenient	Yes	No
	Zhou 2007	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Stringent	Yes	No
	Korn 2011	No	Yes	Yes	No	Consecutive	Yes	Unclear	No	Lenient	Yes	Yes

ACQ=asthma control questionnaire; ACT= asthma control test; IRB=institutional review board.

173 TABLE E3. Presentation for QUADAS-2 results for included studies that used ACT and ACQ.

Tools	Reference	Risk of bias				Applicability concerns		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
ACT	Nathan 2004	?	⊖	😊	⊖	😊	😊	😊
	Schatz2006	?	⊖	😊	⊖	😊	😊	😊
	Vega 2007	?	⊖	😊	😊	😊	😊	😊
	Zhou 2009	?	⊖	😊	😊	😊	😊	😊
	Ko 2009	?	⊖	😊	😊	😊	😊	😊
	Thomas 2009	😊	😊	😊	😊	😊	😊	😊
	Roxo 2010	😊	⊖	😊	😊	😊	😊	😊
	Álvarez-Gutiérrez 2010	?	⊖	😊	😊	😊	😊	😊
	Grammatopoulou 2011	?	😊	😊	😊	😊	😊	😊
	Lai 2011	?	⊖	😊	😊	😊	😊	😊
	Ko 2011	?	⊖	😊	⊖	😊	😊	😊
	Nguyen 2011	?	😊	😊	⊖	😊	😊	😊
ACQ	Juniper 2006	?	⊖	😊	😊	😊	😊	😊
	van den Nieuwenhof 2006	?	⊖	😊	😊	😊	😊	😊
	Leite 2008	😊	😊	😊	😊	😊	😊	😊
	Olaguibel 2010	?	⊖	😊	😊	😊	😊	😊
	Sastre 2010	?	⊖	😊	😊	😊	😊	😊
	O'Byrne 2010	?	😊	😊	😊	😊	😊	😊
Both ACT & ACQ	Wallenstein 2007	?	😊	😊	⊖	😊	😊	😊
	Zhou 2007	?	⊖	😊	😊	😊	😊	😊
	Korn 2011	😊	😊	😊	😊	😊	😊	😊

174 ACQ=asthma control questionnaire ACT=asthma control test; QUADAS=quality assessment of diagnostic accuracy studies. 😊 Low Risk, ⊖ High Risk, ? Unclear Risk.

175

176 TABLE E4. Assessments of asthma control levels with ACT in pre-specified and non pre-specified studies.

Reference	Reference standard	Pre-specified	Controlled asthma							Not well-controlled asthma							Uncontrolled asthma					
		Y/N	Cutoff	TP	FP	FN	TN	Kappa		Cutoff	TP	FP	FN	TN	Kappa		Cutoff	TP	FP	FN	TN	Kappa
Nathan 2004	NAEPP	Y	20	231	41	72	92	0.43		19	92	72	41	231	0.43		NA	NA	NA	NA	NA	NA
		N	20	231	41	72	92	0.43		19	92	72	41	231	0.43		NA	NA	NA	NA	NA	NA
Schatz2006	NAEPP	Y	20	102	45	42	112	0.42		19	112	42	45	102	0.42		15	44	23	28	65	0.35
		N	20	102	45	42	112	0.42		19	112	42	45	102	0.42		15	44	23	28	65	0.35
Vega 2007	GINA	Y	NA	NA	NA	NA	NA	NA		19	219	65	62	261	0.58		NA	NA	NA	NA	NA	NA
		N	NA	NA	NA	NA	NA	NA		19	219	65	62	261	0.58		NA	NA	NA	NA	NA	NA
Wallenstein 2007	NAEPP	Y	NA	NA	NA	NA	NA	NA		19	98	36	59	108	NA		NA	NA	NA	NA	NA	NA
		N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
Zhou 2007	GINA	Y	20	111	33	29	132	0.59		19	132	29	33	111	0.59		NA	NA	NA	NA	NA	NA
		N	20	111	33	29	132	0.59		19	132	29	33	111	0.59		NA	NA	NA	NA	NA	NA
Zhou 2009	GINA	Y	20	75	68	11	249	0.53		19	261	12	71	79	0.53		15	124	24	78	177	0.49
		N	20	75	68	11	249	0.53		19	261	12	71	79	0.53		17	162	39	40	162	0.61
Ko 2009	GINA	Y	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		15	49	11	78	245	0.39
		N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		20	105	80	22	176	0.46
Thomas 2009	GINA	Y	20	1197	76	798	878	0.43		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
		N	20	1197	76	798	878	0.73		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
Roxo 2010	Brazilian guideline	Y	20	62	7	53	187	0.55		19	171	42	11	66	0.58		NA	NA	NA	NA	NA	NA
		N	17	92	22	23	172	0.69		18	170	28	13	80	0.69		NA	NA	NA	NA	NA	NA
Álvarez-Gutiérrez 2010	GINA	Y	20	105	90	17	229	0.49		19	206	14	114	107	0.42		15	84	26	86	245	0.43
		N	21	95	65	26	255	0.53		20	229	17	90	105	0.42		18	132	63	37	209	0.53
Grammatopoulou 2011	NAEPP	Y	20	27	1	8	64	0.79		19	61	4	4	31	0.82		NA	NA	NA	NA	NA	NA
		N	19	31	4	4	61	0.82		19	61	4	4	31	0.82		NA	NA	NA	NA	NA	NA
Lai 2011	GINA	Y	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		15	335	252	362	2903	0.43
		N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		19	546	820	154	2332	0.38
Ko 2011	GINA	Y	NA	NA	NA	NA	NA	NA		19	59	8	121	92	0.20		15	35	16	65	163	0.29
		N	NA	NA	NA	NA	NA	NA		22	132	29	49	70	0.42		19	73	60	26	120	0.38
Korn 2011	GINA	Y	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
		N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		19	64	25	4	57	0.62
Nguyen 2011	GINA	Y	20	165	43	13	102	0.64		19	101	13	43	166	0.65		15	27	4	21	271	0.64
		N	NA	NA	NA	NA	NA	NA		19	101	13	43	166	0.65		NA	NA	NA	NA	NA	NA

177 ACT= asthma control test; FN=false negative; FP=false positive; GINA= the Global Initiative for Asthma; N=no; NA=not available; NAEPP= National Asthma Education
178 and Prevention Program; TN=true negative; Y=yes.

179

TABLE E5. Assessments of asthma control levels with ACQ in pre-specified and non pre-specified studies.

Reference	Referenc e standard	ACQ version	Pre- specified (Y/N)	Controlled asthma							Not well-controlled asthma							Uncontrolled					
				Cutoff	TP	FP	FN	TN	Kapp a		Cuto ff	TP	FP	FN	TN	Kap pa		Cuto ff	TP	FP	FN	TN	Kapp a
Juniper 2006	GINA/N AEPP	7	NA	0.75	621	235	70	397	0.53		1.5	394	55	297	577	0.48		NA	NA	NA	NA	NA	NA
		6	NA	0.75	589	193	102	439	0.55		1.5	325	46	366	586	0.39		NA	NA	NA	NA	NA	NA
		5	NA	0.75	595	228	96	404	0.50		1.5	356	70	335	562	0.40		NA	NA	NA	NA	NA	NA
Van den Nieuwenhof 2006	GINA	6	Y	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
			N	0.5	14	22	3	69	0.40		NA	NA	NA	NA	NA	NA		0.67	22	33	7	46	0.27
Wallenstein 2007	NAEPP	7	Y	NA	NA	NA	NA	NA	NA		NA	106	37	51	107	0.42		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		NA	106	37	51	107	0.42		NA	NA	NA	NA	NA	NA
Zhou 2007	GINA	7	Y	NA	NA	NA	NA	NA	NA		1.5	133	21	32	119	0.65		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
		6	Y	NA	NA	NA	NA	NA	NA		1.5	121	13	44	127	0.63		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
Leite 2008	Brazilian guideline	7	Y	0.75	87	32	1	18	0.40		1.5	79	18	8	33	0.58		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
		6	Y	0.75	98	26	4	30	0.54		1.5	79	9	23	47	0.58		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
		5	Y	0.75	163	57	11	47	0.43		1.5	146	28	28	75	0.57		NA	NA	NA	NA	NA	NA
Olaguibel 2010	GINA	7	Y	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
			N	0.5	161	274	12	916	0.43		NA	NA	NA	NA	NA	NA		1.0	561	148	99	555	0.64
Sastre 2010	GINA	7	Y	NA	NA	NA	NA	NA	NA		1.42	183	54	98	272	0.49		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		1.14	221	82	61	243	0.53		NA	NA	NA	NA	NA	NA
		6	Y	NA	NA	NA	NA	NA	NA		1.5	169	36	113	289	0.50		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		0.83	232	89	50	231	0.54		NA	NA	NA	NA	NA	NA
O'Byrne 2010	GINA	5	Y	0.75	1127	2357	349	4355	0.27		1.5	2359	81	4353	1395	0.14		NA	NA	NA	NA	NA	NA
			N	0.75	1127	2357	349	4355	0.27		0.75	4355	349	2357	1127	0.27		NA	NA	NA	NA	NA	NA
Korn 2011	GINA	7	Y	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	
			N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		1.5	60	35	8	47	0.44
		5	Y	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA
			N	NA	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA		1.5	60	27	8	55	0.54

180

ACQ=asthma control questionnaire; FN=false negative; FP=false positive; GINA= the Global Initiative for Asthma; N=no; NA=not available; NAEPP= National Asthma

181

Education and Prevention Program; TN=true negative; Y=yes.

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183

184 TABLE E6. Diagnostic performances of ACT and ACQ for assessment of asthma control levels in the non pre-specified studies.

Levels of asthma control	Tools	No.	Sensitivity	Specificity	Positive LR	Negative LR	Diagnostic OR	AUC
Controlled	ACT	8	0.77(0.73, 0.81) *	0.86(0.75, 0.92) *	5.35(3.08, 9.30) *	0.27(0.22, 0.32) *	20.16(10.66, 38.12) *	0.8670±0.0221
	ACQ							
	ACQ-7	2	0.92(0.90, 0.93)	0.70(0.63, 0.77)	3.23(2.42, 4.04)	0.13(0.09, 0.16)	29.92(14.99, 44.85)	NA
	ACQ-6	2	0.84(0.82, 0.85)	0.73(0.69, 0.76)	3.10(2.79, 3.41)	0.22(0.21, 0.23)	13.89(13.13, 14.64)	NA
	ACQ-5	2	0.81(0.76, 0.86)	0.64(0.64, 0.65)	2.28(2.17, 2.39)	0.29(0.22, 0.36)	8.48(5.97, 10.98)	NA
Not well-controlled	ACT	11	0.77(0.70, 0.83) *	0.80(0.75, 0.84) *	3.84(2.94, 5.00) *	0.29(0.22, 0.38) *	13.26(8.13, 21.62) *	0.8570±0.0247
	ACQ							
	ACQ-7	3	0.68(0.57, 0.78)	0.75(0.74, 0.91)	3.11(2.63, 6.55)	0.44(0.29, 0.47)	10.74(6.01, 13.92)	NA
	ACQ-6	2	0.65(0.47, 0.82)	0.83(0.72, 0.93)	4.71(2.96, 6.46)	0.41(0.25, 0.57)	11.68(11.31, 12.04)	NA
	ACQ-5	2	0.59(0.52, 0.65)	0.83(0.76, 0.89)	3.70(2.74, 4.65)	0.51(0.46, 0.55)	7.25(5.97, 8.53)	NA
Uncontrolled	ACT	7	0.79(0.72, 0.84)*	0.73(0.70, 0.76) *	2.97(2.60, 3.39) *	0.28(0.21, 0.38) *	10.46(7.11, 15.39)	0.8119±0.0219
	ACQ							
	ACQ-7	2	0.87(0.85, 0.88)	0.68(0.57, 0.79)	3.06(2.07, 4.04)	0.20(0.19, 0.21)	15.66(10.07, 21.25)	NA
	ACQ-6	1	0.76(0.56, 0.90)	0.58(0.47, 0.69)	1.82(1.30, 2.53)	0.41(0.21, 0.81)	4.38 (1.68, 11.45)	NA
	ACQ-5	1	0.88(0.78, 0.95)	0.67(0.56, 0.77)	2.68(1.94, 3.69)	0.18(0.09, 0.34)	15.28(6.40, 36.45)	NA

185 The pooled estimates presented as median (minimum, maximum) and heterogeneity was not assessed if the number of studies were less than four. * Statistical
186 heterogeneity found. ACQ=asthma control questionnaire; ACT=asthma control test; AUC=area under the curve; LR= likelihood ratio; NA=not available; No=number;
187 OR=odds ratio.

TABLE E7. Subgroup analysis of ACT for assessing asthma control levels in the pre-specified studies.

Levels of asthma control	Subgroups	No	Sensitivity	Specificity	Positive LR	Negative LR	Diagnostic OR
Controlled	Real-world study						
	Yes	1	0.60(0.58, 0.62)	0.92(0.90, 0.94)	7.53(6.05, 9.37)	0.43(0.41, 0.46)	17.33(13.48, 22.27)
	No	8	0.78(0.76, 0.81)*	0.78(0.76, 0.80)*	3.65(2.82, 4.73)*	0.26(0.18, 0.36)*	17.14(10.09, 29.13)*
	Race						
	White	6	0.64(0.62, 0.65)*	0.86(0.84, 0.87)*	5.11(2.83, 9.23)*	0.37(0.30, 0.45)*	14.63(8.29, 25.81)*
	Asian	3	0.87(0.79, 0.93)*	0.79(0.70, 0.80)	3.96(3.13, 4.07)	0.16(0.10, 0.26)*	24.97(15.31, 30.11)
	Settings						
	Primary	4	0.77(0.65, 0.86)*	0.80(0.69, 0.88)*	3.95(2.63, 5.94)*	0.28(0.19, 0.42)*	13.87(8.57, 22.43)*
	Tertiary	5	0.77(0.64, 0.87)*	0.87(0.70, 0.95)*	6.21(2.65, 14.55)*	0.26(0.16, 0.40)*	24.14(10.51, 55.48)*
	Age						
	<40y	3	0.86(0.71, 0.93)*	0.71(0.70, 0.72)	3.05(2.47, 3.13)	0.19(0.10, 0.41)*	15.72(6.04, 30.11)*
	≥40y	6	0.64(0.62, 0.66)*	0.88(0.86, 0.89)*	5.73(3.42, 9.61)*	0.33(0.26, 0.42)*	18.37(11.11, 30.38)*
	Asthma definition						
	Physician-diagnosed	4	0.62(0.60, 0.64)*	0.88(0.86, 0.90)*	4.88(2.25, 10.61)*	0.42(0.38, 0.47)	11.88(6.12, 23.08)*
	GINA or lung function test	5	0.86(0.83, 0.89)*	0.77(0.74, 0.79)*	3.63(2.86, 4.61)*	0.19(0.13, 0.26)	22.33(14.04, 35.51)
	Whether lung function was evaluated						
	Yes	5	0.78(0.75, 0.81)*	0.75(0.72, 0.77)*	3.13(2.55, 3.83)*	0.27(0.20, 0.38)*	11.73(7.07, 19.44)*
	No	4	0.62(0.60, 0.64)*	0.91(0.89, 0.92)*	8.37(3.76, 18.63)*	0.29(0.19, 0.45)*	27.77(15.14, 50.93)*
	Moderate-severe asthma						
	Yes	5	0.81(0.78, 0.84)*	0.79(0.76, 0.81)*	4.03(3.02, 5.38)*	0.22(0.12, 0.40)*	20.86(15.38, 28.30)
	No	3	0.76(0.71, 0.77)	0.71(0.69, 0.98)*	2.47(2.47, 50.14)*	0.34(0.23, 0.41)	7.20(6.04, 216.00)*
	Inclusion/exclusion criteria						
	Stringent	6	0.83(0.80, 0.86)*	0.76(0.73, 0.78)*	3.38(2.71, 4.23)*	0.21(0.14, 0.33)*	18.59(9.98, 34.63)*
	Lenient	3	0.60(0.54, 0.76)*	0.92(0.69, 0.96)*	7.53(2.47, 14.94)*	0.43(0.34, 0.48)	17.33(7.21, 30.69)*
	Reference standard						
	GINA	9	0.77(0.68, 0.84)*	0.84(0.74, 0.91)*	4.82(3.06, 7.60)*	0.27(0.20, 0.37)*	17.78(11.07, 28.56)*
	NAEPP	0	NA	NA	NA	NA	NA

	On-site interview						
	Yes	1	0.60(0.58, 0.62)	0.92(0.90, 0.94)	7.53(6.05, 9.37)	0.43(0.41, 0.46)	17.33(13.48, 22.27)
	No	8	0.78(0.76, 0.81)*	0.78(0.76, 0.80)*	3.65(2.82, 4.73)*	0.26(0.18, 0.36)*	17.14(10.09, 29.13)*
Not-well controlled	Real-world study						
	Yes	0	NA	NA	NA	NA	NA
	No	9	0.75(0.63, 0.83)*	0.82(0.76, 0.87) *	4.15(3.18, 5.42) *	0.31(0.21, 0.44) *	13.51(8.49, 21.48) *
	Race						
	White	7	0.74(0.72, 0.76)*	0.77(0.74, 0.79*)	3.18(2.51, 4.02)*	0.30(0.22, 0.41*)	11.84(7.09, 19.77)*
	Asian	4	0.67(0.64, 0.71)*	0.88(0.85, 0.91)*	5.44(3.50, 8.46)*	0.35(0.17, 0.72)*	16.18(8.14, 31.13)*
	Settings						
	Primary	3	0.72(0.68, 0.75*)	0.81(0.76, 0.85)*	4.22(2.08, 8.56)*	0.34(0.25, 0.47)*	12.36(5.48, 27.87)*
	Tertiary	6	0.71(0.68, 0.74)*	0.81(0.78, 0.83)*	4.16(2.79, 6.20)*	0.25(0.13, 0.50)*	17.02(8.65, 33.50)*
	Age						
	<40y	4	0.66(0.63, 0.70)	0.82(0.79, 0.85)*	4.11(2.24, 7.53)*	0.41(0.34, 0.48)	10.31(4.79, 22.16)*
	≥40y	7	0.74(0.72, 0.77)*	0.79(0.76, 0.81)*	3.70(2.87, 4.77)*	0.25(0.14, 0.45)*	15.43(9.39, 25.33)*
	Asthma definition						
	Physician-diagnosed	5	0.76(0.73, 0.79)*	0.75(0.72, 0.78)*	2.81(2.32, 3.40)*	0.32(0.22, 0.46)*	9.17(5.50, 15.31)*
	GINA or lung function test	6	0.68(0.65, 0.71)*	0.88(0.85, 0.90)*	5.63(4.10, 7.73)	0.30(0.18, 0.50)*	18.92(10.66, 33.55)*
	Whether lung function was evaluated						
	Yes	8	0.68(0.66, 0.71)*	0.80(0.77, 0.82)*	3.51(2.82, 4.37)*	0.38(0.27, 0.53)*	9.81(6.69, 14.40)*
	No	3	0.94(0.70, 0.94)*	0.89(0.61, 0.93)*	8.21(2.42, 9.66)*	0.10(0.07, 0.32)*	34.79(29.99, 118.19)
	Moderate-severe asthma						
	Yes	6	0.77(0.74, 0.79)*	0.82(0.79, 0.84)*	4.55(3.14, 6.59)*	0.26(0.20, 0.35)*	18.01(13.88, 23.38)
	No	4	0.71(0.67, 0.75)*	0.75(0.72, 0.79)	2.83(2.19, 3.65)	0.36(0.24, 0.52)*	9.06(4.49, 18.31)*
	Inclusion/exclusion criteria						
	Stringent	7	0.68(0.66, 0.71)*	0.85(0.82, 0.87*)	4.96(3.27, 7.52)*	0.32(0.20, 0.49)*	15.94(8.83, 28.76)*

	Lenient	4	0.77(0.74, 0.80)*	0.76(0.73, 0.78)*	2.90(2.32, 3.64)*	0.29(0.18, 0.47)*	10.24(5.53, 18.96)*
	Reference standard						
	GINA	11	0.75(0.63, 0.83)*	0.82(0.76, 0.87) *	4.15(3.18, 5.42) *	0.31(0.21, 0.44) *	13.51(8.49, 21.48) *
	NAEPP	0	NA	NA	NA	NA	NA
	On-site interview						
	Yes	0	NA	NA	NA	NA	NA
	No	9	0.75(0.63, 0.83)*	0.82(0.76, 0.87) *	4.15(3.18, 5.42) *	0.31(0.21, 0.44) *	13.51(8.49, 21.48) *
Uncontrolled	Real-world study						
	Yes	0	NA	NA	NA	NA	NA
	No	7	0.49(0.42, 0.56)*	0.92(0.86, 0.96) *	6.22(3.69, 10.47) *	0.55(0.48, 0.62) *	11.33(6.50, 19.73) *
	Race						
	White	2	0.53(0.46, 0.59)	0.86(0.82, 0.90)*	3.47(1.58, 7.61)*	0.55(0.48, 0.63)	6.62(3.25, 13.48)
	Asian	5	0.49(0.46, 0.51)*	0.92(0.92, 0.93)*	7.01(4.62, 10.64)*	0.56(0.48, 0.66)*	12.91(7.74, 21.56)
	Settings						
	Primary	3	0.57(0.52, 0.61)*	0.87(0.84, 0.90)*	3.96(2.35, 6.68)*	0.50(0.43, 0.60)	8.15(4.85, 13.70)
	Tertiary	4	0.46(0.43, 0.49)*	0.93(0.92, 0.93)*	8.17(4.47, 14.93)*	0.60(0.52, 0.70)*	14.02(6.82, 28.83)
	Age						
	<40y	3	0.53(0.48, 0.59)	0.92(0.89, 0.94)*	6.96(2.23, 21.74)*	0.53(0.47, 0.61)	13.88(3.76, 51.21)*
	≥40y	3	0.48(0.44, 0.53)*	0.92(0.90, 0.94)*	5.48(3.61, 8.32)	0.59(0.45, 0.77)*	9.72(5.70, 16.58)
	Asthma definition						
	Physician-diagnosed	2	0.55(0.48, 0.61)*	0.83(0.74, 0.92)*	4.18(2.34, 6.02)*	0.55(0.53, 0.56)	7.31(3.12, 17.15)*
	GINA or lung function test	5	0.49(0.45, 0.53)*	0.93(0.92, 0.95)*	7.08(4.24, 11.82)*	0.56(0.46, 0.67)*	13.03(7.01, 24.20)*
	Whether lung function was evaluated						
	Yes	5	0.50(0.46, 0.54)*	0.90(0.88, 0.92)*	4.53(2.99, 6.87)*	0.57(0.48, 0.68)*	8.33(5.59, 12.43)
	No	2	0.49(0.45, 0.52)*	0.96(0.92, 0.99)*	22.35(6.02, 38.67)*	0.50(0.44, 0.56)	48.89(3.61, 219.95)*
	Moderate-severe asthma						

	Yes	3	0.56(0.49, 0.61)	0.90(0.88, 0.99)*	5.15(5.14, 38.67)*	0.44(0.44, 0.56)	11.72(9.20, 87.11)*
	No	1	0.61(0.49, 0.72)	0.74(0.63, 0.83)	2.34(1.57, 3.48)	0.53(0.42, 0.66)	4.44(2.76, 7.14)
	Inclusion/exclusion criteria						
	Stringent	6	0.50(0.47, 0.54)*	0.92(0.90, 0.93)*	5.91(3.45, 10.12)*	0.56(0.47, 0.66)*	10.92(6.09, 19.58)*
	Lenient	1	0.48(0.44, 0.52)	0.92(0.91, 0.93)	6.02(5.22, 6.93)	0.56(0.53, 0.61)	10.66(8.76, 12.98)
	Reference standard						
	GINA	7	0.49(0.42, 0.56)*	0.92(0.86, 0.96) *	6.22(3.69, 10.47) *	0.55(0.48, 0.62) *	11.33(6.50, 19.73) *
	NAEPP	0	NA	NA	NA	NA	NA
	On-site interview						
	Yes	0	NA	NA	NA	NA	NA
	No	7	0.49(0.42, 0.56)*	0.92(0.86, 0.96) *	6.22(3.69, 10.47) *	0.55(0.48, 0.62) *	11.33(6.50, 19.73) *

189 The pooled estimates presented as median (minimum, maximum) and heterogeneity was not assessed if the number of studies were less than four. * Statistical
190 heterogeneity found. ACT=asthma control test; GINA= the Global Initiative for Asthma; LR= likelihood ratio; No=number; NA=not available; NAEPP=National Asthma
191 Education and Prevention Program; OR=odds ratio.

TABLE E8. Subgroup analysis of ACQ for assessing asthma control levels in the pre-specified studies.

Levels of asthma control	Subgroups	No	Sensitivity	Specificity	Positive LR	Negative LR	Diagnostic OR
Controlled	Real-world study						
	Yes	0	NA	NA	NA	NA	NA
	No	3	0.90(0.76, 0.99)*	0.63(0.36, 0.65)*	2.17(1.54, 2.42)*	0.16(0.03, 0.36)*	14.99(5.97, 48.94)*
	Race						
	White	1	0.99(0.94, 1.00)	0.36(0.23, 0.51)	1.54(1.25, 1.90)	0.03(0.00, 0.23)	48.94(6.27, 381.68)
	Asian	0	NA	NA	NA	NA	NA
	Settings						
	Primary	1	0.90(0.87, 0.92)	0.63(0.59, 0.67)	2.42(2.18, 2.68)	0.16(0.13, 0.20)	14.99(11.16, 20.13)
	Tertiary	2	0.88(0.76, 0.99)*	0.51(0.36, 0.65)*	1.86(1.54, 2.17)*	0.20(0.03, 0.36)*	27.46(5.97, 48.94)*
	Age						
	<40y	0	NA	NA	NA	NA	NA
	≥40y	2	0.88(0.76, 0.99)*	0.51(0.36, 0.65)*	1.86(1.54, 2.17)	0.20(0.03, 0.36)*	27.46(5.97, 48.94)*
	Asthma definition						
	Physician-diagnosed	1	0.99(0.94, 1.00)	0.36(0.23, 0.51)	1.54(1.25, 1.90)	0.03(0.00, 0.23)	48.94(6.27, 381.68)
	GINA or lung function test	2	0.83(0.76, 0.90)	0.64(0.63, 0.65)	2.30(2.17, 2.42)	0.26(0.16, 0.36)	10.48(5.97, 14.99)
	Whether lung function was evaluated						
	Yes	3	0.90(0.76, 0.99)*	0.63(0.36, 0.65)*	2.17(1.54, 2.42)*	0.16(0.03, 0.36)*	14.99(5.97, 48.94)*
	No	0	NA	NA	NA	NA	NA
	Moderate-severe asthma						
	Yes	1	0.99(0.94, 1.00)	0.36(0.23, 0.51)	1.54(1.25, 1.90)	0.03(0.00, 0.23)	48.94(6.27, 381.68)
	No	0	NA	NA	NA	NA	NA
	Inclusion/exclusion criteria						
	Stringent	2	0.83(0.76, 0.90)	0.64(0.63, 0.65)	2.30(2.17, 2.42)	0.26(0.16, 0.36)	10.48(5.97, 14.99)
	Lenient	1	0.99(0.94, 1.00)	0.36(0.23, 0.51)	1.54(1.25, 1.90)	0.03(0.00, 0.23)	48.94(6.27, 381.68)
	Reference standard						
	GINA	0	NA	NA	NA	NA	NA
	NAEPP	3	0.90(0.76, 0.99)*	0.63(0.36, 0.65)*	2.17(1.54, 2.42)*	0.16(0.03, 0.36)*	14.99(5.97, 48.94)*

	On-site interview						
	Yes	1	0.99(0.94, 1.00)	0.36(0.23, 0.51)	1.54(1.25, 1.90)	0.03(0.00, 0.23)	48.94(6.27, 381.68)
	No	0	NA	NA	NA	NA	NA
Not well-controlled	Real-world study						
	Yes	0	NA	NA	NA	NA	NA
	No	6	0.40(0.39, 0.41)*	0.90(0.89, 0.91)*	4.30(3.01, 6.13)*	0.38(0.26, 0.55)*	11.32(8.32, 15.58)*
	Race						
	White	3	0.68(0.65, 0.91)	0.74(0.65, 0.83)	2.63(2.57, 3.93)	0.42(0.14, 0.44)	9.41(6.01, 18.10)
	Asian	1	0.81(0.74, 0.86)	0.85(0.78, 0.90)	5.37(3.60, 8.03)	0.23(0.17, 0.31)	23.55(12.88, 43.06)
	Settings						
	Primary	2	0.61(0.57, 0.65)	0.87(0.83, 0.91)	5.24(3.93, 6.55)	0.45(0.42, 0.47)	11.67(9.41, 13.92)
	Tertiary	3	0.81(0.35, 0.91)	0.85(0.65, 0.95)	5.37(2.57, 6.40)	0.23(0.14, 0.69)	18.10(9.33, 23.55)
	Age						
	<40y	1	0.68(0.60, 0.75)	0.74(0.66, 0.81)	2.63(1.95, 3.54)	0.44(0.34, 0.56)	6.01(3.64, 9.92)
	≥40y	4	0.38(0.37, 0.36)*	0.91(0.90, 0.92)*	4.36(2.89, 6.59)*	0.33(0.18, 0.62)*	12.46(8.25, 18.80)*
	Asthma definition						
	Physician-diagnosed	2	0.80(0.68, 0.91)*	0.70(0.65, 0.74)	2.60(2.57, 2.63)	0.29(0.14, 0.44)*	12.06(6.01, 18.01)*
	GINA or lung function test	4	0.39(0.38, 0.40)*	0.92(0.91, 0.93)*	5.48(4.23, 7.10)*	0.43(0.28, 0.64)*	12.20(8.69, 17.12)*
	Whether lung function was evaluated						
	Yes	6	0.40(0.39, 0.41)*	0.90(0.89, 0.91)*	4.30(3.01, 6.13)*	0.38(0.26, 0.55)*	11.32(8.32, 15.58)*
	No	0	NA	NA	NA	NA	NA
	Moderate-severe asthma						
	Yes	3	0.81(0.65, 0.91)*	0.83(0.65, 0.85)*	3.93(2.57, 5.37)*	0.26(0.14, 0.46)*	15.11(7.85, 29.07)
	No	1	0.68(0.60, 0.75)	0.74(0.66, 0.81)	2.63(1.95, 3.54)	0.44(0.34, 0.56)	6.01(3.64, 9.92)
	Inclusion/exclusion criteria						
	Stringent	4	0.39(0.38, 0.40)*	0.92(0.91, 0.93)*	4.95(3.20, 7.66)*	0.43(0.29, 0.65)*	11.35(7.36, 17.49)*
	Lenient	2	0.78(0.66, 0.76)	0.74(0.65, 0.83)	3.25(2.57, 3.93)	0.18(0.14, 0.42)	13.76(9.41, 18.10)

	Reference standard						
	GINA	0	NA	NA	NA	NA	NA
	NAEPP	6	0.40(0.39, 0.41)*	0.90(0.89, 0.91)*	4.30(3.01, 6.13)*	0.38(0.26, 0.55)*	11.32(8.32, 15.58)*
	On-site interview						
	Yes	3	0.68(0.65, 0.91)	0.74(0.65, 0.83)	2.63(2.57, 3.93)	0.42(0.14, 0.44)	9.41(6.01, 18.10)
	No	1	0.81(0.74, 0.86)	0.85(0.78, 0.90)	5.37(3.60, 8.03)	0.23(0.17, 0.31)	23.55(12.88, 43.06)

193 The pooled estimates presented as median (minimum, maximum) and heterogeneity was not assessed if the number of studies were less than four. * Statistical heterogeneity
194 found. ACQ= Asthma Control Questionnaire; GINA= the Global Initiative for Asthma; LR= likelihood ratio; No=number; NA=not available; NAEPP=National Asthma
195 Education and Prevention Program; OR=odds ratio.

196

197 Figure legends

198

199 **FIG. E1.** Graphical display of QUADAS-2 results. **A.** ACT studies (n=15); **B.** ACQ

200 studies (n=9).

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