

Evaluation of Association Between Exercise-Induced Bronchoconstriction and Childhood Asthma Control Test Questionnaire Scores in Children

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Summary. Objective: Asthma control represents a major challenge in the management of asthmatic children; however, correct perception of control is poor. The aim of the study was to evaluate the association between subjective answers given to the Childhood Asthma Control Test (C-ACT) and objective evaluation of exercise-induced bronchoconstriction (EIB) by standardized treadmill exercise challenge. Methods: EIB was evaluated by standardized treadmill exercise challenge and related to C-ACT scores in 92 asthmatic children. Results: Of the 92 studied children only six children had a concordance between a positive challenge test ($\Delta FEV_1 \geq 13\%$) and a positive response to the exercise-related issue of the C-ACT questionnaire (C-ACT total score ≤ 19). There was no significant association between the degree of EIB and the scores relative to the single question on exercise-related problems while a significant association was found when considering the whole questionnaire with C-ACT total score > 19 ($r = -0.40$, $P < 0.001$). The two single questions showing a significant association were those focusing on nocturnal asthma. The areas under the ROC curve (AUC) for the sum of the scores of these questions in relationship to a positive response to the exercise test was 0.74. The AUC of the C-ACT total score was 0.76 and 0.55 for the specific question on EIB related problems. Conclusion: The discrimination power of the C-ACT total score in relationship to EIB was moderately good, and C-ACT questionnaire was capable of correctly predicting the absence of EIB in children reporting a global score > 19 . However, direct questions on EIB are associated with a high number of false positive and negative responses; better associations are found questioning on the presence on nocturnal symptoms. **Pediatr Pulmonol.**

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INTRODUCTION

The issue of asthma control represents a major challenge in the management of asthmatic children. In a study conducted in Switzerland on several hundred asthmatic children, asthma control was found to be unsatisfactory, according to asthma guidelines, in half of the patients who showed disturbed sleep, restricted physical activity, and unacceptable high level of school absences.¹ Nevertheless, 90% of parents were satisfied with the result of the treatment, at clear demonstration that parental expectations of asthma control are lower than those outlined in guidelines.¹ In another study performed in Canada, a similar proportion of parents believed their child's asthma being well-controlled even though this was really the case in only half of subjects.²

Unrestricted communication among pediatricians, child, and parents in order to evaluate signs and symptoms, history of exacerbations, adherence to the

treatment, and quality of life are recommended by international^{3,4} and national guidelines.⁵

With the purpose of improving patient-to-provider communication a simple method for quantifying asthma

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control was first developed for adults and adolescents, the Asthma Control Test (ACT),⁶ and successively for younger patients, the Childhood Asthma Control Test (C-ACT).⁷ The ACT is constructed with five questions, each one with five possible answers (scored from 1, worse, to 5, best), while the C-ACT is composed by four questions for the child (4–11 years of age) and three for the parents. For both tests a cut-off point of 19 or less was suggested to be indicative of poorly controlled asthma.^{7,8} No specific question on exercise induced bronchoconstriction (EIB) is considered for adults while a specific query on symptoms when running, exercising, or playing sports (QC2) is asked the children in C-ACT, as these symptoms are a prominent finding in young asthmatics, frequently involved in vigorous activities.⁹ Since EIB can be either under perceived¹⁰ or over estimated¹¹ by children, we aimed to evaluate the association between subjective answers given to C-ACT and objective evaluation of EIB by standardized treadmill exercise challenge.

PATIENTS AND METHODS

Study Population

Children, aging between 4 and 11 years, with asthma diagnosed according to the American Thoracic Society guidelines,¹² and seen at the outpatients clinic of the Department of Paediatrics of University of Verona (referred from primary care physicians), were asked to fill a validated Italian translation of C-ACT questionnaire (Childhood ACT English version available at www.asthmacontrol.com—Italy/Italian final version 09 June 06—Mapi Research Institute) at the time of a scheduled visit. Appropriate permission to use C-ACT questionnaire was requested and obtained. All of the subjects performed a standardized treadmill challenge which was conducted by an investigator (MP) who was blinded to any clinical information. Before the exercise challenge, a pediatrician (IC), unaware of C-ACT score, rated patients' asthma control according to the extent of asthma symptoms and lung function as described by GINA.⁴

Skin testing for determining allergic sensitization was done following standard methods.¹³

Both parents and children gave informed consent. The study was approved by the Verona Research Ethics Committee.

C-ACT Test

The C-ACT is a straightforward, self-administered questionnaire with seven questions on asthma symptoms, and effect of asthma on daily functioning. The first four items are answered by children (4–11 years of age), while the last three by parents. Each issue

included four response options for children, from 0 (worse) to 3 (best), and six response options for parents, from 0 (worse) to 5 (best). The possible lowest and highest scores were thus 0 (totally uncontrolled asthma) to 27 (total asthma control), respectively, and a score of 19 or less was shown to be indicative of poorly controlled asthma.⁷

Exercise Challenge Test and Lung Function Evaluation

A standardized exercise test protocol was used.^{14,15} Briefly, children performed baseline spirometry and then ran for 6 min on a treadmill at a speed to achieve a heart rate of 85% of the maximum predicted value [$220 - \text{age (y)}$]. The laboratory was air conditioned ($19 - 21^\circ\text{C}$; relative humidity $< 50\%$) during all exercise tests. Nose clips were applied to ensure mouth breathing. After the exercise challenge, FEV₁ was measured at 1, 3, 5, 10, 15, 20, and 30 min after completing exercise tests. The severity of EIA was expressed as the maximum change after exercise from the baseline value of lung function ($\Delta\text{FEV}_1\%$). Children whose FEV₁ fell by 13% or more were classified as having EIB.¹⁶

Asthma treatment was not stopped the day of the visit to the clinic as our aim was not to investigate the severity of EIB, but to ascertain if children were able to recognize its presence/absence in daily life. None of the children participating in the study were allowed to take reliever medication in the 6–8 hr before testing. The habitual use of short acting bronchodilators before planned exercise was, however, assessed in every child in order to evaluate whether or not this practice was appropriate.

Measurements of lung function, best of three blows according to ATS criteria,¹⁷ were made from full forced vital capacity (FVC) manoeuvres using an electronic spirometer (Jaeger, Master Screen IOS, Germany), calibrated before the arrival of each subject using a 3-L syringe (Cardinal Health, Germany 234 GmbH). The FVC manoeuvres were carried out with the child standing and with a nose clip.

STATISTICAL ANALYSIS

The strength of the (linear or nonlinear) relationship existing between the continuous variable (ΔFEV_1) and the ordinal categorical variables (QC2, QC4, QP3, C-ACT total score) was quantified using the Spearman's rank correlation r .

The hypothesis of absence of association between ΔFEV_1 and one of the categorical variables was also tested using one-way ANOVA (on log-transformed data, log base 10 of $10 - \Delta\text{FEV}_1$). Gender, age, and treatment with inhaled steroids were included as covariates in the analysis.

In Figure 1a the relationship between ΔFEV_1 and C-ACT total score was modeled by a piecewise linear model. The breakpoint was estimated using the method suggested by Muggeo¹⁸ and implemented in the “segmented” R package.¹⁹ The resulting cut-off was 18.6. This value was approximated to 19.0 because this is also the threshold used in the C-ACT questionnaire.

Sample size was calculated at the beginning of the study using the method described in Kraemer²⁰ and based on the two-sided Spearman’s rank correlation test with the following conditions: Significance level = 0.05, power = 0.80, H0 correlation coefficient = 0.0, and H1 correlation coefficient = 0.3. StudySize (ver. 2.0, <http://www.studysize.com>) was used for the calculation. The required sample size was N = 93.

The estimation of the AUC was performed by non-parametric ROC analysis and the hypothesis of equal areas under two ROC curves from the same sample was tested using the method described in DeLong et al.²¹

Two-sided *P*-values < 0.05 were considered statistically significant.

All analyses were conducted using Stata software (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

RESULTS

Clinical characteristics and asthma treatment of the 92 children included in the study are reported in Table 1. Of the studied children, 20 (21.8%) had a positive exercise challenge test ($\Delta FEV_1 \geq 13\%$). Nine children reported the regular use of short acting bronchodilators immediately before exercise. Of these patients only three subjects had a positive exercise challenge (Table 1).

The C-ACT total score for untreated patients was (mean value and SD) 22.2 ± 2.4 , for patients treated with inhaled steroids only was 22.2 ± 2.9 , and for

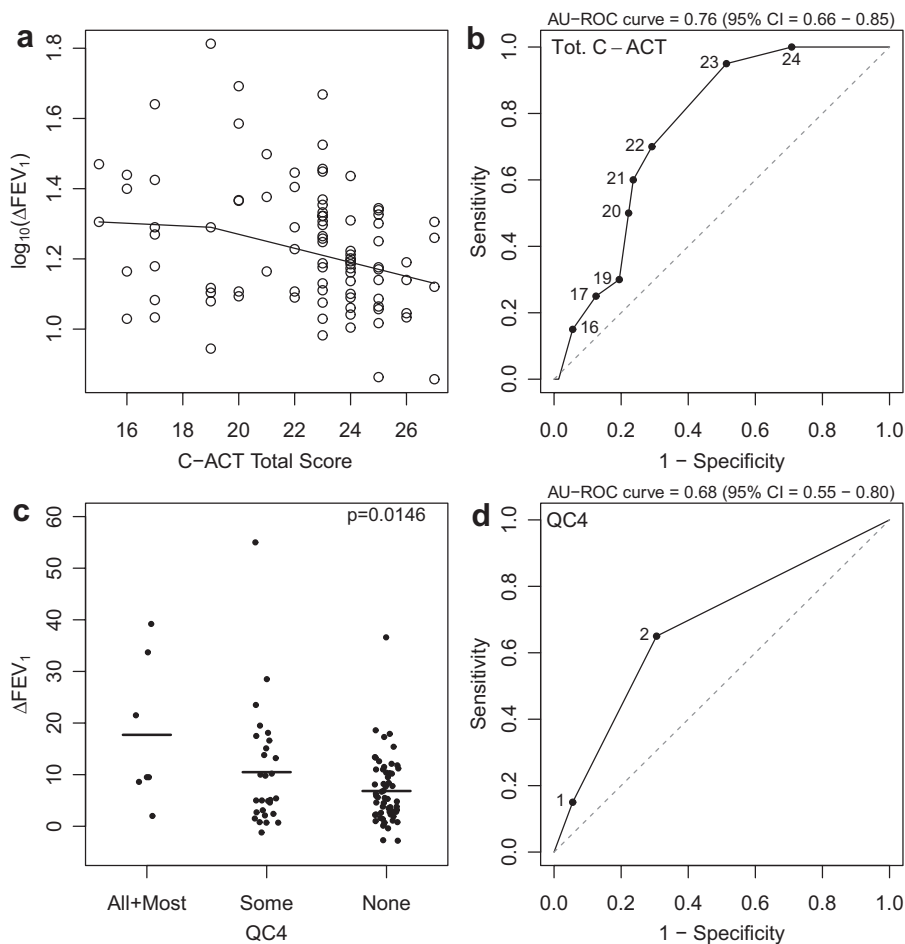


Fig. 1. Relationships between ΔFEV_1 levels versus (a) the C-ACT total score and (c) the score relative to the questions on nocturnal symptoms in the child section (QC4); horizontal lines represent mean values. Predictive power of C-ACT scores for diagnosis of EIB ($\Delta FEV_1 \geq 13\%$): ROC curves relative to (b) the C-ACT total score and (d) the questions on nocturnal symptoms in the child section (QC4).

TABLE 1—Patients' Characteristics

	n (tot) = 92
Mean age, y (SD)	8.9 (± 2.1)
Gender, n (%)	
Male	61 (66.30)
Female	31 (33.70)
Treatment, n (%)	
Only reliever	51 (55.44)
FP	26 (28.26)
M	0
M + FP	0
S/FP	0
S/FP + M	15 (16.30)
Levels of asthma control (GINA), n (%)	
Controlled	41 (44.57)
Partly controlled	45 (48.91)
Uncontrolled	6 (6.52)
Normally use short-acting β_2 -agonist prior to exercise, n (%)	9
With $\Delta FEV_1 \geq 13\%$	3 (33.4%)
With $\Delta FEV_1 < 13\%$	6 (66.6%)

FP, fluticasone propionate; M, montelukast; M + FP, montelukast + fluticasone propionate; S/FP, salmeterol/fluticasone propionate; S/FP + M, salmeterol/fluticasone propionate + montelukast

patients treated with salmeterol/fluticasone propionate and montelukast was 21.7 ± 3.5 .

The relationship between ΔFEV_1 and C-ACT total score was first considered. As can be seen, these relationships show a (Fig. 1a) statistically significant association above the cut-off of 19 ($r = -0.40$, 95%CI = -0.57 to -0.18 , $P = 0.0006$), whereas no statistically significant association was observed below this cut-point. The discrimination power of the C-ACT total score in relationship to the outcome $\Delta FEV_1 \geq 13\%$ was moderately good. The AUC was 0.76 (95%CI = 0.66–0.85) and the ROC curve is depicted in Figure 1b. Of the studied children, 34 (37.0%) had either a C-ACT score ≤ 19 or a $\Delta FEV_1 \geq 13\%$. Nevertheless, only in six children there was a concordance between a positive challenge test ($\Delta FEV_1 \geq 13\%$) and a C-ACT total score indicative of poorly controlled asthma (C-ACT ≤ 19) (Table 2). The sensitivity of this cut-off was 0.30, specificity 0.81, positive predicted value 0.30, and negative predicted value 0.81.

Aiming to further investigate the relevance of the C-ACT questionnaire for predicting ΔFEV_1 , a set of additional analyses was performed.

TABLE 2—Inadequate Asthma Control Estimated Either With C-ACT Total Score ≤ 19 and/or $\Delta FEV_1 \geq 13$

C-ACT total score	$\Delta FEV_1 \geq 13\%$	$\Delta FEV_1 < 13\%$	Total patients
>19	14	58	72
≤ 19	6	14	20
Total patients	20	72	92

The strength (measured by the Spearman's correlation ratio) of the relationship existing between ΔFEV_1 and the score related to the query on symptoms when running, exercising, or playing sports (QC2: How much of a problem is your asthma when you run, exercise or play sports?) was very low and not statistically significant ($r = -0.10$, $P = 0.3269$). A one-way ANOVA test on the logarithm of ΔFEV_1 accepts the hypothesis of absence of association between the two variables ($R^2 = 0.04$, $P = 0.2807$). Considering confounding factors such as age, treatment, and allergic sensitization and analysing the relationship between ΔFEV_1 and QC2 in a multivariate setting, no correlation was evidenced. All these findings clearly testify that no association between ΔFEV_1 and QC2 is present. Looking at individual data, 18 subjects (false positives) stated that exercising was a problem (QC2 score ≤ 1) though with a negative challenge (specificity = 0.75), whereas 15 subjects (false negatives) reported that exercising was not a problem (QC2 score ≥ 2) despite a positive exercise test (sensitivity = 0.25). The AUC was 0.55 (95%CI = 0.42–0.68).

In consideration of the evident discrepancy between the answer to QC2 and the actual response to the exercise test, and of the better performance of the total C-ACT score, we analysed the “weight” of each other single question in predicting the level of bronchial reactivity to exercise.

It was found that the most predictive questions were the number 4 in the child section (QC4: Do you wake up during the night because of your asthma?) and the number 3 in the parent section (QP3: During the last 4 weeks, on average, how many days per month did your child wake up during the night because of asthma?), both focusing on nocturnal symptoms. In particular, the analysis of the relationship between ΔFEV_1 and QC4 (Fig. 1c,d) evidenced a weak and statistically significant association ($r = 0.21$, 95%CI = 0.01–0.39, $P = 0.0485$). The one-way ANOVA test on the logarithm of ΔFEV_1 rejects the hypothesis of absence of association between the two variables ($R^2 = 0.09$, $P = 0.0146$). Similarly, the association between ΔFEV_1 and QP3 (Fig. 2a,b) was $r = 0.21$ (95%CI = 0.01–0.40, $P = 0.0461$) and $R^2 = 0.06$ ($P = 0.0203$). Furthermore, the AUC estimated for the seven different issues of the C-ACT questionnaire showed that QC4 and QP3 have the highest discriminating power with an AUC of 0.68 (95% CI = 0.55–0.80).

Interestingly, the discriminating power of the sum of the QC4 and QP3 scores (AUC = 0.74, 95%CI = 0.61–0.86) was approximately the same of the entire questionnaire and their differences are not statistical significant ($P = 0.6517$) (Fig. 2c,d). The association between ΔFEV_1 and QC4 + QP3 was $r = 0.25$ (95%CI = 0.05–0.44, $P = 0.0152$).

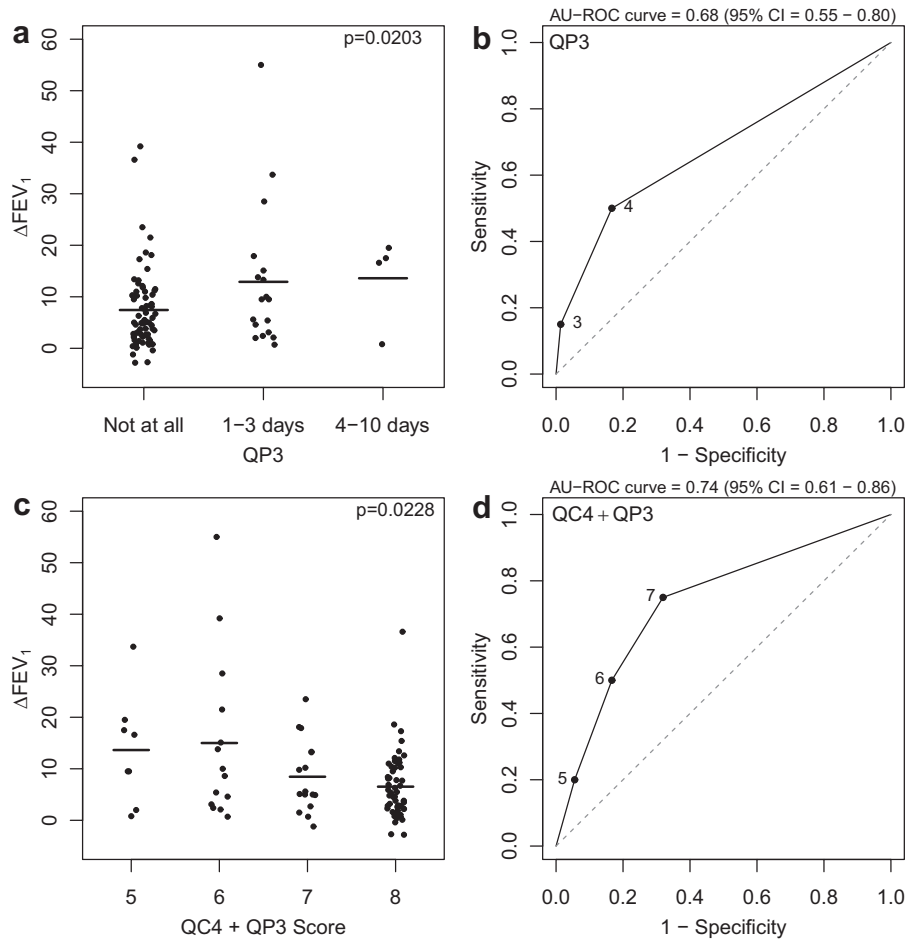


Fig. 2. Relationships between ΔFEV_1 levels versus scores relative to the questions on nocturnal symptoms in (a) the parent section (QP3) and (c) the sum of QC4 and QP3; horizontal lines represent mean values. Predictive power of C-ACT scores for diagnosis of EIB ($\Delta FEV_1 \geq 13\%$): ROC curves relative to the questions on nocturnal symptoms in (b) the parent section (QP3) and (d) the sum of QC4 and QP3.

COMMENT

The issue of exercise induced symptoms was properly included in the C-ACT, which is a validated questionnaire aimed to contribute to the routine evaluation of asthmatic children and to evaluate asthma control.⁷ In fact, EIB is common in asthmatic children and it is important to recognize, being responsible for limitations to daily life activities²² and potentially causing emotional and behavioral problems.²³

This study was aimed to evaluate the association between subjective answers given to C-ACT and objective evaluation of EIB in a population representative of a real-life situation for a majority of asthmatic children being evaluated for routine purposes and therefore cannot be directly extrapolated to more selected populations such as steroid treated subjects.

The results of this study confirm that, overall, C-ACT questionnaire is capable of significantly reflecting

the level of EIB, as assessed by a standardized exercise challenge in a group of mild or moderate, partly or well-controlled asthmatic children.

In particular, as reported in Table 2, a C-ACT score > 19 had a good ability to predict the absence of EIB in the group of children participating in the present study, whereas a lower association between these issues have been found for those with C-ACT score ≤ 19 , only six of whom (30%) were also presenting a positive response to exercise challenge.

The lack of a significant correlation between the C-ACT test question specifically focusing on exercise symptoms (QC2) and EIB is not very surprising since the questionnaire has been designed and validated as a whole to assess asthma control while the individual items have not been validated against physiological measurements.

Furthermore, the inappropriate perception of symptoms observed in a number of children in this study

was also expectable due to the range of differential diagnosis for exercise limitation in children and to the poor perception of airway obstruction in children in general.

In fact, it has been previously demonstrated that around fifty percent of children with asthma who reported a negative history for EIB presented a positive response to exercise challenge,²⁴ therefore showing an under-perception of their clinical status. On the other hand, it was also observed that a number of children declaring exercise-induced dyspnoea actually suffer for physiologic exercise limitation or poor training, or dysfunctional breathing, and that only a minority of them really experience EIB.^{25–27} Therefore, it seems reasonable to suggest that including exercise testing in the assessment of asthmatic children would provide a better insight of exercise-induced dyspnoea and of its etiology, therefore addressing to a more appropriate treatment.

As a further speculation, from a pediatrician's viewpoint, a potential explanation for the weakness of QC2 of C-ACT questionnaire, if considered separately, with regard to EIB issue could be represented by a misinterpretation of the question itself by children. In fact, the QC2 specifically asks "How much of a problem is your asthma during exercise", which is a very specific question about asthma directed to a young child who could even not always be aware of the correct meaning of the "asthma" word. Poorly understandable questions may significantly affect the results of questionnaires directed to the patients in general and to children in particular. For example, it has been reported that while the question "Does your chest hurts or feels tight after you run or play hard" had an OR = 2.8 for defining the presence or absence of EIB, the query "Do you have more problems breathing than most kids after you run or play hard" had an OR = 13.7,²⁸ with a clear different impact in picturing the clinical status of the patient about this specific issue.

Surprisingly, when considering the single items of the C-ACT questionnaire, a significantly better correlation between the questions focusing on nocturnal symptoms of asthma (QC4 and QP3) and Δ FEV1, as compared to the question on exercise symptoms (QC2), was found. This may very well be explained by the fact that both nocturnal symptoms and exercise induced airway obstruction are markers of more severe asthma, but it could also have an alternative explanation. In fact, if a child falsely perceives EIB, it could due to normal physiologic exercise limitation or dysfunctional breathing.^{25,29} In such situations it is obvious to expect that the patient does not present with nocturnal complains. This will result in a falsely low score for the question on exercise and in two true high scores for the issues related nocturnal symptoms. On the other hand, EIB symptoms can be masked by a spontaneous limitation

of physical activity due to uncontrolled asthma, resulting in a falsely negative score for the QC2 question of C-ACT questionnaire. In this case, nocturnal symptoms should be more realistically perceived and correctly scored in the C-ACT questionnaire.

In conclusion, the relationship between asthma and exercise shows wide inter- and intra-patient variability, and it is likely influenced not only by the disease itself but by additional psychosocial and physical variables. Therefore, only a standardized exercise challenge can properly assess the specific issue of the degree of EIB and it is not surprising if individual components of C-ACT do not have stand-alone validity. Nevertheless, the satisfactory correlation between the total C-ACT score and the results of the exercise challenge confirms that C-ACT is a valid complementary tool^{29,30} to be used along with objective parameters in the follow-up of asthmatic children.³¹

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