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RAPP-children: A new tool for assessing quality of life in patients with asthma and rhinitis

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Abstract

Background: RhinAsthma Patient Perspective (RAPP) is a short, validated questionnaire for assessing health-related quality of life (HRQoL) in adult patients with comorbid asthma and rhinitis, while a paediatric version is still not available.

Objective: The current study aimed to develop and validate the RAPP-children questionnaire.

Methods: RAPP-children was derived by combining RhinAsthma-children subscales into five unique items. At baseline (T0) and after 30 days (T1), 150 children (6–11 years) with comorbid asthma (predominantly intermittent or mild persistent) and rhinitis were given the following: RAPP-children, RhinAsthma-children, Paediatric Asthma Quality of Life Questionnaire (PAQLQ, age >6 years), Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), Childhood Asthma Control Test (CACT), KiddyKindl[®] (age 6 years) or KidKindl[®] (age >6 years), and a Visual Analogue Scale for nasal symptoms (VAS). At the final visit, a Global Rating of Change (GRC) scale was administered. The approved study was registered on the central registration system ClinicalTrials.gov (ID: NCT03276416).

Results: RAPP-children fairly reproduced RhinAsthma-children scores (concordance correlation coefficients between 0.91 and 0.95). RAPP-children showed adequate convergent validity (absolute Spearman's ρ larger than 0.5 with PAQLQ, PRQLQ, CACT, KiddyKindl/KidKindl, and VAS), internal consistency (Cronbach's α > 0.70), repeatability (intra-cluster correlation coefficient between 0.61 and 0.8) in the presence of clinical stability (GRC = 0), discriminant validity (sensitivity to asthma control status and rhinitis severity), and sensitivity to symptom improvements (GRC > 1). The minimal important difference (MID) was –20. Floor and ceiling effects were minimal. RAPP-children showed fair usability also in younger children (6–8 years).

Conclusion & Clinical Relevance: RAPP-children is a valid, five-item questionnaire for assessing HRQoL in children aged 6 to 11 years with concomitant asthma and rhinitis. Although further investigation is required in moderate and severe asthmatics, this tool can be useful in clinical trials and in routine medical practice for improving the management of respiratory allergy in children.

KEYWORDS

assessment, asthma, daily practice, paediatrics, quality of life, rhinitis

1 | INTRODUCTION

Health-related quality of life (HRQoL) is an important measure of patients' subjective experience with their disease.¹ Measures of HRQoL are thought to indicate how much an individual's illness interferes with his or her daily life and how well the patient is adapting to the illness across several areas of functioning, namely the social, emotional, and physical ones.² The assessment of HRQoL in clinical practice has recently been encouraged for its potential to involve patients in the management of their care,³ to improve doctor/patient communication and partnership, to affect care and health outcomes, and to improve patient satisfaction.⁴ Some methodological issues should be taken into account when the patient is a child^{5,6}: lack of advanced linguistic skills,⁷⁻⁹ lack of attention or motivation,¹⁰ lack of memory,¹¹ and poorly designed, difficult or boring questions.¹²

Despite the specific recommendations provided by international guidelines for the assessment of the subjective perspective of HRQoL in asthma and rhinitis,¹³ clinical management of patients with comorbid diseases is still often based on symptoms and biological parameters only. The relationship between upper and lower airway pathophysiology within the so-called "united airway disease" suggests that the daily co-occurrence of multimorbidity symptoms should be considered in the assessment of allergic children.¹⁴⁻¹⁶ However, most of the available HRQoL instruments consider asthma and rhinitis as distinct diseases^{17,18} and may present drawbacks in terms of completion time and item redundancy.

The RhinAsthma Patient Perspective (RAPP) is a simple, eight-item questionnaire that has been developed and fully validated for routine use to assess HRQoL in adult patients with comorbid rhinitis and asthma.¹⁹⁻²² For paediatric patients, the only self-administered questionnaires available are RhinAsthma-adolescents²³ and RhinAsthma-children.²⁴ A preliminary validation study of RhinAsthma-children identified a set of 17 meaningful items (out of the initial set of 21) divided into five sub-domains (lower airways, self-esteem, upper airways, social relationships, and medical care discomfort).²⁴

The current study aimed at developing and validating a shortened version of the RhinAsthma-children questionnaire [RhinAsthma-Children Patient Perspective (RAPP-children)] for the assessment of HRQoL in children with concomitant asthma and rhinitis in clinical practice.

2 | METHODS

2.1 | Study population

Children were assessed for eligibility at the outpatient clinic of the Clinical and Environmental Epidemiology of Pulmonary and Allergic

Paediatric Diseases Unit within IRIB-CNR, Palermo, Italy, between January 2018 and July 2019.

The inclusion criteria were the following: a) doctor diagnosis of asthma according to GINA (Global Initiative for Asthma) guidelines²⁵; b) doctor diagnosis of rhinitis according to ARIA guidelines (Allergic Rhinitis and its Impact on Asthma)²⁶; and c) age 6-11 years.

The exclusion criteria were the following: a) immunological, metabolic, cardiac or neurological diseases; b) major malformations of the respiratory system; c) poor understanding of written or spoken Italian; and d) active smoking.

The current study was approved by the local Institutional Ethics Committee (Palermo 1, Italy, Approval Number: 7/2017), and informed consent was obtained from all parents before study entry. The study was conducted in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki. The approved study was registered on the central registration system ClinicalTrials.gov (ID: NCT03276416).

2.2 | Assessments

The study involved three visits: 1) screening visit (-2 days); 2) baseline visit (T0, day 0); and 3) final visit (T1, +30 days). At the screening visit, children underwent a clinical examination and their eligibility for the study was assessed. At both T0 and T1, children repeated the clinical examination and filled a battery of questionnaires, under the supervision of their parents and one researcher (LM): RAPP-children, RhinAsthma-children, Paediatric Asthma Quality of Life Questionnaire (PAQLQ, age > 6 years), Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), Childhood Asthma Control Test (CACT), *KiddyKindl*[®] (age 6 years) or *KidKindl*[®] (age > 6 years), and a Visual Analogue Scale for nasal symptoms (VAS). At the final visit, a Global Rating of Change (GRC) scale was administered.

Asthma control was defined according to both GINA guidelines²⁵ (C = controlled, PC = partly controlled, or NC = non-controlled) and the total CACT score (CACT > 19 indicating controlled asthma).²⁷

2.3 | RhinAsthma-children

RhinAsthma-children (for children aged 6 to 11 years) is a validated questionnaire based on a one-week recall, for assessing HRQoL in children with comorbid rhinitis and asthma. It consists of 17 items scored from 1 to 3, and the total scores (ranging from 17 to 51) were converted on a scale from 0 (best HRQoL) to 100 (worst HRQoL).²⁴

2.4 | RAPP-children development

In the pilot validation study of the RhinAsthma-children, a factor analysis (carried out on the initial set of 21 items) identified five underlying factors accounting for the covariance structure of 17 items, while four items were excluded due to uncertain factor allocation.²⁴ These results are indicative of high item-to-item correlation within the five subscales, and low item-to-total correlation for the excluded items. RAPP-children was therefore created by combining the RhinAsthma-children subscales into 5 unique items (Table 1). As for RhinAsthma-children, the 5 items were scored from 1 to 3, and the total scores (ranging from 5 to 15) were converted on a scale from 0 (best HRQoL) to 100 (worst HRQoL).

2.5 | PAQLQ

Paediatric Asthma Quality of Life Questionnaire (for children aged 7 to 17 years) is a tool based on a one-week recall, for assessing HRQoL in children with asthma. It includes 23 items, and the total score ranges from 1 (worst HRQoL) to 7 (best HRQoL).¹⁷

2.6 | PRQLQ

Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (for children aged 6 to 12 years) is a tool based on a one-week recall, for assessing HRQoL in children with rhinitis. It includes 23 items, and the total score ranges from 0 (best HRQoL) to 6 (worst HRQoL).¹⁸

2.7 | CACT

Childhood Asthma Control Test (for children aged 6 to 11 years) is a self-administered questionnaire, based on a four-week recall, investigating child and parent perception of asthma control. It includes 7 items, and the total score ranges from 0 (poor asthma control) to 27 (optimal asthma control). CACT $\leq$ 19 indicates non-controlled asthma.²⁸

TABLE 1 RAPP-children items and response categories

How often, during the last week, due to your asthma and allergic rhinitis...			
1) Did whistle breathing, breathlessness, laboured breathing or cough bother you?	1. not at all	2. a little	3. much
2) Have you felt sad, sick or different from your friends?	1. not at all	2. a little	3. much
3) Did sneezing, nose-blowing or stuffy nose bother you?	1. not at all	2. a little	3. much
4) Did you have problems in enjoying yourself, running, travelling or staying focused at school?	1. not at all	2. a little	3. much
5) Did taking drugs or going to the doctor bother you?	1. not at all	2. a little	3. much

2.8 | KiddyKindl® / KidKindl®

KiddyKindl® (for children aged 4 to 6 years) and KidKindl® (for children aged 7 to 13 years) are generic, self-administered questionnaires based on a one-week recall, for assessing the child's perception of his/her HRQoL.²⁹ KiddyKindl® and KidKindl® include, respectively, 12 and 24 items. In accordance with the Kindl® manual (www.kindl.org), the total scores of both questionnaires were expressed on a scale from 0 (worst HRQoL) to 100 (best HRQoL); then, the two scores were pooled together.

2.9 | VAS

A VAS ranging from 0 (not at all bothersome) to 10 (extremely bothersome) was used to assess the severity of general nasal symptoms on the visit day.³⁰

2.10 | GRC

A 7-point GRC scale was administered at T1 to measure the self-perceived change in disease-related health status compared to T0. The GRC scale was based upon the question "How is your allergy (asthma and rhinitis) compared to the last visit?," and the response categories were as follows: 0 (no change), ± 1 (slightly better/worse), ± 2 (better/worse), and ± 3 (much better/worse). A clinically significant improvement was defined as a GRC > 1 .³¹

2.11 | Statistical analysis

Since RAPP-children consisted of five items, the target sample size was set to 150 children (30 sample units per variable) analogously to the previous validation study performed in adults.¹⁹ Indeed, collecting 3 to 20 sample units per variable is generally recognized as a rule of thumb in some multivariate analyses.³² Moreover, the sample size of 150 children yields a 99% power to detect a correlation of ± 0.5 (acceptable) with a type-1 error rate (α level) of 5%. The following psychometric characteristics of RAPP-children were assessed:

1. **Criterion validity:** At both T0 and T1, the concordance correlation coefficient (CCC) and its 95% confidence interval (CI) was calculated to assess the extent to which RAPP-children measured the same construct as RhinAsthma-children. Indeed, the CCC is appropriate for assessing whether a new instrument can reproduce the results of a traditional gold-standard assay. The following benchmarks have been suggested for interpreting the CCC: 0 to 0.90 "poor," 0.91 to 0.95 "moderate," 0.96 to 0.99 "substantial," and >0.99 "almost perfect" concordance.³³
2. **Convergent validity:** At both T0 and T1, correlation of RAPP-children scores with the scores from the other instruments measuring related constructs was assessed using the Spearman's ρ correlation coefficient. Coefficients exceeding $|\rho| \geq 0.5$ (with the sign in the expected direction) were considered acceptable.³⁴
3. **Internal consistency:** At both T0 and T1, scale homogeneity was assessed using Cronbach's α correlation coefficient. α coefficients between 0.70 and 0.90 were considered acceptable, while very high values (>0.90) were considered as indicative of item redundancy.³⁵
4. **Reliability:** This property concerns the repeatability of RAPP-children scores in the presence of clinical stability, and was assessed by estimating the intra-cluster correlation coefficient (ICC) for the pair of repeated measurements (T0 and T1) in children with GRC = 0. The following benchmarks were used for ICC interpretation: 0 to 0.20 "poor," 0.21 to 0.40 "fair," 0.41 to 0.60 "moderate," 0.61 to 0.80 "substantial," >0.80 "excellent" repeatability.^{36,37}
5. **Discriminant validity:** The instrument's ability to differentiate between sub-samples that are known or expected to differ was evaluated comparing RAPP-children scores according to disease severity and asthma control statuses, using the Kruskal-Wallis test.
6. **Responsiveness:** The ability of the questionnaire to detect significant differences over time in patients reporting a clinically significant improvement (GRC > 1) was assessed through a paired Wilcoxon signed-rank test to compare mean RAPP-children scores at T0 and T1.
7. **Clinical relevance:** The ability of RAPP-children to predict a worse disease status (moderate rhinitis, uncontrolled asthma, or both) was assessed by reporting the sensitivity (SE), specificity (SP), false-positive rate (FPR), false-negative rate (FNR), and the overall accuracy for different RAPP-children cut-offs. The best cut-off was defined as the RAPP-children score maximizing the Youden's J statistic (sensitivity + specificity-1). The mean change of RAPP-children scores from T0 to T1 (Δ RAPP) was compared between children with no/small improvement (GRC ≤ 1) and those reporting a clinically significant improvement (GRC > 1), through the Kruskal-Wallis test. The ability of RAPP-children to detect a clinically significant improvement (GRC > 1) was assessed by reporting SE, SP, FPR, FNR, and the overall accuracy for different Δ RAPP cut-offs. The minimal important difference (MID) was defined as the Δ RAPP cut-off point maximizing Youden's J statistic. Clinical relevance was considered fair if the 95% CI of the area under the receiver operating characteristic curve (AUC) did not include 0.5.

TABLE 2 Characteristics of the study sample at T0

Age	8.6 (1.6)
Gender	
Female	51 (34)
Male	99 (66)
Asthma severity (GINA)	
Intermittent	59 (39)
Mild persistent	83 (55)
Moderate persistent	8 (6)
Asthma control (GINA)	
Controlled	75 (50)
Partly controlled	23 (15)
Non-controlled	52 (35)
CACT total score	21.1 (4.6)
Asthma control (CACT)	
Controlled (CACT > 19)	99 (66)
Non-controlled (CACT ≤ 19)	51 (34)
Rhinitis severity (ARIA)	
Mild intermittent	57 (38)
Moderate intermittent	16 (11)
Mild persistent	34 (23)
Moderate persistent	43 (28)
RAPP-children total score	35.8 (21.4)
RhinAsthma-children total score	33.2 (20.5)
PAQLQ total score	6.2 (0.8)
PRQLQ total score	0.8 (0.5)
KiddyKindl/KidKindl total score	79.5 (11.0)
VAS	6.6 (2.5)
GRC (collected at T1)	
-3	1 (1)
-2	3 (2)
-1	11 (7)
0	24 (16)
+1	36 (24)
+2	29 (19)
+3	46 (31)

Note: Quantitative variables are expressed as mean (SD); categorical variables are expressed as no. (%).

8. **Scale range and floor/ceiling effect:** The extent to which the children used the whole answer scale (all the possible RAPP-children scores) was assessed through the score frequency distribution. Possible floor and ceiling effects (ie possible missing extremes in the lower or upper end of the scale) were considered present if over 15% of respondents achieved the lowest (0) or highest (100) possible score.³⁸

A subgroup analysis was performed to assess the usability of RAPP-children in younger children. In particular, the 72 children aged 6-8 years were included in the sub-analysis, by pooling the data collected at T0 and T1. The sub-sample size was therefore equal to 144, that is close to the sample size originally set for the whole group analysis (150). The analyses requiring a longitudinal assessment (reliability, clinical relevance) were not replicated due to the small sample size.

All the statistical analyses were performed using R version 3.6.1; p-values lower than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Children's characteristics

Table 2 summarizes the characteristics of the study sample at the baseline visit. The mean age was 8.6 years; 51 children (34%) were females and 99 (66%) were males. Asthma was intermittent in 39%, mild persistent in 55%, and moderate persistent in 6% of the children. According to GINA guidelines, asthma was controlled in 50%, partly controlled in 15%, and non-controlled in 35% of the children. According to the CACT total score (mean value equal to 21.1), asthma was controlled in 66% and non-controlled in 34% of the children. Rhinitis was mild intermittent in 38%, moderate intermittent in 11%, mild persistent in 23%, and moderate persistent in 28% of the participants; 57 children (38%) were receiving treatment for rhinitis. The mean RAPP-children score was 35.8 in the whole sample; it was 37.1 in males, and 33.3 in females ($P = .42$, Kruskal-Wallis test). The correlation (Spearman's ρ) between RAPP-children scores and age was 0.05 ($P = .52$).

3.2 | RAPP-children validation

1. **Criterion validity:** The CCC for RAPP-children and RhinAsthma-children scores was 0.93 [0.90-0.95] at T0 and 0.92 [0.89-0.94] at T1 (Table 3). Figure 1 shows the scatter plots of the relationship between the two questionnaires at the two visits.
2. **Convergent validity:** The correlation between RAPP-children scores and PAQLQ scores was -0.54 ($P < .001$) at T0 and -0.51 ($P < .001$) at T1. The correlation between RAPP-children scores and PRQLQ scores was 0.53 ($P < .001$) at T0 and 0.63 ($P < .001$) at T1. The correlation between RAPP-children scores and CACT scores was -0.64 ($P < .001$) at T0 and -0.57 ($P < .001$) at T1. The correlation between RAPP-children scores and KiddyKindl/KidKindl scores was -0.52 ($P < .001$) at T0 and -0.50 ($P < .001$) at T1. The correlation between RAPP-children scores and VAS was -0.53 ($P < .001$) at T0 and -0.55 ($P < .001$) at T1 (Table 3).
3. **Internal consistency:** Cronbach's α correlation coefficient for RAPP-children was 0.72 at T0 and 0.77 at T1 (Table 3).
4. **Reliability:** The ICC for the pair of repeated measurements (T0 and T1) in the 24 children with GRC = 0 was 0.77 [0.56-0.90] (Table 3).
5. **Discriminant validity:** At both visits, mean RAPP-children scores were significantly different among children with different asthma control status (based on both GINA guidelines and CACT scores) and rhinitis severity (mild vs. persistent), as reported in Table 4. Figure 2 represents the distribution of the RAPP-children scores by combinations of asthma control status (CACT) and rhinitis severity: "CACT > 19/ mild rhinitis" (69 children at T0 [46%] and 75 children at T1 [50%]), "CACT > 19/ moderate rhinitis" (30 children at T0 [20%] and 40 children at T1 [27%]), "CACT $\leq$ 19/ mild rhinitis" (22 children at T0 [15%] and 16 children at T1 [11%]), "CACT $\leq$ 19/

TABLE 3 Criterion validity, convergent validity, internal consistency, and reliability of RAPP-children: indicators and results

Psychometric property	Indicator	Results
Criterion validity	Concordance correlation coefficient (CCC) for RAPP-children and RhinAsthma-children	T0: CCC = 0.93 [0.90-0.95] T1: CCC = 0.92 [0.89-0.94]
Convergent validity	Spearman's ρ correlation coefficient of RAPP-children and other instruments	^a PAQLQ, T0: $\rho = -0.54$ ($P < .001$) ^a PAQLQ, T1: $\rho = -0.51$ ($P < .001$) PRQLQ, T0: $\rho = 0.53$ ($P < .001$) PRQLQ, T1: $\rho = 0.63$ ($P < .001$) CACT, T0: $\rho = -0.64$ ($P < .001$) CACT, T1: $\rho = -0.57$ ($P < .001$) Kindl, T0: $\rho = -0.52$ ($P < .001$) Kindl, T1: $\rho = -0.50$ ($P < .001$) VAS, T0: $\rho = -0.53$ ($P < .001$) VAS, T1: $\rho = -0.55$ ($P < .001$)
Internal consistency	Cronbach's α correlation coefficient of RAPP-children	T0: $\alpha = 0.72$ T1: $\alpha = 0.77$
Reliability	Intra-cluster correlation coefficient (ICC) for RAPP-children repeated measurements (T0-T1) in children with GRC = 0	ICC = 0.77 [0.56-0.90]

^aTwenty-two 6-year-old children excluded (PAQLQ not available for that age).

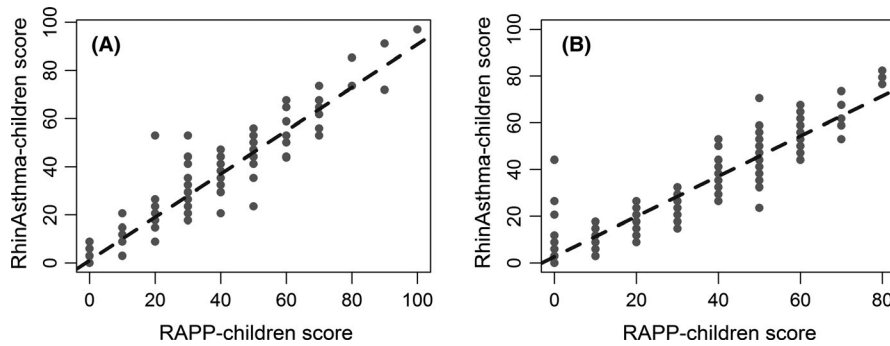


FIGURE 1 Scatter plots of RAPP-children and RhinAsthma-children scores at T0 (A) and T1 (B). Regression lines are superimposed (dashed lines)

moderate rhinitis" (29 children at T0 [19%], and 19 children at T1 [13%]). Mean RAPP-children scores were significantly different between children with intermittent and persistent asthma at T1. Mean RAPP-children scores were not significantly different between children with intermittent and persistent rhinitis.

6. *Responsiveness*: 75 children reported a clinically significant improvement at T1 (GRC > 1, 57.3% with CACT > 19/ mild rhinitis, 13.3% with CACT ≤ 19/ moderate rhinitis), while 75 children did not (GRC ≤ 1, 34.7% with CACT > 19/ mild rhinitis, 25.3% with CACT ≤ 19/ moderate rhinitis). In children with GRC > 1, the mean RAPP-children score decreased from 31.2 to 21.2 ($P < .001$) (Figure 3A).
7. *Clinical relevance*: Clinical relevance indicators for different RAPP-children and Δ RAPP cut-off points are reported in Table 5. The best cut-off for detecting a worse rhinitis status only (CACT > 19/ moderate rhinitis vs. CACT > 19/ mild rhinitis) was RAPP ≥ 30. The best cut-off for detecting a worse asthma status only (CACT ≤ 19/ Mild rhinitis vs. CACT > 19/ mild rhinitis) was RAPP ≥ 40. The best cut-off for detecting a worse status for both the diseases (CACT ≤ 19/ moderate rhinitis vs. CACT > 19/ mild rhinitis) was RAPP ≥ 50. The mean Δ RAPP was −1.87 in children reporting no/ small improvement (GRC ≤ 1), while it was −12.53 in children reporting a clinically significant improvement (GRC > 1) ($P = .004$) (Figure 3B). Δ RAPP ≤ −20 maximized Youden's J statistic and therefore represents the MID for the instrument. When using the MID, the percentage of correctly classified children (overall accuracy) was 61%. The 95% CI for the AUCs never included 0.5.
8. *Scale range and floor/ceiling effect*: The children used the whole answer scale of RAPP-children (Figure 4). The lowest possible score (0) was achieved by 9% of respondents at T0 and 19% at T1. The highest possible score (100) was achieved by 2% at T0, while nobody reached this score at T1.

The results reported in Table S1 and S2, concerning the subgroup of younger children (6–8 years), were similar to the overall results.

4 | DISCUSSION

RAPP-children is a new, simple, five-item questionnaire for the assessment of HRQoL in children aged 6 to 11 years with concomitant asthma and rhinitis. It was developed from the RhinAsthma-children

questionnaire by combining some of the original items, and its psychometric properties were tested on a sample of 150 outpatient children.

In the current study, the assessment of the criterion validity showed a moderate ability of RAPP-children to measure the same construct as RhinAsthma-children (CCC between 0.91 and 0.95), indicating that the new instrument can satisfactorily reproduce the scores from the original, longer questionnaire. Absolute correlations of RAPP-children scores with the scores from related instruments (PAQLQ, PRQLQ, CACT, KiddyKindl/KidKindl, and VAS) were larger than 0.5 with the sign in the expected direction, indicating a more than acceptable convergent validity. It should be noted that the recall time of RAPP-children (1 week) differs from the recall time of some other instruments (eg CACT refers to the last 4 weeks); in this case, it might be hypothesized that some of the correlation coefficients reported in Table 3 have been underestimated, thus rendering conservative the results.

TABLE 4 RAPP-children discriminant validity: mean score comparison by disease severity and asthma control status

	RAPP-children score, mean (SD)	
	T0	T1
Intermittent asthma	34.2 (20.6)	23.2 (21.0)
Persistent asthma	36.8 (22.0)	32.1 (22.6)
p-value	0.392	0.016
Controlled asthma	27.9 (18.9)	22.7 (19.7)
Partially controlled asthma	36.5 (15.0)	33.1 (26.2)
Uncontrolled asthma	46.9 (22.5)	36.7 (21.9)
p-value	<0.001	0.002
CACT > 19	28.0 (18.4)	23.1 (20.4)
CACT ≤ 19	51.0 (18.6)	46.6 (18.8)
p-value	<0.001	<0.001
Intermittent rhinitis	33.2 (19.3)	28.2 (21.0)
Persistent rhinitis	38.3 (23.1)	29 (23.6)
p-value	0.225	0.989
Mild rhinitis	30.7 (18.8)	24.2 (20.8)
Moderate rhinitis	43.7 (22.8)	35.4 (23.0)
p-value	<0.001	0.003

Note: The p-value is from the Kruskal-Wallis test.

^a Significant p-values are in bold.

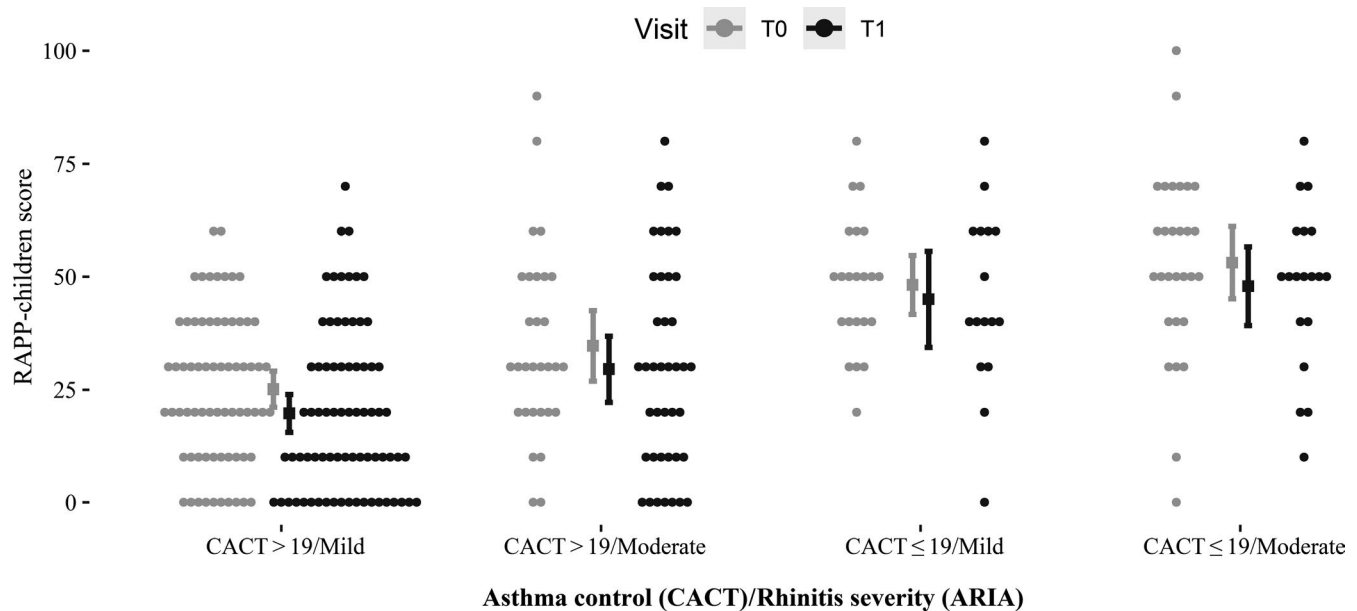


FIGURE 2 RAPP-children discriminant validity. Dot plots of RAPP-children scores by combinations of asthma control status (according to CACT scores) and rhinitis severity (according to ARIA guidelines). The squared points indicate the mean scores; the vertical bars correspond to the 95% confidence intervals for the mean

The assessment of internal consistency of RAPP-children highlighted a good trade-off between scale homogeneity (Cronbach's $\alpha > 0.70$) and item redundancy (Cronbach's $\alpha < 0.90$). The reliability assessment showed substantial repeatability (ICC between 0.61 and 0.8) of RAPP-children scores in the presence of clinical stability (GRC = 0), even if only 24 children had GRC = 0. The Zou's formula³⁹ can be used to assess the adequacy of the sample size for this sub-analysis; indeed, given the observed ICC value of 0.77, testing the null hypotheses of having lower than "moderate repeatability" (ICC < 0.41) with 24 children would ensure a statistical power of 88%, a value that is larger than the conventional 80% used in sample size calculations.

RAPP-children scores varied significantly among sub-samples characterized by different asthma control status (based on both

GINA guidelines and CACT scores) and rhinitis severity (mild vs. persistent according to ARIA guidelines), indicating fair discriminant validity. Although the more severe asthma statuses were represented by a substantial percentage of children with a non-controlled disease (34%), a comprehensive assessment of RAPP-children mean differences among all the asthma severity statuses was unfeasible due to the low number of moderate persistent asthmatics (only 6%) and the absence of severe asthmatics.

RAPP-children scores were not able to differentiate children with intermittent or persistent disease. Similar behaviour was observed in the Italian validation study of the RAPP questionnaire previously carried out in adults, and may be indicative of a higher sensitivity of the instrument's scores to differences in symptom severity rather than in symptom frequency.

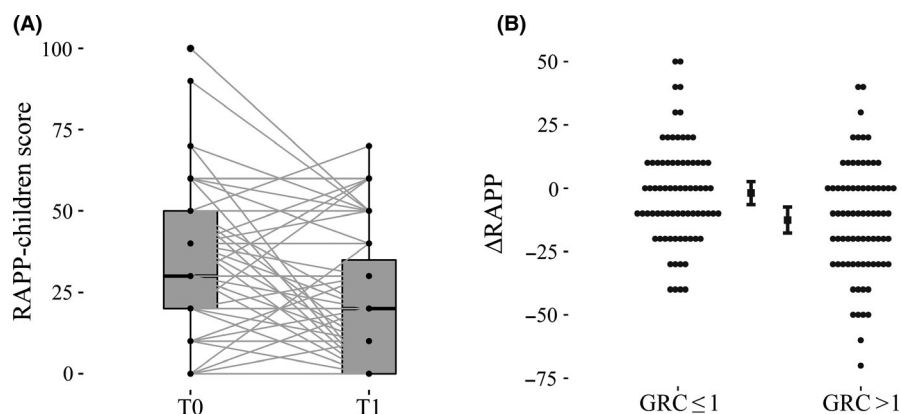


FIGURE 3 RAPP-children responsiveness (A) and clinical relevance (B). Panel A: box-plots of RAPP-children scores by visit in children reporting a clinically significant improvement (GRC > 1). The central line indicates the median. Panel B: dot plots of RAPP-children score changes (Δ RAPP) by GRC class: no/small improvement (GRC ≤ 1) vs. clinically significant improvement (GRC > 1). The squared points indicate the mean scores; the vertical bars correspond to the 95% confidence intervals for the mean

Cut-off point	SE (%)	SP (%)	FPR (%)	FNR (%)	Overall accuracy (%)	Youden's <i>J</i>
^a CACT > 19/Moderate rhinitis vs. CACT > 19/ Mild rhinitis (AUC = 0.62 [0.54-0.70])						
RAPP ≥ 20	76	40	62	23	51	0.153
RAPP ≥ 30	60	58	59	25	59	0.183
RAPP ≥ 40	37	75	58	29	63	0.121
^a CACT ≤ 19/ Mild rhinitis vs. CACT > 19/ Mild rhinitis (AUC = 0.84 [0.77-0.90])						
RAPP ≥ 30	92	58	63	3	65	0.504
RAPP ≥ 40	79	75	54	7	76	0.539
RAPP ≥ 50	53	88	47	12	80	0.401
^a CACT ≤ 19/ Moderate rhinitis vs. CACT > 19/ Mild rhinitis (AUC = 0.86 [0.79-0.92])						
RAPP ≥ 40	81	75	48	8	77	0.562
RAPP ≥ 50	71	88	35	10	83	0.583
RAPP ≥ 60	42	96	20	17	83	0.382
GRC > 1 vs. GRC ≤ 1 (AUC = 0.63 [0.55-0.72])						
ΔRAPP ≤ -10	61	53	43	42	57	0.146
ΔRAPP ≤ -20	45	76	35	42	61	0.213
ΔRAPP ≤ -30	29	89	27	44	59	0.186

^aT0 and T1 pooled.

Rows corresponding to the optimal cut-offs are in bold.

The assessment of responsiveness showed that RAPP-children was able to detect significant differences over time in children reporting a clinically significant improvement (GRC > 1).

Several RAPP-children cut-offs were derived to help health care providers to get specific indications about the status of the two diseases. Interestingly, increasing cut-offs were found for the detection of a worse rhinitis status only (RAPP ≥ 30), a worse asthma status only (RAPP ≥ 40), and a worse status for both the diseases (RAPP ≥ 50). The cut-off provided may indeed be useful for clinicians to address deeper investigations about the diseases and, consequently, to reconsider the treatment plans. Beside the best cut-off, defined as the one maximizing the Youden's *J* statistic (sensitivity + specificity-1), more sensitive but less specific cut-offs, and more specific but less sensitive cut-offs were also provided. Indeed, the overall accuracy was quite similar among all the cut-offs studied. However, it should be noted that under-representation of the more severe asthma statuses (moderate and severe) might have biased the estimation of the

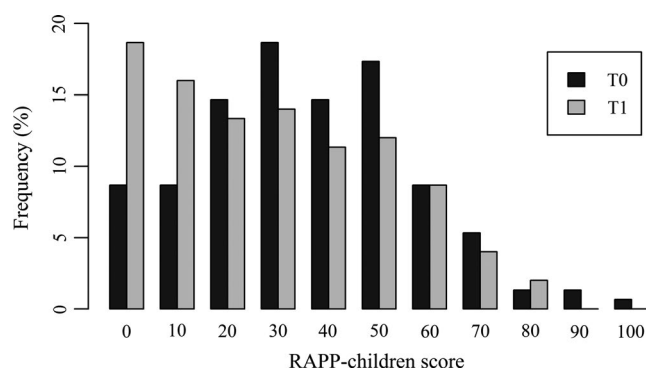


FIGURE 4 RAPP-children score distribution at T0 and T1

TABLE 5 Sensitivity (SE), specificity (SP), false-positive rate (FPR), false-negative rate (FNR), overall accuracy, and Youden's *J* statistic for different RAPP-children and ΔRAPP cut-offs

overall accuracy of the cut-offs; in fact, due to the large majority of children in the "negative status" (CACT > 19/ Mild rhinitis), the overall accuracy was deflated for highly sensitive cut-offs and inflated for highly specific cut-offs.

The mean change of the RAPP-children score from T0 to T1 (ΔRAPP) was significantly different in children reporting a clinically significant improvement (GRC > 1) and in those reporting no/small improvement (GRC ≤ 1). The AUC significantly larger than 0.5 indicated fair clinical relevance of the instrument; in particular, a ΔRAPP ≤ -20 made it possible to correctly classify 61% of children as experiencing a clinically significant improvement or not. In this sense, a 20-point score decrease would represent the MID, that is the smallest score decrease that a child would identify as beneficial. As before, a more sensitive but less specific cut-off (ΔRAPP ≤ -10) and a more specific but less sensitive one (ΔRAPP ≤ -30) were provided. It is worth noting that the MID for RAPP-children, that is -20, may appear substantially different than the MID for the adult versions, that is -2.¹⁹⁻²¹ This is due to the fact that the analyses in the adult papers were carried out on the raw total score scale (8 to 40), while in the current study the raw total scores (5 to 15) were first converted on a 0-100 scale (5 = 0, 6 = 10, ..., 14 = 90, 15 = 100). Actually, also for the RAPP-children, the MID is -2 if the raw total score scale is considered.

At T0, the children used the whole answer scale of the instrument (all the possible RAPP-children scores from 0 to 100), and floor and ceiling effects were minimal (<10%). These results would not be indicative of useless or missing extreme values in the lower or upper end of the scale. At T1, score distribution was much more positively asymmetric; although this would be consistent with the symptom improvement reported by many children (50% had a GRC > 1), this

result may again be ascribed to the under-representation of the more severe asthma statuses (moderate and severe). In general, it may be expected that the participants do not use the full scale when their disease states are better medically managed (as an extreme example, if the questionnaire would be administered to healthy children, it would be expected that all the children get a score of 0). For this reason, the high frequency (over 15%) of respondents who achieved the lowest (0) score at T1 might not be indicative of a floor effect *sensu stricto*.

The RAPP-children questionnaire is self-administered. The importance of the child perspective has been previously highlighted²⁸; although the independent input of children and parents could provide a broader perspective of the disease status, previous studies observed some disagreement between children and parent-reported variables.^{28,40} Indeed, parents may be less aware of the frequency of their child's symptoms, especially when symptoms are mild enough not to interfere with children's daily activities.⁴¹ In the current study, reading comprehension was tested during the screening visit. Children were supervised by their parents and one researcher who only helped to clarify the questions if needed; therefore, the final answers (and consequently the study results) were not likely to be affected by the parent/researcher inputs.

The new tool is simple to administer in clinical practice and contains a very limited number of items (five) and response categories (three), which may significantly reduce the completion time, also by avoiding the use of distinct questionnaires for asthma and rhinitis. In this view, RAPP-children may also favour attention and engagement in children aged ≥ 6 years.⁴² Up to now, two questionnaires investigating both asthma and rhinitis symptoms have been validated in children, namely RhinAsthma-children²⁴ and CARATKids.⁴³ However, these questionnaires are burdened by a larger number of items compared with the RAPP-children. Besides, the short recall time of RAPP-children (1 week) may be more suitable for children, since they may have difficulties in remembering symptoms that occurred more than 1 week before.¹¹ Finally, it is worth noting that RAPP-children showed fair usability also in the subgroup of younger children (6–8 years).

The main limitation of the current study is the low percentage of children with moderate persistent asthma (6%) and the absence of children with severe asthma; in fact, this might have affected the comprehensiveness of the validity assessments and, consequently, the generalization of the results. As highlighted above, this issue might have affected the assessment of discriminant validity (impossibility to assess RAPP-children mean differences among all asthma severity statuses), clinical relevance (deflated overall accuracy for highly sensitive cut-offs, and inflated overall accuracy for highly specific cut-offs), and floor effect (positively asymmetric score distributions). Although these limitations did not affect the overall validity assessment of RAPP-children in the current study population, further investigations are needed in moderate and severe asthmatics.

5 | CONCLUSIONS

RAPP-children is a new, simple, five-item questionnaire for the assessment of HRQoL in children aged 6 to 11 years with concomitant asthma and rhinitis. It is reliable, sensitive to individual changes, and clinically relevant. It can capture the specific burden of respiratory allergy on HRQoL, therefore integrating the information derived from generic health status measurement. Although further investigation is required in moderate and severe asthmatics, RAPP-children can be useful in clinical trials and in routine medical practice for improving the management of respiratory allergy in children.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Table S1. Criterion validity, convergent validity, and internal consistency of RAPP-children for the 72 children aged 6-8 years: indicators and results (T0 and T1 pooled).

Psychometric property	Indicator	Results
Criterion validity	Concordance correlation coefficient (CCC) for RAPP and RhinAsthma	CCC = 0.93 [0.91-0.95]
Convergent validity	Spearman's ρ correlation coefficient of RAPP and other instruments	*PAQLQ, T0: $\rho = -0.39$ ($p < 0.001$) PRQLQ, T0: $\rho = 0.48$ ($p = 0.001$) CACT, T0: $\rho = -0.60$ ($p < 0.001$) Kindl, T0: $\rho = -0.42$ ($p < 0.001$) VAS, T0: $\rho = -0.51$ ($p < 0.001$)
Internal consistency	Cronbach's α correlation coefficient of RAPP	$\alpha = 0.74$

*Twenty-two six-year-old children excluded (PAQLQ not available for that age).

Table S2. RAPP-children discriminant validity for the 72 children aged 6-8 years: mean score comparison by disease severity and asthma control status (T0 and T1 pooled).

	RAPP-children score, mean (SD)
Intermittent asthma	28.8 (20.3)
Persistent asthma	32.6 (21.5)
p-value	0.301
Controlled asthma	25.5 (19.9)
Partially controlled asthma	33.7 (21.1)
Uncontrolled asthma	38.5 (20.2)
p-value	0.003
CACT > 19	23.8 (17.9)
CACT ≤ 19	47.4 (18.3)
p-value	< 0.001
Intermittent rhinitis	28.8 (19.7)
Persistent rhinitis	32.6 (22.0)
p-value	0.390
Mild rhinitis	26.9 (19.9)
Moderate rhinitis	36.0 (21.5)
p-value	0.018

The p-value is from the Kruskal-Wallis test.
Significant p-values are in bold.