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Comparison between the health-related quality of life of children/adolescents with asthma and that of their caregivers: a systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the health-related quality of life (HRQoL) of children/adolescents with asthma and that of their caregivers, comparing the two. **Methods:** This was a systematic review and meta-analysis based on the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses, with a strategy of searching five health-related databases (MEDLINE/PubMed, EMBASE, ScienceDirect, SciELO, and LILACS). We included studies that evaluated the HRQoL of children/adolescents with asthma and that of their caregivers with the Pediatric Asthma Quality of Life Questionnaire and the Pediatric Asthma Caregiver's Quality of Life Questionnaire, respectively, using the total scores and the scores on the domains activity limitation, symptoms (children/adolescents only), and emotional function. **Results:** We identified 291 articles, and we evaluated 133 of those. A total of 33 articles, collectively including 4,101 subjects, were included in the meta-analysis. An analysis stratified by study design showed no differences between the HRQoL of the caregivers and that of the children/adolescents in the activity limitation domain and in the total score. However, the mean emotional function domain scores were significantly higher (better) among children/adolescents with asthma than among their caregivers in longitudinal studies—$\Delta = 0.82$ (0.21-1.44)—and randomized clinical trials—$\Delta = 0.52$ (0.29-0.79)—although not in cross-sectional studies—$\Delta = -0.20$ (−0.03 to 0.43). **Conclusions:** The total HRQoL scores proved to be similar between children/adolescents with asthma and their caregivers. However, the two groups differed in their perception of their emotional function, the caregivers scoring significantly lower than the children/adolescents in that domain.

Keywords: Asthma; Quality of life; Surveys and questionnaires.

INTRODUCTION

Asthma is a chronic inflammatory disease that affects individuals of all ages, especially children. Asthma is considered a global health problem, affecting 300 million people worldwide,[1] and it is estimated that there are approximately 20 million individuals with asthma in Brazil. In pediatric patients, the prevalence of asthma is 20%.[2,3]

Asthma affects not only the patient but also their family. Over time, asthma can negatively affect the quality of life (QoL) of children and adolescents, as well as that of their parents and family members.[4]

The World Health Organization Quality of Life Group defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns".[5] Therefore, for a complete picture of patient health status, conventional clinical indices and health-related QoL (HRQoL) must be assessed.[6]

Parents and family members play an important role in the QoL of children and adolescents with asthma. Parental perception of asthma severity is an important determinant of asthma management and control.[7,8] In the process of caring for a child or adolescent with asthma, parents and family members should have a correct perception of the disease.[9]

Pediatric chronic disease negatively affects family function and HRQoL. Parents and family members of children and adolescents with chronic disease have concerns and responsibilities related to the health needs of their children, educational/medical services, disease costs, missed social opportunities, and work absenteeism, as well as having to cope with physical and emotional problems.[10]

In this context, the objective of the present study was to evaluate the HRQoL of children and adolescents with asthma and that of their caregivers, comparing the two.

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METHODS

This was a meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria,[11] with a strategy of searching five health-related databases for studies assessing disease control in children and adolescents with asthma, as well as the HRQoL of the patients and their parents and family members.

We included studies that evaluated the HRQoL of children/adolescents with asthma and that of their caregivers with the Pediatric Asthma Quality of Life Questionnaire (PAQLQ)[12] and the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ),[13] respectively, using the total scores and the scores on the domains activity limitation, symptoms (children/adolescents only), and emotional function. The primary outcome measure was a comparison of the total scores and the scores on the domains activity limitation and emotional function between the two groups (i.e., children/adolescents with asthma and their parents/caregivers).

Search strategy

The search strategy included the following terms and Boolean operators: (Asthma AND (PAQLQ OR "Pediatric Asthma Quality of Life Questionnaire") AND (PACQLQ OR "Pediatric Asthma Caregiver's Quality of Life Questionnaire"). We searched the following databases: MEDLINE (PubMed); EMBASE and ScienceDirect (Elsevier); and SciELO and LILACS (BIREME). All searches were performed in October of 2018, and no date limits were applied to the searches.

Searches were limited to title, keyword, and abstract fields. In the MEDLINE (PubMed) database, for example, we employed the following search strategy: (Asthma[Title/Abstract] OR Asthma[MeshTerms]) AND (PAQLQ[Title/Abstract] OR PAQLQ[MeshTerms] OR "Pediatric Asthma Quality of Life Questionnaire"[Title/Abstract] OR "Pediatric Asthma Quality of Life Questionnaire"[MeshTerms]) AND (PACQLQ[Title/Abstract] OR PACQLQ[MeshTerms] OR "Pediatric Asthma Caregiver's Quality of Life Questionnaire"[Title/Abstract] OR "Pediatric Asthma Caregiver's Quality of Life Questionnaire"[MeshTerms]). Searches were not limited by language of publication or target audience. Potentially eligible articles were exported from the aforementioned health-related databases as .txt (MEDLINE), .bib (BibiTeX), or .ris (RIS) files including the following data: author names, article title, keywords, journal of publication, year of publication, type of article, and abstract.

Identification, selection bias, inclusion criteria, and study characteristics

The StArt (State of the Art through Systematic Review) software, developed by the Federal University of São Carlos Software Engineering Research Laboratory (located in the city of São Carlos, Brazil) and designed specifically for systematic reviews,[14] was used in order to design a flow chart of the article selection process, including the following steps: a) Identification: identification of potentially eligible studies; b) Selection: exclusion of duplicates and screening by reading titles and abstracts; c) Eligibility: screening by reading the full text; and d) Inclusion: eligible studies meeting the inclusion criteria. Each step of the process was performed by two researchers and reviewed by a third, the criteria for article selection being as follows: inclusion of all articles selected by both researchers; exclusion of all articles selected by neither researcher; inclusion of all articles selected by only one researcher but meeting the inclusion criteria according to the reviewer. To identify additional studies (gray literature) for inclusion, we carried out a hand search of the references cited in the studies selected during the Eligibility step of the article selection process (i.e., screening by reading the full text).

The studies included in the systematic review were cross-sectional studies or early-phase longitudinal studies, case-control studies, or randomized clinical trials that used primary or secondary data on total and domain scores on the PAQLQ (children/adolescents with asthma) and PACQLQ (parents/caregivers).[12,13] We excluded studies in which the HRQoL of children/adolescents with asthma and that of their parents/caregivers was assessed by instruments other than the PAQLQ and PACQLQ.

Data extraction and presentation

We extracted and tabulated data on the characteristics of each eligible study, including the name of the first author, year of publication, study site, study design, patient age, and study participants. The eligibility criteria for data extraction were the same as the criteria used in order to classify the sample and included patient age, sex, race, asthma severity/level of asthma control, physician-diagnosed rhinitis/atopy, lung function, and fractional exhaled nitric oxide. For comparative analysis, we extracted data on total and domain scores on the PAQLQ and PACQLQ.[12,13]

Data are presented so as to demonstrate values for each study design, general study characteristics (author(s) and year of publication), and participant characteristics, as well as weighted means of total scores, activity limitation domain scores, and emotional function domain scores on the HRQoL questionnaires.

Statistical analysis

For the meta-analysis of the outcome measures, we used the Review Manager software, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, UK),[15] using random-effects models and inverse variance weighting to calculate the (bivariate) mean difference rate, with 95% CIs, heterogeneity (I^2), and total overall effect size (Z). The level of significance was set at $p < 0.05$ for mean total and domain HRQoL scores for within-group and between-group comparisons by study design: cross-sectional studies, longitudinal (cohort) studies, and randomized clinical trials.

Systematic review registration

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) prior to research activities (Registration no. CRD42017081293).

RESULTS

A total of 129 articles were retrieved from the health-related databases: MEDLINE/PubMed (n = 22), EMBASE (n = 55), ScienceDirect (n = 43), SciELO (n = 4), and LILACS (n = 5). Another 5 were added from the gray literature. Therefore, a total of 134 articles were initially selected for inclusion. Of those 133 articles, 100 were excluded. Of those, 9 were duplicates (appearing in more than one database), 78 were screened out following a review of titles and abstracts, and 13 were screened out following full-text assessment. Therefore, as can be seen in Figure 1, a total of 33 studies were included in the meta-analysis.[16-48]

Of the 33 included studies,[16-48] 28 (85%) were published in the last decade, evaluating children and adolescents in the 2- to 18-year age bracket. With regard to study design, 15 (45.4%) were randomized clinical trials, 11 (33%) were cross-sectional studies, and 7 (21.2%) were longitudinal (cohort) studies. With regard to study site, 17 (48%) were conducted in Europe, 12 (36%) were conducted in North or South America, 4 (12%) were conducted in Asia, and 1 (3%) was conducted in Africa (Table 1).

Table 2 shows the weighted values for the 33 studies included in the systematic review. The studies collectively included a total of 4,101 participants (children/adolescents with asthma and their parents/caregivers) assessed for QoL by total PAQLQ and PACQLQ scores, respectively.[12,13]

Figure 2 shows a comparison of activity limitation domain scores between children/adolescents with asthma and their caregivers, by study design. A total of 8 cross-sectional studies collectively assessed 1,295 participants (caregivers/children), showing high heterogeneity (I^2 = 97%) and a total effect size with no significant difference in mean scores between the two groups (Z = 1.06; p = 0.290). A total of 6 longitudinal studies collectively assessed 661 participants, showing high heterogeneity (I^2 = 98%) and Z = 0.07 (p = 0.940). A total of 8 randomized clinical trials collectively assessed 840 participants, showing high heterogeneity (I^2 = 98%) and Z = 0.96 (p = 0.340).

These results were reflected in the total weighted mean, with no between-group differences in activity limitation domain scores among 2,796 participants and with high within-group heterogeneity (I^2 = 98%; p < 0.001), high but not significant between-group

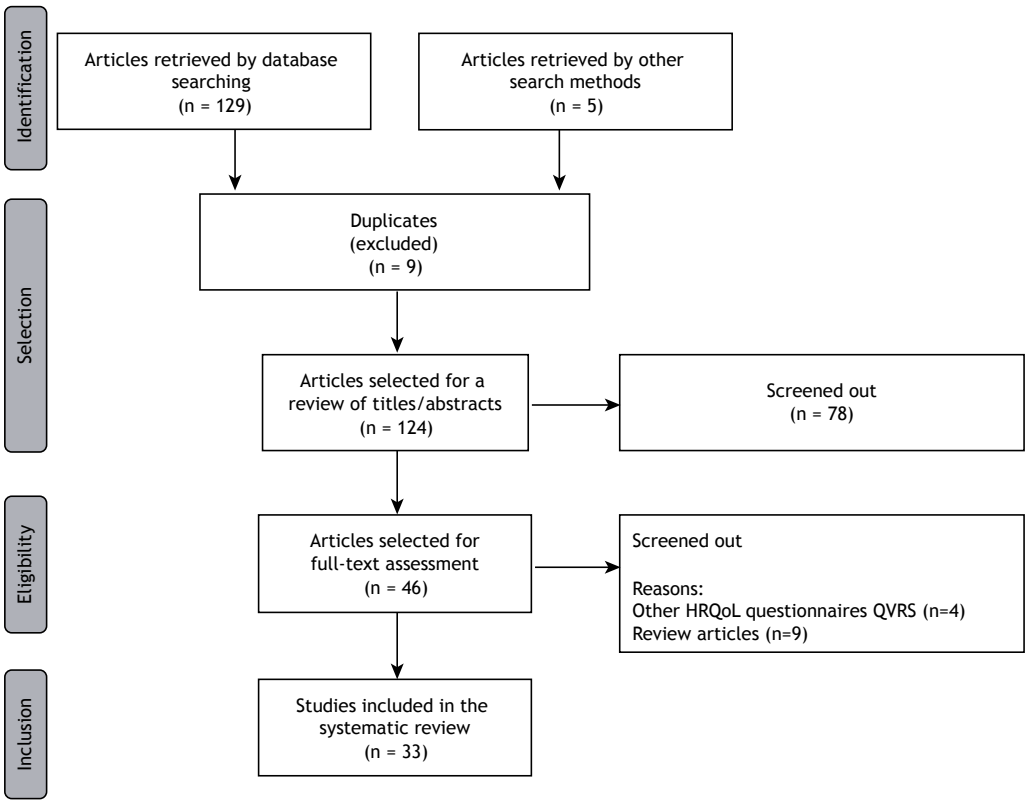

Figure 1. Flow chart of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria.[11] HRQoL: health-related quality of life.

Table 1. General characteristics of the included studies (N = 33), including the total number of participants (N = 4,101).

Author	Year	Country	Study design	Age of asthma patients, years	Study participants, n
Ahmed et al.[16]	2016	Nigeria	Longitudinal	7-17	43
Almomani et al.[17]	2017	Jordan	RCT	7-18	206
Ammari et al.[18]	2017	UK	RCT	7-17	76
Berger et al.[19]	2010	USA	RCT	6-11	186
Burks et al.[20]	2013	USA	Cross-sectional	5-17	79
Bushnell et al.[21]	2003	USA	Cross-sectional	7-17	104
Cano-Garcinuño et al.[22]	2007	Spain	RCT	9-13	245
Ducret et al.[23]	2013	Switzerland	Longitudinal	4-12	54
Erickson et al.[24]	2002	USA	Cross-sectional	9-17	99
Fleming et al.[25]	2015	UK	Longitudinal	6-17	271
Halterman et al.[26]	2011	USA	Longitudinal	12-15	30
Juniper et al.[27]	2010	Canada	Cross-sectional	6-16	35
Kamps et al.[28]	2003	The Netherlands	RCT	2-16	74
Lang et al.[29]	2015	USA	Longitudinal	10-17	56
Lenney et al.[30]	2013	UK	RCT	6-14	63
Liu et al.[31]	2016	China	RCT	9-13	72
Meza et al.[32]	2012	Colombia	Longitudinal	2-15	168
Minard et al.[33]	2011	Canada	Cross-sectional	7-17	63
Minard et al.[34]	2016	Canada	Cross-sectional	7-17	126
Moreira et al.[35]	2008	Portugal	RCT	8-17	34
Murray et al.[36]	2017	UK	RCT	3-17	284
Mussaffi et al.[37]	2007	Israel	RCT	7-17	115
Nair et al.[38]	2014	India	Longitudinal	7-17	69
Ovšonková et al.[39]	2012	Slovakia	Cross-sectional	7-17	72
Strunk et al.[40]	2008	USA	RCT	6-17	55
Szabó et al.[41]	2010	Hungary	Cross-sectional	7-17	102
Tibosch et al.[42]	2010	The Netherlands	Cross-sectional	6-16	339
van Bragt et al.[43]	2015	The Netherlands	RCT	6-11	29
van Gent et al.[44]	2007	The Netherlands	Cross-sectional	7-10	413
Voorend-van Bergen et al.[45]	2014	The Netherlands	RCT	4-18	197
Voorend-van Bergen et al.[46]	2015	The Netherlands	RCT	4-18	270
Williams et al.[47]	2003	UK	Cross-sectional	7-17	42
Yun et al.[48]	2012	USA	RCT	7-17	30

RCT: randomized controlled trial.

homogeneity (I^2 = 0%; p = 0.789), and a low total overall effect size (Z = 1.81; p = 0.070).

Figure 3 shows a comparison of emotional function domain scores between children/adolescents with asthma and their caregivers, by study design. A total of 8 cross-sectional studies collectively assessed 1,295 participants, showing high heterogeneity (I^2 = 82%; p < 0.001) and a low overall effect size (Z = 1.73; p = 0.080). A total of 5 longitudinal studies collectively assessed 390 subjects, showing high heterogeneity (I^2 = 93%; p < 0.001). However, there was a significant difference between children/adolescents with asthma and their caregivers regarding the weighted means (Δ = 0.82; 95% CI: 0.213-1.44), with a high overall effect size (Z = 2.61; p = 0.009). A total of 7 randomized clinical trials collectively assessed 806 participants, showing high heterogeneity (I^2 = 82%; p < 0.001), the significant difference between children/adolescents with asthma and their caregivers regarding the weighted means (Δ = 0.63; 95% CI: 0.36-0.90) being reflected in the overall effect size (Z = 4.49; p < 0.001).

The total weighted mean of emotional function domain scores showed that they were higher (better) among children/adolescents with asthma than among their caregivers. A total of 2,491 participants were assessed. Although heterogeneity was high (I^2 = 93%; p < 0.001), the total overall effect size was moderate (Z = 4.52; p < 0.001), with a statistically significant difference between the two groups (Δ = 0.52; 95% CI: 0.29-0.75). In addition, there was moderate between-group heterogeneity among study designs (I^2 = 73.4%; p < 0.05), with longitudinal studies showing the highest mean (Δ = 0.82; 95% CI: 0.21-1.44) and cross-sectional studies showing the lowest mean (Δ = −0.20; 95% CI: −0.03 to 0.43).

A comparison of the weighted means of total HRQoL scores between children/adolescents with asthma

Table 2. Weighted characteristics of the analyzed sample (N = 4,101).[a]

Characteristic	Result
Total sample[b]	4,101 (100.0)
Children/adolescents with asthma	
Male sex (n = 4,101)	2,495 (60.8)
Age, years (n = 3,660)	10.3 ± 4.0
White (n = 1,018)	699 (68.7)
Mild/moderate asthma (n = 1,149)	896 (78.0)
Pharmacological treatment (n = 2,549)	
MDI	1,240 (48.7)
SABA	814 (31.9)
LABA	495 (19.4)
Controlled asthma (n = 1,063)	576 (54.2)
ACQ (n = 585)	1.0 ± 0.8
C-ACT (n = 553)	21.4 ± 2.6
ACT (n = 1,000)	20.2 ± 2.8
Rhinitis (n = 422)	157 (37.2)
Atopia (n = 441)	307 (69.5)
Lung function	
FEV_1, % predicted (n = 2,303)	92.0 ± 14.6
FVC, % predicted (n = 1,427)	97.3 ± 13.8
FEV_1/FVC (n = 495)	0.8 ± 0.1
FeNO (n = 858)	31.4 ± 16.9
PAQLQ (children/adolescents)	
Activity limitation (n = 2,796)	5.1 ± 1.1
Symptoms (n = 2,618)	5.2 ± 1.1
Emotional function (n = 2,796)	5.6 ± 1.0
Total score (n = 4,101)	5.5 ± 1.0
PACQLQ (caregivers)	
Activity limitation (n = 2,491)	5.3 ± 1.2
Emotional function (n = 2,607)	5.1 ± 1.1
Total score (n = 4,101)	5.4 ± 1.0

MDI: metered dose inhaler; SABA: short-acting β_2 agonist; LABA: long-acting β_2 agonist; ACQ: Asthma Control Questionnaire; C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; FeNO: fractional exhaled nitric oxide; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; and PACQLQ: Pediatric Asthma Caregiver's Quality of Life Questionnaire. [a]Values expressed as n (%) or mean ± SD. [b]Total number of individuals assessed (children/adolescents + parents/caregivers).

and their caregivers (N = 4,101; Figure 4) showed high within-group heterogeneity by study design and a statistically insignificant total effect size, being reflected in the overall between-group heterogeneity (I^2 = 96%; Δ = 0.03 [95% CI: −0.10 to −0.17]), with a total overall effect size of Z = 0.49 (p = 0.620).

DISCUSSION

Asthma is a chronic noncommunicable disease with a high global burden, resulting in high rates of work/school absenteeism, as well as in increased emergency room visits and hospitalizations, primarily due to a lack of medical diagnosis and to government neglect of asthma management.[1]

In the last two decades, the assessment of HRQoL in children/adolescents with asthma and their families has gained a prominent role in the management (treatment and control) of asthma. Pharmacological treatment adherence and symptom control, as well as self-perceived physical, emotional, and social well-being among patients and their families, play a crucial role in effective disease management.[49]

In the present study, we conducted a meta-analysis of studies assessing total and individual domain scores on previously validated and widely used HRQoL questionnaires, performing an analysis stratified by study design. Longitudinal studies and randomized clinical trials showed that mean emotional function domain scores were significantly higher (better) among children/adolescents with asthma than among their caregivers, the difference between mean scores being greatest in longitudinal studies. Although there was no significant difference in mean emotional function domain scores across cross-sectional studies, the magnitude of the difference between the two groups remained the same in the overall analysis. These results corroborate the hypothesis that parents/caregivers are more emotionally affected by asthma than are their children, because parents/caregivers have concerns and responsibilities related to the health needs of their children. Self-perceived emotional functioning among parents/caregivers can vary depending on the age of the children, the negative impact of asthma on emotional function being greater on parents/caregivers of younger children.[41,50,51] With regard to activity limitation domain scores, no significant differences were found between children/adolescents with asthma and their caregivers. Previous studies[47,51] have shown that activity limitation assessment is affected by the fact that caregivers tend to assign lower activity limitation domain scores to asthma patients than do the patients themselves. With regard to total HRQoL scores, no significant differences were found between children/adolescents with asthma and their caregivers.

HRQoL questionnaires play an important role in assessing the health status of children and adolescents with asthma. However, the level of agreement between children/adolescents with asthma and their caregivers regarding HRQoL was found to range from low to moderate. Of the 33 studies included in the present review, 6 were aimed at correlating the QoL of children with that of their caregivers.[16,33,38,39,47,52] Nair et al.[38] correlated the QoL of children with asthma and that of their parents with asthma treatment. In 69 children in the 7- to 17-year age bracket, asthma treatment had no impact on the scores on the emotional function domain of the PAQLQ, and caregivers failed to understand the psychological effects of asthma on their children. In addition, asthma treatment had no impact on PACQLQ scores.

Minard et al.[33] studied 63 children in the 7- to 17-year age bracket, comparing the original versions of the PAQLQ and PACQLQ with their electronic

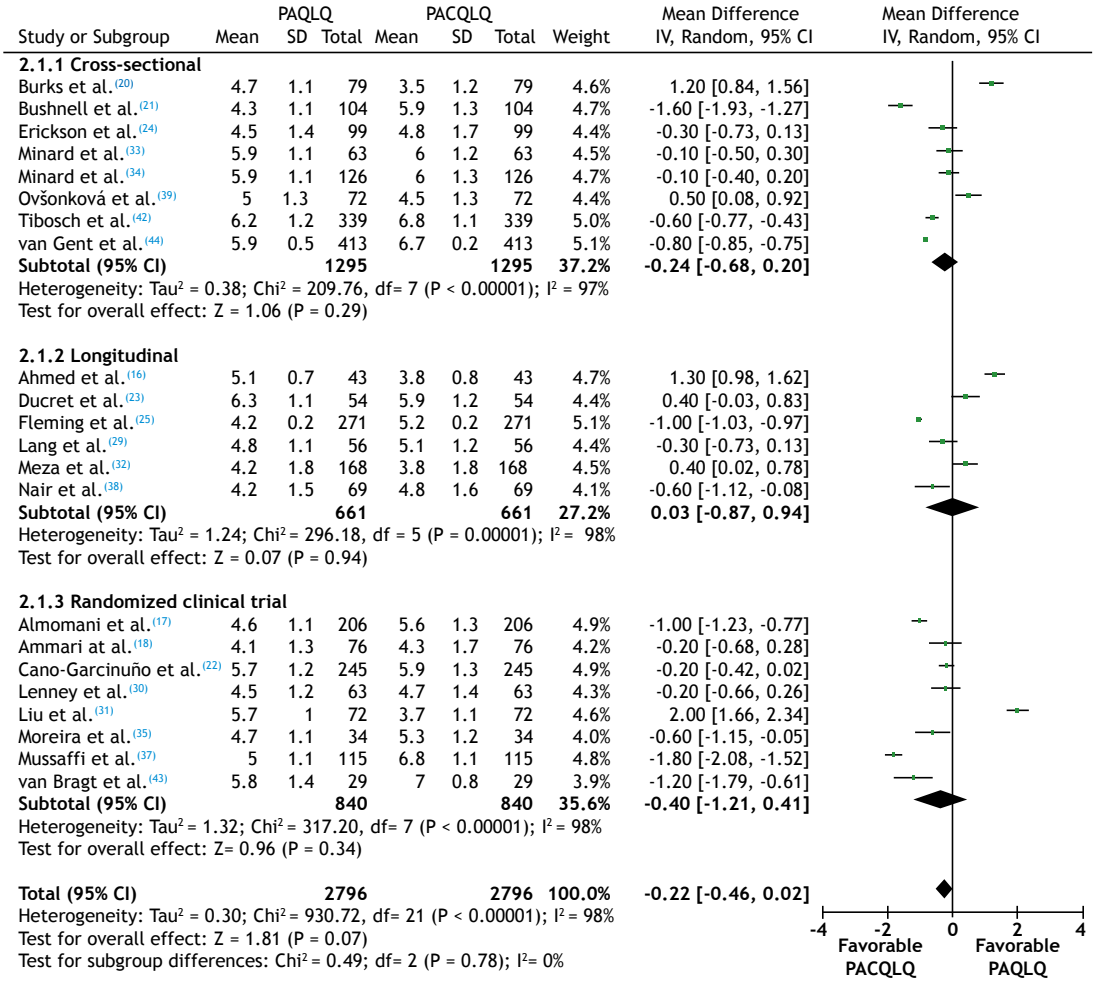

Figure 2. Comparison between mean Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) activity limitation domain scores.

versions and correlating PAQLQ scores with PACQLQ scores; the authors demonstrated the validity of the electronic versions of the questionnaires and the relationship between children/adolescents and their caregivers. In addition, they found no changes in activity limitations or symptoms.

Burks et al.[20] studied 79 patients in the 5- to 17-year age bracket and their caregivers, assessing the level of agreement between PAQLQ and PACQLQ scores. The scores were similar, with a moderate correlation between emotional function and overall QoL; however, children/adolescents had higher (better) activity limitation domain scores than those assigned by their caregivers (4.62 vs. 3.49; $p < 0.001$), a finding that suggests that QoL parameters should be assessed in both pediatric patients and their caregivers.

In a study involving 43 children/adolescents in the 7- to 16-year age bracket with varying levels of asthma severity,[16] activity limitation domain scores were found to be more severely affected in girls than in boys and in children/adolescents with severe/uncontrolled asthma than in those with less severe asthma. In addition, a significant positive correlation was found between total QoL scores and emotional function domain scores (4.98 vs. 4.86; $p = 0.015$). Williams & Williams[47] found a low correlation between the overall scores of children/adolescents and those of their caregivers ($r = 0.19$; $p = 0.18$), as well as no correlation between the QoL scores of the children/adolescents and the judgment of the clinician in charge regarding asthma control ($r = 0.02$; $p = 0.98$). The authors also found a low correlation between the activity limitation domain scores achieved by the children/adolescents and those assigned by their caregivers ($r = 0.01$; $p = 0.45$); the children/adolescents reported less limitation in activities than did their caregivers (4.8 vs. 4.1). Szabó et al.[41] reported that caregivers of children/adolescents with asthma have at least mild depressive symptoms and tend to have increased symptoms of anxiety.

The present meta-analysis showed high heterogeneity across studies in an analysis stratified by study design (within-group comparisons). Considerable variability was found across studies, as is often the case in

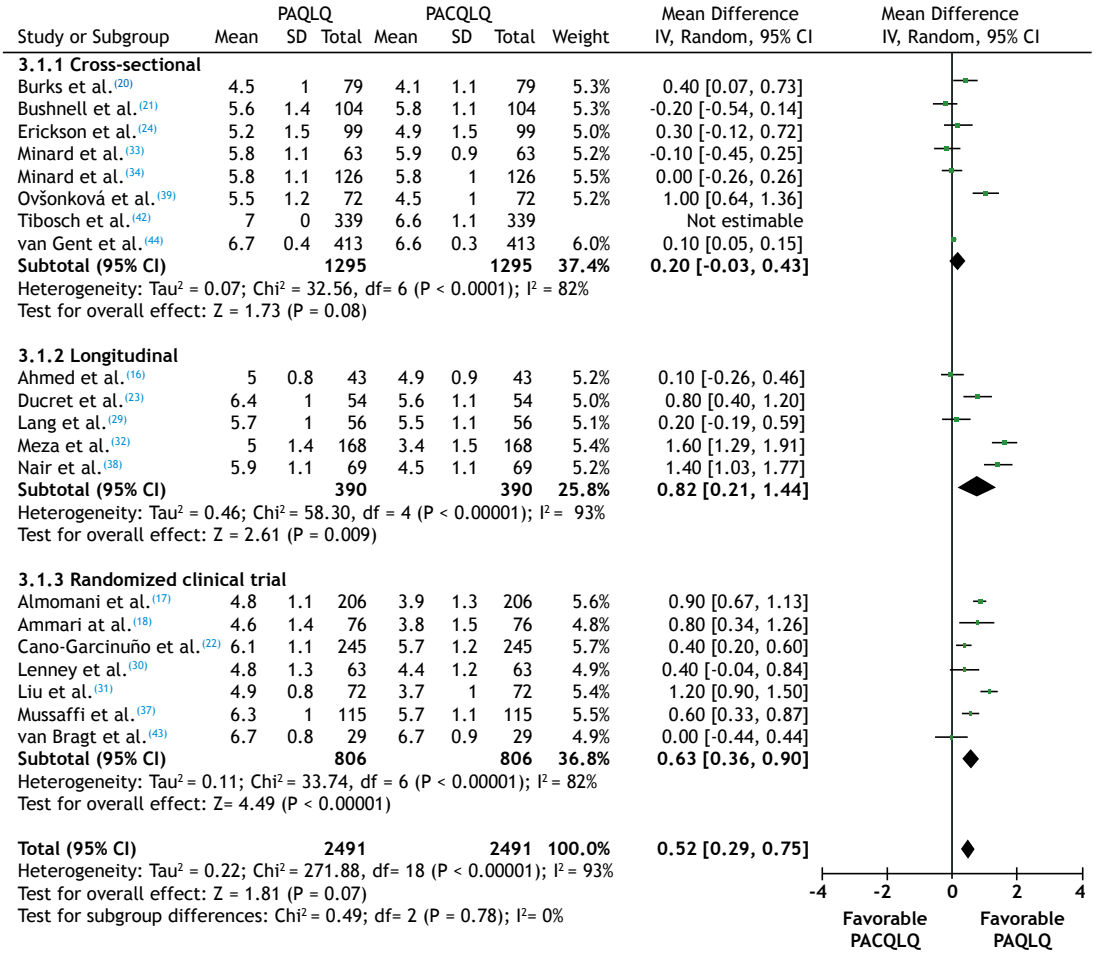

Figure 3. Comparison between mean Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) emotional function domain scores.

systematic reviews. Because asthma is multifactorial and the prevalence of asthma varies widely (2-33%), high heterogeneity is expected. In addition, factors such as study design, disease severity, geographic location, and socioeconomic status can increase heterogeneity.

Ovšonková et al.[39] showed that the level of asthma control has a statistically significant impact on the QoL of children/adolescents with asthma and on that of their caregivers, a better QoL in asthma patients translating to a better QoL in their caregivers. Voorend-van Bergen et al.[45] examined the validity of a Web-based diary in assessing asthma control in children/adolescents in the 4- to 18-year age bracket; for those under 12 years of age, the diary was completed by the caregivers. In that age group, the median PACQLQ score was 6.5, whereas, among adolescents, the mean PAQLQ score was slightly lower (6.2), PACQLQ and PAQLQ scores being significantly higher in children/adolescents with well-controlled asthma than in those with partly controlled or uncontrolled asthma ($p < 0.001$).[53]

Although every effort was made to minimize bias, the present study has some limitations. Because the results of the studies included in our meta-analysis were obtained by using subjective tools (HRQoL questionnaires), there is a possibility of recall bias. In addition, there is a possibility that patient age and level of education affected their understanding of the questions. Furthermore, there were differences across studies regarding the time elapsed between questionnaire administration and intervention implementation. Moreover, none of the included studies assessed the time spent by caregivers in the caregiving role; for example, children in whom symptoms are more severe tend to receive more attention and care from their caregivers.[37]

Our meta-analysis clearly showed that asthma can affect emotional function domain scores in patients and caregivers, the two groups differing in their perception of their emotional function. However, there were no differences between the two groups regarding activity limitation domain scores and total scores. Therefore, pediatric asthma patients and their families should be closely monitored, with special attention being given to the impact of asthma on their psychological and emotional functioning.

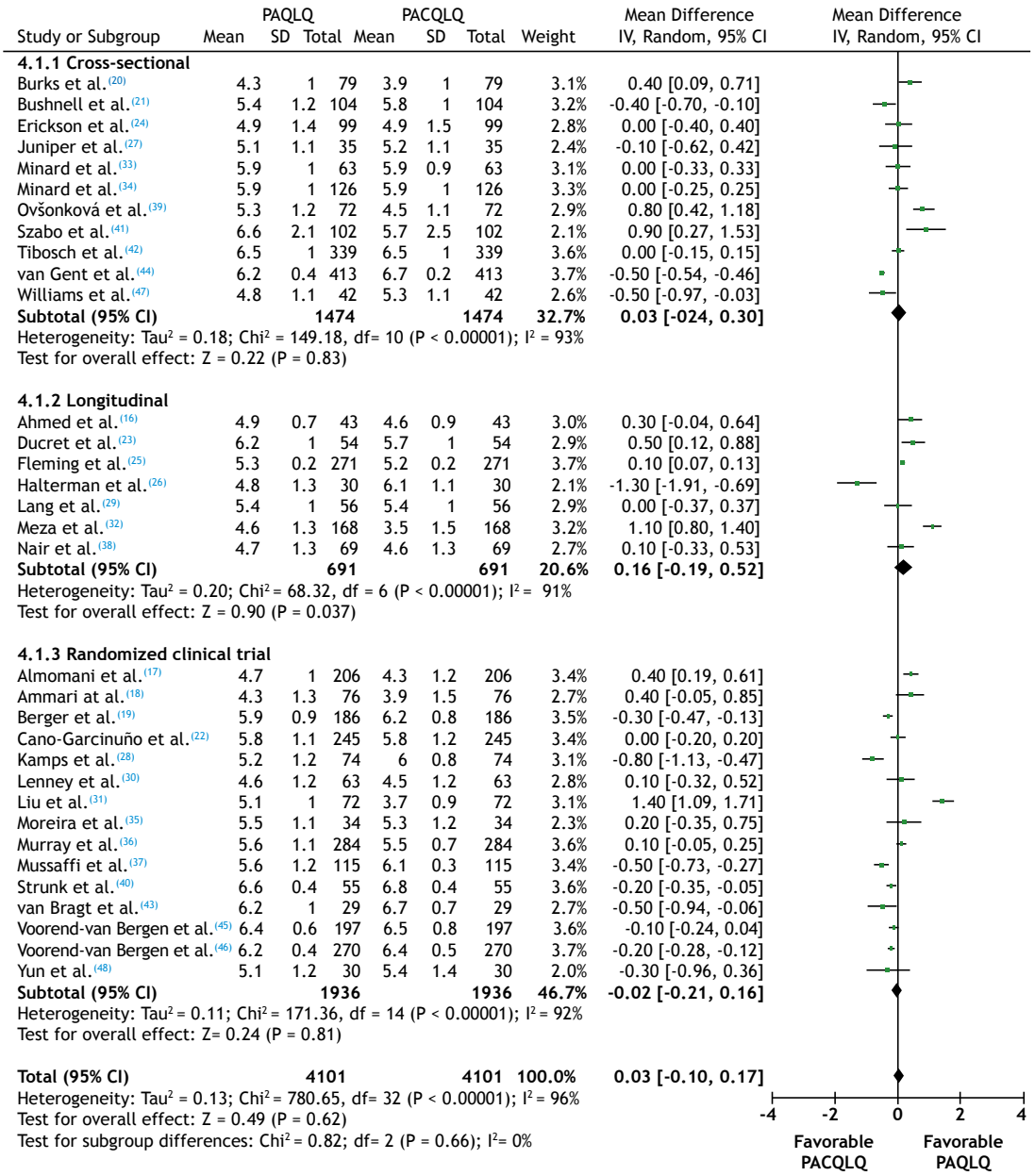

Figure 4. Comparison between mean total Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) scores.

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