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Quality of Life in Children with Functional Constipation: A Systematic Review and Meta-Analysis

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Objective To systematically review the literature on health-related quality of life (HRQoL) in children with functional constipation and to identify disease-related factors associated with HRQoL.

Study design The Pubmed, Embase, and PsycINFO database were searched. Studies were included if they prospectively assessed HRQoL in children with functional constipation according to the Rome criteria. Articles were excluded if patients had organic causes of constipation and if HRQoL was only assessed after successful therapeutic interventions. A meta-analysis was performed calculating sample size–weighted pooled mean and SD of HRQoL scores. The quality of the studies was also assessed.

Results A total of 20 of 2658 studies were included, providing HRQoL data for 2344 children. Quality of evidence was considered to be poor in 9 of the 20 studies (45%); 13 of the 20 studies reported sufficient data to be included in the meta-analysis. Pooled total HRQoL scores of children with functional constipation were found to be lower compared with healthy reference samples (65.6 vs 86.1; $P < .01$). Similar HRQoL scores were found according to self-report and parent proxy report. Hospital-based studies reported lower HRQoL scores as compared with community-based studies. Two studies reported on HRQoL scores of children with and without fecal incontinence, but no significant difference was found.

Conclusions HRQoL is compromised in children with functional constipation. *(J Pediatr 2019;214:141-50)*.

Childhood functional constipation is a major global health problem with a worldwide prevalence ranging from 0.5% to 32%.[1] The etiology of this disorder is multifactorial and the final common pathway of developing constipation is believed to be due to complex interactions between physiologic, psychological, social, cultural, and behavioral factors. Childhood constipation poses a significant effect on families in terms of worrying, social isolation, economic constraint, and burden on national healthcare systems.[2-4]

Health-related quality of life (HRQoL) is influenced by social, cultural, psychological, and disease-related factors.[5] The assessment of HRQoL can be valuable in monitoring the effects of a disorder such as functional constipation on a child's well-being and areas of dysfunction. Moreover, HRQoL has been recommended to be used as a secondary outcome in clinical trials for pediatric functional constipation.[6]

Two previous reviews have reported HRQoL in children with functional constipation.[7,8] Both reviews included few pediatric studies—3 and 7, respectively. The results of the included studies were based on patients attending tertiary care centers. Furthermore, owing to the limited number of studies and the heterogeneity of used instruments assessing HRQoL, both reviews did not attempt to perform a meta-analysis.

Therefore, we aimed to systematically review the literature on HRQoL and functional constipation in children, perform a meta-analysis of HRQoL domains across studies, and identify disease-related factors that potentially affect HRQoL in children with functional constipation.

Methods

For this systematic review, PubMed, EMBASE, and PsycINFO were searched up to July 2018. Medical Subject Headings, Emtree terms, and free text words related to children, functional constipation, and quality of life were used to search related literature. The full search strategy is listed in **Appendix 1** (available at www.jpeds.com). No language restrictions were applied. Reference lists of

HRQoL	Health-related quality of life
NOS	Newcastle Ottawa Scale
PedsQL	Pediatric Quality of Life Inventory

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relevant manuscripts were manually searched for additional studies. The guidelines of the PRISMA checklist were followed (**Appendix 2**; available at www.jpeds.com).

Articles were considered to be eligible for inclusion if they met the following criteria: (1) studies that prospectively assessed quality of life using a generic or disease specific questionnaire (2) in children 0-18 years of age (3) with a diagnosis of functional constipation according to the Rome II, III, or IV criteria and (4) were published in full manuscript form. Articles were excluded if patients with organic causes of constipation were included and if quality of life was only assessed after successful therapeutic interventions. Studies performed in different clinical settings were included (ie, community, primary care, and specialist care populations).

Two authors independently screened abstracts using the Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). After screening the abstracts, selected full-length articles were assessed for eligibility. In case of disagreement during the selection process, consensus was reached after consulting a third author. If the full text of a potentially eligible study was not available or if additional data were needed, the corresponding author was contacted by email.

Primary outcomes were the pooled HRQoL domain scores of children with functional constipation across studies. Secondary outcomes were the differences in HRQoL scores between self-report (child) and parent proxy report, between community- and hospital-based studies, between children with and without symptoms of fecal incontinence, and between studies from different geographical regions. Furthermore, we identified disease-related factors that potentially affect HRQoL of children with functional constipation.

Data Extraction

Data extracted from each manuscript included general study information (authors, publication year, country where the study was performed, study design), population characteristics (setting, sample size, symptoms, age and sex of included patients), criteria used for the diagnosis of functional constipation, instrument used to assess quality of life, and study results pertaining to HRQoL. Moreover, if factors associated with quality of life (eg, environmental, lifestyle, and psychosocial factors) were reported, these findings were evaluated as well.

Data Analyses

Mean and SD scores of the different instruments used to assess quality of life were extracted. A systematic review was carried out extracting predefined data from each paper. In addition, a meta-analysis of studies using the Pediatric Quality of Life Inventory (PedsQL) was performed by calculating the sample size–weighted pooled mean and pooled SD scores of the different HRQoL domains (ie, total, social, emotional, school, physical, psychosocial) with Microsoft Excel version 2016 (Microsoft Corp, Redmond, Washington).[9] Healthy reference scores of the PedsQL are available and the cutoff point for impaired HRQoL is considered 1 SD below this population mean (ie, total score of 69.7).[10,11] Total HRQoL scores of patients with functional constipation were compared with these healthy reference scores.

Statistical analysis was performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, California). For the calculation of the primary outcome (pooled total HRQoL scores), self-reported (child) scores were used in the statistical analysis for all studies reporting data on both self-reported and parent proxy-reported HRQoL. For the secondary outcomes, pooled HRQoL scores were calculated for the different domains of the PedsQL according to self-reported data and parent proxy-reported data. However, owing to methodologic reasons (ie, the small and unequal sample sizes of self-reported and parent proxy-reported data), we were unable to compare self-reported and parent proxy-reported scores statistically.

Moreover, total pooled HRQoL scores were compared between community- and hospital-based studies, between children with functional constipation with and without fecal incontinence, and between studies from different geographical regions with similar cultures (ie, Western countries, Middle Eastern and Asian countries). Unpaired *t* tests and 1-way ANOVA tests were performed to compare the weighted pooled mean and SD scores between groups. A *P* value of .05 was considered statistically significant.

Quality Assessment

Quality of evidence was assessed by 2 authors, using the Newcastle Ottawa Scale (NOS).[12] The NOS is a validated tool for assessing the quality of observational case-control and cohort studies.[13] Studies with a cross-sectional study design were evaluated with the modified NOS.[14] The NOS and modified NOS consist of 8 and 7 items, respectively, categorized into 3 categories, namely, the selection of study groups, comparability of study groups, and the outcome or exposure. Every category can be awarded with 1 or 2 stars, with a maximum of 9 stars per study. The more stars rewarded, the higher the quality of the article. Generally, studies with <5 stars are identified as being subject to a potential risk of bias.[15] After initial independent assessment all discrepancies were resolved by discussion. For the current systematic review, 1 adjustment was made to the NOS and modified NOS regarding the question on assessment of outcome; we assigned 1 star for self-reported or proxy-reported outcomes, because quality of life in children is subjective by definition and always assessed by either self-report or parent proxy report.[16] An overview of the NOS for case-control and cross-sectional studies is listed in **Appendix 3** (available at www.jpeds.com).

Results

A total of 2658 records were identified through the database search and manual search. After excluding 1912 records based on title and abstract, the full-text publications of 90 records were assessed for eligibility (**Appendix 4**; available at www.jpeds.com). Of these 90 records, a total of 20 studies

Table I. Description of included studies

Authors	Year	Study design	Population	Age, y	Sample size FC (n females)	Symptoms of FI, n (%)	Method of data collection	Instrument	Aim	Results
Studies including generic quality of life										
Clarke et al[17]	2008	Case control	Hospital setting (tertiary hospital)	8-18	n = 51 children (31 F)*	41 (80)	Child and parental questionnaire	PedsQL	Comparison with healthy controls (n = 79)	Child and parent reported QoL was significantly lower in children with slow-transit FC compared with healthy control children (total score, 72.90 vs 85.99; $P < .001$ self-report, and 64.43 vs 72.90; $P = .0034$ parent proxy report respectively).
Dolgun et al[18]	2013	Prospective cohort	Hospital sample (tertiary hospital)	2-18	n = 26 children and mothers (7 F)	13 (50)	Child and parental interview	PedsQL in Turkish	Follow-up 6 months	Self-report of children with FC showed that psychosocial health QoL scores improved significantly after 6 months of follow-up as compared with baseline (71.13 vs 80.90; $P = .008$).
Elkhayat et al[19]	2016	Case control	Hospital sample (tertiary hospital)	4-12	n = 50 children (25 F)	–	Child and parental interview	PedsQL in Arabic	Comparison with healthy controls (n = 50)	Total QoL scores children with FC were significantly lower as compared with healthy children (47.22 vs 79.76; $P = .000$ self- report and 43.78 vs 76.76; $P = .000$ parent-proxy report). All QoL domain scores were significantly lower in children with FC compared with healthy children as well.
Faleiros et al[20]	2006	Cross-sectional cohort	Hospital sample (tertiary hospital)	5-12	n = 57 children (32 F)	29 (52)	Parental questionnaire	CHQ-PF50	Comparison with other defecation disorders (n = 43)	Children with FC had significantly higher physical QoL scores as compared with children with functional nonretentive fecal incontinence (26.3 vs 9.4; $P < .05$).
Hartman et al[21]	2014	Cross-sectional cohort	Hospital sample (multicenter, secondary and tertiary hospitals)	2-18	n = 269 children (156 F)	58 (22)	Child and parental questionnaire	PedsQL	Comparison self-reported and parent-reported QoL	The psychosocial health and emotional functioning QoL scores were significantly lower as reported by the parents as compared with self-report (71.7 vs 74.0; $P < .05$ for psychosocial health and 65.9 vs 69.8; $P < .05$ for emotional functioning).
Karami et al[22]	2017	Case control	Hospital setting (tertiary hospital)	4-12	n = 104 children (53 F)†	–	Child and parental questionnaire	PedsQL	Comparison with healthy controls (n = 104)	QoL of children with FC was significantly lower as compared with healthy children (total score self-report: 54.04 vs 83.99; $P = .000$ and parent proxy report: 49.72 vs 79.94; $P = .000$).

(*continued*)

Table I. Continued

Authors	Year	Study design	Population	Age, y	Sample size FC (n females)	Symptoms of FI, n (%)	Method of data collection	Instrument	Aim	Results
Kilinçaslan et al[23]	2014	Cross-sectional cohort	Hospital sample (tertiary hospital)	2-6	n = 65 children (37 F)‡	9 (14)	Parental questionnaire	PedsQL in Turkish	Follow-up at 3 and 6 months	QoL scores of children with FC improved significantly at 6 months follow-up as compared with baseline (82.87 vs 74.24; $P < .001$). All QoL domain scores also improved significantly.
Kovacic et al[24]	2015	Prospective cohort	Hospital sample (5 tertiary hospitals)	2-18	n = 410 children (195 F)	226 (55)	Parental questionnaire	PedsQL	Comparison constipation alone (n = 184) and constipation plus FI (n = 226)	Children with constipation-associated FI had significantly lower QoL scores compared with children with FC without FI (total score 79 vs 84; $P < .03$).
Lewis et al[25]	2016	Cross-sectional cohort	Online panel	4-18	n = 122 mothers of children (52 F)	–	Parental questionnaire	PedsQL	Comparison with children without FGIDs (n = 730)	QoL of children with FC was significantly lower as compared with children without FGIDs (total score 76.3 vs 89.6; $P < .001$).
Olgaç et al[26]	2013	Case control	Hospital sample (tertiary hospital)	4-16	n = 53 children (34 F)	–	Child and parental questionnaire	KINDL	Comparison with healthy controls (n = 50)	QoL of children with FC was significantly lower as compared with healthy children (total score 64.7 vs 72.7; $P < .05$)
Rajindrajith et al[27]	2017	Cross-sectional cohort	School sample (4 schools)	13-18	n = 138 children (43 F)	11 (8)	Child questionnaire	PedsQL in Sinhalese	Comparison with IBS-C (n = 30)	No significant differences in QoL were found in children with FC as compared with children with IBS-C (total score 79.6. vs 81.0; $P = .65$).
Ranasinghe et al[28]	2017	Cross-sectional cohort	School sample (5 schools)	13-18	n = 114 children (62 F)	8 (7)	Child questionnaire	PedsQL in Sinhalese	Comparison with healthy controls (n = 1583)	QoL of children with FC was significantly lower as compared with healthy children. Children with constipation-associated FI had lower total and domain scores than those without fecal incontinence (total score 57.4 vs 71.5; $P = .006$).
Robin et al[29]	2018	Cross-sectional cohort	Online panel	2-18	n = 186 children (–)	–	Parental questionnaire	PedsQL	Comparison with healthy controls (n = 1069)	QoL of children with FC was impaired (total score 67.75)
van Tilburg et al[30]	2015	Cross-sectional cohort	Online panel	2-3	n = 17 (–)	–	Parental questionnaire	PedsQL	Comparison with healthy controls	QoL of children with FC was significantly lower as compared with healthy children (total score 77.17 vs 90.3; $P < .001$).
Varni et al[31]	2015	Case control	Hospital setting (9 tertiary hospitals)	2-18	n = 115 children (–)	–	Child and parental questionnaire	PedsQL	Comparison with healthy controls (n = 114)	QoL of children with FC was significantly lower as compared with healthy children (total score 71.1 vs 85.6; $P < .01$).

(*continued*)

Table I. Continued

Authors	Year	Study design	Population	Age, y	Sample size FC (n females)	Symptoms of FI, n (%)	Method of data collection	Instrument	Aim	Results
Wang et al[32]	2013	Case control	Hospital setting (2 tertiary hospitals)	3-6	n = 152 children (72 F)	–	Parental questionnaire	PedsQL in Chinese	Comparison with healthy controls (n = 176)	QoL of children with FC was significantly lower as compared with healthy children (total score 74.1 vs 92.1; $P < .05$). All QoL domain scores were significantly lower in children with FC compared with healthy children as well.
Youssef et al[33]	2005	Case control	Hospital setting (tertiary hospital)	5-18	n = 80 children (26 F)§	23 (29)	Child and parental questionnaire	PedsQL	Comparison with healthy controls (n = 46), GERD (n = 56) and IBD (n = 42)	QoL in children with FC was significantly lower as compared with IBD, GERD and healthy controls (total score 70.4 vs 83.8, 79.9 and 87.7, respectively; all $P < .05$). There was no difference in QoL between children with constipation with or without FI (total score 69 vs 74; $P > .05$).
Studies including disease-specific quality of life										
Bongers et al[34]	2009	Cross-sectional cohort	Hospital setting (tertiary hospital)	8-18	n = 114 children (36 F)	114 (100)	Child questionnaire	DDL	Descriptive	A higher frequency of FI episodes was found to be significantly associated with a lower emotional and social QoL in children with constipation-associated FI (correlation, −0.32 [$P = .001$] and correlation, −0.28 [$P = .002$], respectively).
Varni et al[35]	2017	Cross-sectional cohort	Hospital setting (9 tertiary hospitals)	5-18	n = 108 children (52 F)	–	Child questionnaire	PedsQL-GI symptom scale and PedsQL	Descriptive	All of the Gastrointestinal Symptoms Scales were significantly correlated with generic QoL for children with FC.
Varni II et al[36]	2015	Case control	Hospital setting (9 tertiary hospitals)	2-18	n = 116 children (–)	–	Child and parental questionnaire	PedsQL-GI symptom scale	Comparison with healthy controls (n = 283)	Children with FC reported significantly more symptoms and worry in comparison with healthy controls ($P = .0038$).

CHQ-PF50, Child Health Questionnaire-Parent Form 50; *DDL*, Defecation Disorder List; *F*, female; *FC*, functional constipation; *FGID*, functional gastrointestinal disorder; *FI*, fecal incontinence; *GERD*, gastrointestinal reflux disease; *IBD*, inflammatory bowel disease; *IBS-C*, irritable bowel syndrome with constipation; *KINDL*, the German Quality of Life Questionnaire; *n/a*, not applicable; *PedsQL-GI*, Pediatric Quality of Life Inventory Gastrointestinal Symptom Scale; *QoL*, quality of life.

*Modified FC criteria: all children had evidence for slow-transit constipation.

†Modified FC criteria: having >2 of the following symptoms for >2 months: defecation ≤2 week, incontinence >1 a week, avoiding defecation, history of painful defecation, fecal impaction.

‡Modified FC criteria: having >2 of the following symptoms for >2 months: frequency of bowel movements <3 per week, >1 episode of fecal incontinence per week, large stools in the rectum or palpable on abdominal examination, passing of stools so large that they may obstruct the toilet, display of retentive posturing and with-holding behaviors, painful defecation.

§Modified FC criteria: difficulty passing stools for >3 months and passage of <3 stools per week.

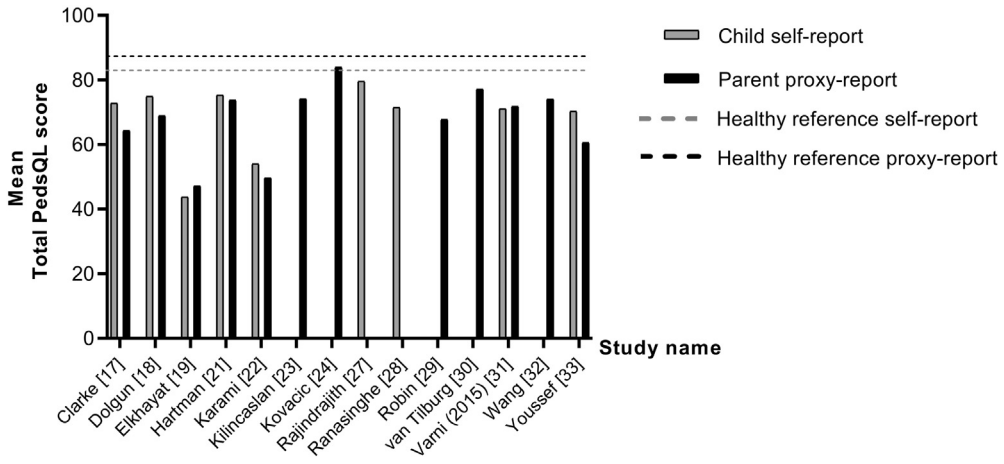

Figure 1. Overview of the mean total HRQoL scores per study.

were included in this systematic review, of which 13 studies were included in the meta-analysis.

The characteristics of the included studies are presented in Table I. Year of publication of the included studies ranged from 2005 to 2018. Most studies (n = 11) had a cross-sectional design, 7 studies had a case-control design, and 2 were prospective cohort studies. Most children were recruited from hospital-based samples (n = 15 [75%]) and 5 studies (25%) included children from community-based samples. Of these community-based studies, 2 recruited children from schools and 3 recruited children using an online panel. Most studies (n = 11) were conducted in Western countries, 5 studies were conducted in Middle Eastern countries, 3 in Asian countries, and 1 study was carried out in South America.

Patient Characteristics

All 19 studies described a total of 2344 children, with ages ranging from 2 to 18 years and sample sizes ranged from 17 to 410 children with functional constipation.[24,30] Sixteen studies described the sex of the children; 48% of children in these studies were girls.

The Pediatric Rome criteria were used to diagnose functional constipation in all included studies; 4 studies used the Rome II criteria, 15 used the Rome III criteria, and 1 study diagnosed children according to the Rome IV criteria. However, 4 studies used modified Rome criteria for the diagnosis of functional constipation (Table I).[17,22,23,33] A total of 10 studies described the proportion of patients suffering from fecal incontinence, ranging from 7% to 100% of children per study. Eight studies reported on the duration of symptoms of constipation, ranging from a mean of 5.7 months to 10.1 years.[17,32]

Table II. Pooled PedsQL domain scores: Difference between child self-report and parent proxy report

PedsQL subscales	No. of studies	Child self-report, pooled mean (SD)	Parent proxy report, pooled mean (SD)
Total score	6	64.95 (12.99)	62.03 (11.46)
Social score	4	67.71 (14.55)	66.21 (17.42)
Emotional score	4	65.83 (15.79)	56.71 (13.26)
School score	4	69.62 (5.97)	70.50 (4.56)
Physical score	5	72.25 (13.10)	68.46 (14.61)
Psychosocial score	3	71.34 (2.56)	70.65 (0.98)

Assessment of HRQoL

The assessment of HRQoL was performed with 5 different instruments. As shown in Table I, 16 studies used generic HRQoL instruments, including the PedsQL (n = 15), the Child Health Questionnaire-Parent Form 50 (n = 1), and the German Quality of Life Questionnaire (KINDer Lebensqualität [KINDL], n = 1).[17-33] Three studies used disease-specific questionnaires; the PedsQL Gastrointestinal Symptom Scale (n = 2) and the Defecation Disorder List (n = 1).[34-36] A detailed description of the different HRQoL instruments is included in Appendix 5 (available at www.jpeds.com).

HRQoL was assessed by both child self-report and parent proxy report in 9 studies (45%), only by the parent proxy report in 7 studies (35%), and only by self-report in 4 studies (20%).

HRQoL Scores

An overview of HRQoL scores of included studies is provided in Table I. Twelve studies (60%) compared HRQoL scores between children with functional constipation and healthy controls, and all found statistically significant lower HRQoL in children with functional constipation. Of these 12 studies, 11 used the PedsQL and 1 study used the KINDL questionnaire.[26] Three studies (15%) compared HRQoL of children with functional constipation vs children with other gastrointestinal disorders and reported

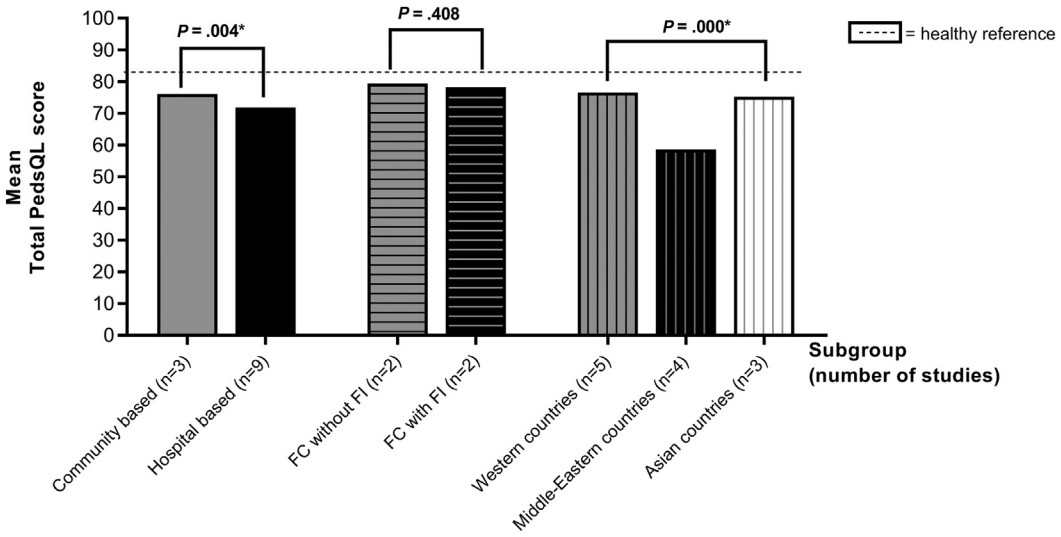

Figure 2. Subgroup analysis of the mean pooled total HRQoL scores. *Statistically significant. *FC*, functional constipation; *FI*, fecal incontinence.

significantly lower quality of life scores in children with functional constipation as compared with inflammatory bowel disease and gastroesophageal reflux disease, equal quality of life scores as compared with children with irritable bowel syndrome, and significantly higher quality of life scores as compared with children with functional nonretentive fecal incontinence.[20,27,33]

Pooled HRQoL Domain Scores

Fifteen studies used the PedsQL to assess the HRQoL and were potentially eligible to include in the meta-analysis. Mean total PedsQL scores of children with functional constipation were lower when compared with healthy reference scores as reported by previous studies[10,11] (**Figure 1**). Two studies were excluded from the meta-analysis because 1 study did not provide the mean HRQoL score and the other study did not provide the SD scores.[17,25] The remaining 13 studies were used to calculate sample size–weighted pooled mean HRQoL scores of children with functional constipation. The mean pooled total HRQoL score was 65.6, which was significantly lower compared with healthy reference populations of included studies (86.1; $P < .001$).

Pooled Subgroup HRQoL Scores

For the secondary outcome, we calculated the pooled mean HRQoL scores as reported by self-report and parent proxy report for every subdomain of the PedsQL (**Table II**). Six studies reported on both self-report and parent proxy report; in these studies the total HRQoL score was 64.95 as reported by children vs 62.03 as reported by parents.[18,19,21,22,31,33] The age of children who filled out the self-report questionnaires ranged from 4 to 18 years whereas parent proxy-reported scores were available for children with ages ranging from 2 to 18 years. However, owing to the limited number of studies and unequal numbers of patients with self-reported and parent proxy-reported data, we were unable to compare the groups statistically.

Moreover, the mean total HRQoL scores were compared between different subgroups (**Figure 2**). Children recruited from hospital based studies had significantly lower total HRQoL scores as compared with children recruited from community-based studies (71.9 vs 76.2; $P = .004$). Two studies reported on both children with and without fecal incontinence. No significant differences were found in total HRQoL scores between children with functional constipation with and without fecal incontinence.[24,28] Furthermore, a statistically significant difference was found between total HRQoL scores of children recruited from different geographical regions, with the lowest score in Middle Eastern countries (58.7 vs 76.6 in Western countries and 75.3 in Asian countries; $P = .000$).

Factors Associated with Quality of Life

In total, 7 studies described factors associated with quality of life. One study evaluated potential differences in HRQoL scores between boys and girls.[22] This case-control study including 51 boys and 53 girls with functional constipation found no significant differences in HRQoL scores.[22] Another study reported on the association with several psychological factors. This cohort study including 114 children with functional constipation reported psychological maladjustment to be correlated with lower HRQoL scores.[28]

Parental factors were reported to be associated with HRQoL scores in 3 studies. One study reported an association with psychological distress and found that lower psychological distress of the mother was associated with better emotional functioning of children with functional constipation.[23] A Chinese cohort study showed that the HRQoL of the caregiver was positively associated with the child's HRQoL.[32] Parental factors associated with lower HRQoL of children included a poor relationship between caregiver and child,

low level of education of parents, and low economic status of the family.[32] Higher parental stress and worse family dysfunction were reported in children with functional constipation and fecal incontinence as compared with functional constipation without fecal incontinence.[24] One study reported on the prevalence of functional gastrointestinal disorders among parents of included children, but found no difference in the parental prevalence rates between children with and without functional constipation.[29]

An association between the duration of symptoms and HRQoL was described in 1 study; a longer duration of constipation symptoms was associated with lower HRQoL of children with functional constipation.[32] Moreover, a study reporting on disease-specific HRQoL described that discomforting symptoms from both the upper and lower gastrointestinal tract (such as nausea, reflux, blood in stools) were negatively correlated with generic HRQoL.[35]

Two studies reported on the effect of treatment on HRQoL scores.[18,23] One study showed a significant increase of all but 1 of the PedsQL domains (ie, the school subscale) after 6 weeks of treatment with laxatives and education.[23] The other study found a significant increase of psychosocial well-being in children with functional constipation after 6 months of treatment with laxatives, dietary advice, and education.[18]

Quality Assessment

An overview of the quality assessment of the included studies is provided in **Appendix 6** (available at www.jpeds.com). The quality of all included studies was assessed using the NOS (n = 8) and modified NOS (n = 12). A total of 9 studies (45%) scored <5 stars, indicating a potential risk of bias.

Discussion

This systematic review and meta-analysis shows that HRQoL scores are lower in children with functional constipation as compared with healthy reference populations, underscoring the negative impact of constipation on quality of life of children. No differences were found between child self-report and parent proxy report of HRQoL. Interestingly, pooled HRQoL scores were found to be lower in hospital-based studies as compared with community-based studies and HRQoL scores differed significantly between children from different geographical regions.

There are several reasons for children with functional constipation to have a poor HRQoL. These children are suffering from a multitude of somatic symptoms that are negatively correlated with HRQoL.[37] Somatic symptoms can hamper children in their daily activities, such as school and social activities, which decreases their HRQoL. Moreover, symptoms of fecal incontinence are considered troublesome and distressing, and children often have to deal with feelings of shame, peer rejection, and bullying.[34,38,39] Although previous studies suggest that symptoms of fecal incontinence associated with constipation significantly decrease HRQoL as compared with children with constipation alone, this meta-analysis could not confirm this finding.[24,34] This difference could be explained by the limited number of studies in our meta-analysis investigating this issue, which does not enable us to draw firm conclusions.

Another possible explanation for the decreased quality of life scores in children with functional constipation might be the chronic nature of the condition. Studies report that 40% of patients with functional constipation are refractory to treatment after 6-12 months of follow-up and 25% of children remained to be symptomatic into adulthood.[40,41] It is generally known that chronic childhood disorders can have a significant impact on a child's (emotional) growth and development which could also potentially impair HRQoL.[42-48]

Psychological comorbidity could also play a role. Children with functional constipation are known to have a higher prevalence of negative personality traits and psychological maladjustment, resulting in a decreased HRQoL.[28] Indeed, a high prevalence of behavioral problems in children with functional constipation has been reported.[49] These behavioral challenges associated with constipation could not only affect the HRQoL of the child, but could also lead to problems in the child–parent interaction and high parental stress. Children often struggle with the motivation to take their daily medication, including oral laxatives and enemas, and have resistance to do their frequent toilet training exercises, resulting in potential conflict between children and their parents. Symptoms of fecal incontinence in particular, which are often associated with feelings of frustration toward the child, have a serious impact on the entire family.[24,50] However, the causality dilemma remains whether parental factors may lead to constipation and lower HRQoL in their children or vice versa.

Although we were not able to perform subgroup analyses to compare the pooled HRQoL scores between self-report and parent proxy report, pooled HRQoL scores were quite similar between children and parents, possibly indicating that both can be used in clinical and research settings. Traditionally, self-reported health information of children has not always been considered reliable, owing to children's insufficient linguistic and cognitive abilities to understand and respond to rating scales of relatively lengthy questionnaires.[51] However, parents could have a different perception of the impact of the disease on the lives of their children, and often struggle with other aspects of the condition, such as the future of their child and social or educational consequences. To support this finding, previous studies have shown that parents of children with chronic health problems often perceive the HRQoL of their children as lower than reported by themselves.[52,53] Therefore, over recent years, several HRQoL instruments have developed modified versions for children, adapted and validated for different age levels as young as 5 years.[52,54] In contrast, children with constipation often show some degree of denial of their frustrating symptoms and could therefore overrate their HRQoL. Therefore, to gain a complete overview of the impact of the disease on quality of life, the combination of both self-reported data and proxy-reported data are recommended to measure

HRQoL.[52] This information is particularly important when evaluating younger children with functional constipation. Large cohort studies comparing the agreement between self-report and proxy-reported HRQoL are needed to confirm our results.

Our subgroup analysis shows that significantly lower HRQoL scores were reported in children recruited from hospital-based studies, possibly explained by the fact that children from hospital-based studies might have had a longer and more severe disease course, negatively affecting their HRQoL. We also found differences in HRQoL of children with functional constipation between different continents, with the lowest scores reported in the Middle East and higher scores in Western countries. However, it is important to note that all of the studies conducted in Middle Eastern countries included children from hospital-based settings, possibly contributing to a lower HRQoL. Because the PedsQL is a generic rather than a disease-specific HRQoL instrument, these differences could also potentially be explained by general quality of life aspects such as living conditions, socioeconomic factors, and public health systems in different parts of the world. In addition, this finding may also reflect differences in cultural perceptions of the disorder or in the management options available in different countries.

This systematic review and meta-analysis have several strengths. We have pooled the HRQoL data from 2344 children and illustrated the effects of functional constipation on HRQoL of children, providing a broader perspective in understanding HRQoL of children with functional constipation. By including studies using a validated tool to assess quality of life and the standardized pediatric Rome criteria to diagnose constipation, we have attempted to create a homogeneous population of children in our meta-analysis. However, several limitations should be taken into account. We included case-control and cross-sectional cohort studies with small sample sizes and poor quality assessment ratings. In addition, the number of studies included in the meta-analysis was limited because we had to exclude 7 studies; this factor could have affected our results. Finally, most studies refrained from providing data on possible psychological and behavioral comorbidity of children, factors that potentially influence the HRQoL scores. Limited data were available on the somatic and psychological comorbidity of parents and siblings, and these are factors that could potentially have an effect on the HRQoL of included children.

This systematic review and meta-analysis reveal the low HRQoL in children with functional constipation, showing lower pooled HRQoL scores compared with healthy references samples. We therefore recommend the use of HRQoL instruments (generic or disease specific) in both research and clinical settings to assess the efficacy of treatments and follow-up. This finding is supported by the Core Outcome Set for children with functional constipation, in which quality of life of both children and parents are recommended as important endpoints of clinical trials after structured survey of healthcare professionals, parents, and children.[55] The Rome foundation used this Core Outcome Set to establish recommendations for pharmacologic trials and advised to include quality of life as an important secondary outcome measure in future research.[6] We also identified modifiable risk factors, such as parental distress and duration of symptoms that may affect HRQoL of children with functional constipation. ■

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