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REVIEW

Health-related quality of life among children, adolescents, and adults with bladder exstrophy–epispadias complex: a systematic review of the literature and recommendations for future research

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Abstract

Purpose Bladder exstrophy–epispadias complex (BEEC) is a rare spectrum of genitourinary malformations. Children risk long-term urinary and genital dysfunctions. To achieve a comprehensive understanding, this study aimed to review the literature on generic and disease-specific health-related quality of life (HRQOL) in BEEC patients, and methodologies used.

Methods A literature search was conducted in Pubmed/CINAHL/Embase/PsycINFO/Cochrane, from inception to May 2018. A meta-analysis of HRQOL in BEEC patients compared to healthy references was performed.

Results Twenty-one articles (published 1994–2018), describing HRQOL of children and adolescents ($n=5$) and adults only ($n=5$), or integrated age populations ($n=11$), were identified (median sample size 24, loss to follow-up 43%, response rate 84%). Overall HRQOL was reduced in BEEC patients compared to healthy references in 4/4 studies. Impaired physical or general health in BEEC patients has been described in 9 articles, diminished mental health in 11, restricted social health in 10, and sexual health/functioning or body perception impairments in 13 articles. Urinary incontinence was the most common factor related to worse HRQOL (12 studies). In six studies, HRQOL was better than healthy norms. In eligible studies ($n=5$), the pooled estimate of the effect of BEEC indicated worse HRQOL for children and adults ($0>$ effect sizes <0.5). Thirty-six HRQOL assessments were used, none developed and validated for BEEC.

Conclusions HRQOL in BEEC patients may be negatively impacted, particularly considering mental and social HRQOL. Sexual health/functioning or body perception impairments may be present in adolescents and adults. However, HRQOL is heterogeneously assessed and subsequent findings are differently reported. Additional research is warranted and can be improved.

Keywords Bladder exstrophy · Epispadia · Bladder exstrophy–epispadias complex · Malformation · Health-related quality of life · Patient-reported outcome

Abbreviations

BE	Bladder exstrophy is a congenital malformation with a closing defect of the lower part of the abdominal wall. When the child is born, the bony pelvis is open in the front; the bladder and urethra are open and exposed on the outside of the abdomen; the belly button low; and genital malformations are present (see epispadias)
BEEC	Bladder exstrophy–epispadias complex refers to a spectrum of birth defects including epispadias (mildest form), bladder exstrophy (intermediate form), and cloacal exstrophy (severest form), which involves malformations of the urinary tract, intestinal tract, genital tract, musculoskeletal system, and sometimes the spinal cord

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BNR	Bladder neck repair refers to different reconstructive procedures/methods of the bladder neck in order to improve urinary continence by increasing the outlet resistance
CIC	Clean intermittent catheterization is a method to empty the bladder of urine by passing a thin, plastic tube through the urethra or a catheterizable stoma intermittently under clean but not sterile conditions
CE	Cloacal exstrophy is an abdominal defect with the urinary bladder and parts of the intestines exposed externally on the abdomen. The bony pelvis is open. Imperforate anus is common. Spinal defects may also be present. In males, the penis is short, split or even missing. In females, the clitoris is split and there may be duplication anomalies of the internal genitalia.
E	Epispadias, isolated or in combination with bladder exstrophy, is a closing defect of urethra. In boys, the urethra is opened like a plate on the dorsal side of the penis. The penis is most often short and broad, and curved dorsally. In girls, the urethra opens between a bifid, split clitoris. The vaginal opening may be narrow and ventrally displaced
ES	Effect size
HRQOL	Health-related quality of life
KS	Kidney stones
SDQ	Strength and Difficulties Questionnaire
UD	Urinary diversion encompasses surgical procedures which reroute and drain urine flow from its normal pathway. It may include detaching the ureters and connecting them to an intestinal segment creating a stoma on the abdominal surface. The patient will wear an ostomy bag into which the urine drains continuously (non-continent urinary diversion). It can also refer to an internal reservoir with a bowel segment, together with the residual bladder or not, to store urine between intermittent catheterizations through a continent stoma (continent urinary diversion)

Introduction

Bladder exstrophy–epispadias complex (BEEC) refers to a rare spectrum of genitourinary malformations ranging in severity from epispadias (E, incidence 2.4 in 100,000 births), the mildest form, to bladder exstrophy (BE, incidence 1–2 in 50,000 births) and cloacal exstrophy (CE, incidence 05–1:200,000), the severest form [1]. Boys are more commonly affected, girls:boys 1:2 [1, 2]. BE is a closing defect of the lower part of the abdominal wall characterized by an open bladder exposed on the outside of the abdomen, and a ventrally open bony pelvis. BE includes E, a closing defect of urethra. E also appears as isolated forms in males and females. CE generally involves BE, omphalocele, imperforate anus, and spinal defects. BEEC patients undergo a series of operations during childhood, starting in infancy. The primary goals of surgery are urinary continence with preserved renal function, as well as cosmetically and functionally acceptable abdomen and genitalia [1, 3]. Today, there are many surgical approaches of BE. Complete primary repair of exstrophy comprises one correction of the bladder and urethra. A modern staged repair divides the bladder closure, E repair, and bladder neck reconstruction (BNR) into three surgical interventions in boys and two in girls [1, 3, 4]. An adjunctive osteotomy and closure of the symphysis can be used, which may decrease failure of abdominal wall and bladder closure [5]. Urinary diversion (UD) encompasses surgical procedures which reroute and drain urine flow from its normal pathway, and can be used as primary or secondary treatment [1].

Although neonatal and surgical care of BEEC patients has advanced [2, 6], urinary incontinence is reported in 10–81% of patients, independent from reconstruction method, definition of continence, or time to follow-up [7–15]. In the achievement of continence, additional bladder surgery is needed in 21–79% of the cases [9, 10, 13–15] and 13–64% require clean intermittent catheterization (CIC) for bladder emptying [7, 10–12]. Scarring due to multiple surgeries may harm BEEC patients' body perception [16]. This, and genital appearance/function may disturb their romantic relationships [16–18] and sexual health in adolescence and adulthood [18–21].

This study aimed to review the literature on health-related quality of life (HRQOL) among BEEC patients across all ages and to describe questionnaires that have been used. This is essential in order to understand BEEC individuals' subjective experience of health and well-being, and strengths and weaknesses of the applied methodologies. This can have important implications for clinical practice, health care policy, and for research [22–25], and permit recommendations to be made for future research.

Materials and methods

Descriptive definitions and criteria

This study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [26]. HRQOL was defined as the individuals' subjective perception of the impact of disease and treatment on physical, psychological, and social functioning, and well-being [27],

including proxy-reported HRQOL [28]. The questionnaires used in HRQOL evaluations were appraised for adherence to desirable attributes delineated by the Scientific Advisory Committee of the Medical Outcomes Trust [29]. Psychometric properties of the questionnaires were categorized [30] according to a predefined protocol (Table 1).

Search strategy and data selection

HRQOL articles of BE, E, and/or CE patients in English language were identified via the databases Pubmed, Cochrane, Embase, CINAHL and PsycINFO, from inception up to May 14, 2018, without limitations to publication year or accessibility to full-texts. A combination of keywords and database-specific terms/search strings was used such as "patient-reported outcome," "quality of life," "health-related quality of life," "psychosocial functioning" in combination with "bladder exstrophy," "epispadia," "cloaca," or "bladder exstrophy–epispadias complex." The article selection is outlined in Fig. 1. All authors independently reviewed titles and abstracts. Articles were autonomously read by the first (MDB) and last author (GH). Peer-reviewed articles in English or free instrument manuals of HRQOL questionnaires were found via the beforehand mentioned databases or the questionnaire's home page. Two authors (MDB, SSJ) evaluated information focusing on questionnaire development and field testing. If discrepancies in the instrument evaluation were found, a consensus discussion occurred among all authors.

Meta-analysis

A meta-analysis of HRQOL scores (overall/physical/mental/social HRQOL) in BEEC patients compared to healthy references was conducted. The effect sizes (ESs) were calculated as Cohen's d and Cohen's criteria were used for a standardized interpretation, ESs > 0.2 small, > 0.5 moderate, and > 0.8 large [31]. I^2 statistics was calculated to assess heterogeneity [32]. Significant level was $p < 0.05$.

Results

Articles reporting HRQOL among individuals with BEEC

Twenty-one articles were identified (published 1994–2018). Five articles (24%) described HRQOL among children and adolescents only [33–37], five articles (24%) HRQOL among adults only [38–42], and eleven articles (52%) included HRQOL reports of children and/or adolescents with adults [17, 43–52]. Sixteen European and four multi-center studies [39, 42, 46, 47], one of which was international [46], were found. Four studies lacked comparison of the patients' HRQOL with external references [38, 45, 46, 52]. Table 2 provides article information.

Four studies of HRQOL in children with BE [37], BEEC [33–35], or children with CE [36] reported on 8–69 families (lost to follow-up 17–50%, response rates 79–100%). Except in CE children who were reared as females, male distribution varied between 40 and 69%. In the integrated age population studies, six articles described HRQOL in BE patients [17, 43, 47, 48, 51, 52], four BEEC patients [44–46, 50], and one study in females with isolated E [49]. Samples varied from nine to 122 patients (lost to follow-up 6–72%, response rates 53–100%). Except in two studies of females [49, 51], 50–71% of the affected patients were males. Of five studies including 17–25 adults ≥ 18 years (lost to follow-up 42–56%, response rates 29–100%), two focused on BE/BEEC females [40, 41] and one of BEEC males [42]. In the remaining studies, 64–71% were BE/BEEC males [39, 41]. Online resource 1 details clinical traits of the samples. Surgical characteristics were heterogeneously and occasionally sparsely described, and urinary incontinence diversely defined. Accordingly, 33–67% of children, 29–67% of integrated age populations, and 16–74% of adults were urinary incontinent. Catheterization was used by 53–58% of children, 4–56% of integrated age populations, and 20–95% of adults (Online Resource 1).

Thirty-six assessments were used to obtain HRQOL data. Six were self-developed questionnaires used in five studies [38, 39, 45, 46, 50], four were interviews [17, 37, 43, 44], and four instruments used in five studies [17, 40, 42, 47, 49] were not available in peer-reviewed journals and/or free manuals. The remaining 22 questionnaires included seven generic HRQOL questionnaires [53–70], eleven measurements of psychological/mental health [16, 71–91], and four of sexual health/functioning [92–95]. Their measurement characteristics are detailed in Online Resource 2, and psychometric standards in Online Resource 3.

Meta-analysis

Due to the lack of reports of statistical and/or a healthy reference data, 5/21 studies could be included in the meta-analysis. Figure 2a–f shows forest plots of self-reports of BE/BEEC patients compared to healthy references. Table 3 details the data.

Overall HRQOL

Two studies showed impaired HRQOL in CE children [36] and BEEC children [35] compared to healthy norms (child- and parent report), but higher HRQOL compared to children with other diseases [35, 36]. In CE children, overall HRQOL

Table 1 Attributes for reviewing health status and quality-of-life instruments according to the Scientific Advisory Committee of the Medical Outcomes Trust [29] and attribute content reported in the article

Attribute	Definition	Information reported or categorization of the fulfillment of attribute criteria			
		+	?	−	0
Conceptual and measurement model	Description and a rationale of the concept and the populations that a measure is intended to assess, and the relationship between these concepts	We reported the target population and the concept that the measurement intended to assess			
Reliability	The degree to which an instrument is free from random error				
Internal consistency	The precision of a scale, based on the homogeneity (inter-correlations) of the scale's items at one point in time typically using the Cronbach's alpha coefficient	Cronbach's alpha(s) calculated per dimension AND Cronbach's alpha(s) between 0.70 and 0.95	Doubtful design or method	Cronbach's alpha(s) < 0.70 or > 0.95, despite adequate design and method	No information found on internal consistency
Reproducibility	The level to which the questionnaire score remains stable over time among respondents assumed not to have changed scores, or inter-rater reliability (agreement among two or more observers) at one point in time	Minimal standards are 0.70 for group comparisons and 0.90–0.95 for individual comparisons, intraclass correlation coefficients, or weighted Kappa > 0.70	Doubtful design or method	Intraclass correlation coefficient or weighted Kappa < 0.70, despite adequate design and method	No information found on reproducibility reliability
Validity	The degree to which the instrument measures what it purports to measure				
Content validity	Evidence that the instrument was appropriately relative to its intended use. Content validity entails evaluation of the clarity, comprehensiveness, redundancy of items and scales of an instrument, most commonly using an expert panel (health care professionals), proxy (parents), or patients themselves	A clear description is provided of the measurement aim, the target population, the concepts that are being measured, and the item selection must involve the target population. Item selection can also involve investigators or experts	Doubtful design or method	No target population involvement	No information found on content validity

Table 1 (continued)

Attribute	Definition	Information reported or categorization of the fulfillment of attribute criteria			
		+	?	−	0
Construct validity	Evidence that supports a proposed interpretation of scores based on theoretical implications associated with the constructs being measured. Methods used to evaluate construct validity include checking dimensionality, homogeneity and overlapping between variables, logical interactions with other measures or patterns of scores for groups known to differ (known-groups validity)	Specific hypotheses were formulated AND strongly support the results	Doubtful design or method (e.g., no hypotheses)	Weak confirmation of hypotheses, despite adequate design and methods	No information found on construct validity
Criterion validity	Defined as the extent to which scores of the instrument are related to a criterion providing an indication of the true value for the measurement, such as another validated instrument	Convincing arguments for the external criterion and a strong relationship between the external criterion and the scores of the instrument (e.g., correlation > 0.70)	Doubtful design or method	Weak relationship with the criterion, despite adequate design and method	No information found on criterion validity
Responsiveness	The ability of the instrument to detect change over time was proved (sometimes referred to as "sensitivity to change")	Evidence that the instrument can detect change in a relevant population in accordance with the conceptual aim of the instrument	Doubtful design or method	Failed evidence that the instrument can detect change in a relevant population in accordance with the conceptual aim of the instrument	No information found on responsiveness
Interpretability	The degree to which one can understand meaning of the questionnaire scores by information such as a qualitative category or other external measure with familiar meaning	Mean and SD scores of relevant subgroups of patients, and/or strategies to handle missing items are defined and/or further instructions on how to score the instrument	Doubtful design or method	Lack of necessary definitions	No information found on interpretability
Burden	The time, effort, and other demands placed on those to whom the instrument is administered (respondent burden) or on those who administer the instrument (administrative burden)	We reported the most available information of respondent and administrative burden			

Table 1 (continued)

Attribute	Definition	Information reported or categorization of the fulfillment of attribute criteria			
		+	?	–	0
Alternative modes of administration	Evidence on reliability, validity, responsiveness, interpretability, and burden for each mode of administration. Mode of administration, includes, for example, self-report, interviewer-administered, trained observer rating, computer-assisted performance-based measures	We reported if there was more than one mode of administration that were correctly evaluated			
Cultural and language adaptations or translations	An assessment of conceptual and linguistic equivalence and evaluation of measurement properties in another culture/language	We reported if this had been conducted with a minimum of one other culture/language			

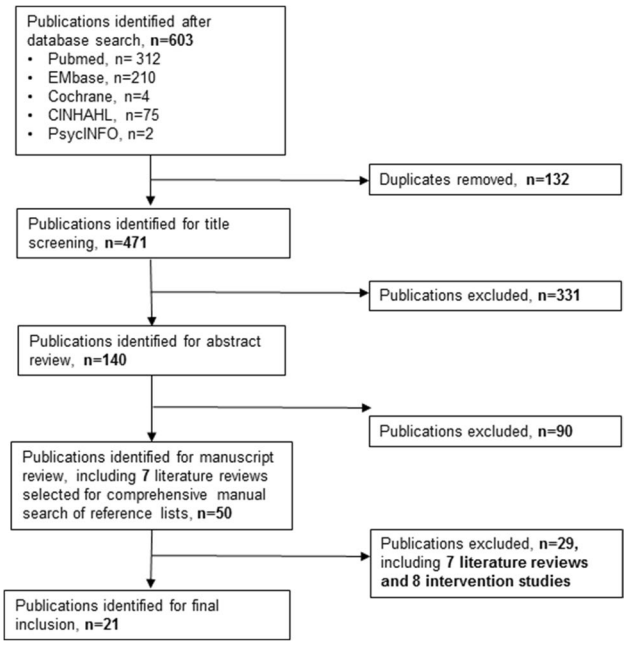

Fig. 1 PRISMA flowchart describing identification, criteria, and selection of studies. Criteria for article selection: articles reporting cross-sectional or longitudinal empirical studies of the multidimentional concept health-related quality of life of people with bladder exstrophy, epispadias and/or cloacal exstrophy in peer-reviewed English publications

did not correlate with the number of surgical procedures or hospital admissions [36].

In the combined age population studies, overall HRQOL scores were lower in BE children and adolescents [47] and BE females, mean 32 years [51], compared to general populations. However, 8–17-year-old BE patients had better overall HRQOL compared to children with kidney stones (KS). Ebert et al. [45] described 65% of 6–28-year-old BEEC patients "rarely to always" experience HRQOL impairments in daily life. Feitz et al. [43] described 14% of 17–55-year-old BE patients to believe their HRQOL was negatively affected. BE children had better overall HRQOL compared to adolescents [47], and patients with isolated E compared to those with BE [35]. BEEC patients' impairments were due to urinary incontinence, voiding problems, inability to participate in group sports, and reluctance to shower in group [45]. Urinary incontinence had a low impact on HRQOL in females with isolated E [49], low-moderate impact in 30% of BEEC females [40], but impacted HRQOL in 38% of adult male and female BE patients [41].

No studies of adults only, described generic overall HRQOL.

Table 2 Characteristics of health-related quality-of-life studies in patients with a condition of the bladder exstrophy–epispadias complex in order of publication year and age of the study population

Study (reference)	Publication year	Objective of the study	Population diagnosis, age, and male distribution	Country	Health-related quality-of-life assessment and additional measures	Lost to follow-up and response rates (number, %)	Sample size	External control/reference group	Location for data collection
Children and adolescents									
Stjernqvist et al. [37]	1999	To describe the impact of bladder exstrophy on the behavior, self-esteem and quality of life of children as well as on the parents, and analyze the need for psychological intervention	BE Median age 11 years (3–18) 7 (47%) males	Sweden	• Semi-structured Höök–Cederblad interview • Child Behavior Check List questionnaire • I Think I Am questionnaire • The Multi-attribute Health Status Mark II classification system • Parental interview	No patients lost to follow-up reported 100% response rate	15	Yes, but no statistical evaluation performed	Hospital
Baker et al. [36]	2003	To investigate social cognition, behavior and competence, psychological and behavioral problems, and perceived quality of life in children with cloacal exstrophy and compare them with children with cloacal anomalies	CE with gender ambiguity Mean 11.6 years (5–18) 1 XX chromosome child reared as female, 1 XY chromosome child reared as male, 6 XY chromosome children reared as females	United Kingdom	• Child health-related quality of life • Child Behavior Checklist • Social Cognition Questionnaire	50% ($n=8$) excluded: five children refused, three were currently undergoing psychiatric treatment 100% response rate	8	Yes, use of normative data and comparison with 12 age-matched children diagnosed with cloacal anomalies who were born with no genital ambiguity	NR
Dodson et al. [33]	2010	To study parent-reported HRQOL for adolescents with bladder exstrophy epispadia	BEEC Median age 14 years (11–18) 38(69%) males	USA	• Child Health Questionnaire-Parent form	18% patients lost to follow-up Of 84 eligible patients, 69 completed the consent form Response rate 80%	55	Yes with normative reference values	Clinic or completed at home
Schaeffer et al. [34]	2012	To determine HRQOL as reported by adolescents with bladder exstrophy or epispadias	BEEC Mean 14 years (11–18) 38(67%) males	USA	• Child Health Questionnaire-Child form-87	17% patients lost to follow-up 72 of 87 eligible patients completed consent forms Response rate 79%	57	Yes normative references values	Clinic or at home
Hurrel et al. [35]	2015	To screen pediatric bladder exstrophy–epispadia complex patients for a range of general psychosocial difficulties in a multidisciplinary outpatient clinic setting	BEEC Mean 8.41 years (1–18) 50 (63%) males	United Kingdom	• PedsQL 4.0 generic score scales • PedsQL 4.0 Family Impact Module • Strengths and Difficulties Questionnaire • Pediatric Index and Emotional Distress • Hospital Anxiety and Depression Scale	26% patients lost to follow-up, 28 patients Response rate: parent report 90% Child report 87%	69 parents, 54 children	Yes normative reference values	Questionnaires were completed at clinic prior to psychology consultation

Table 2 (continued)

Study (reference)	Publication year	Objective of the study	Population diagnosis, age, and male distribution	Country	Health-related quality-of-life assessment and additional measures	Lost to follow-up and response rates (number, %)	Sample size	External control/reference group	Location for data collection
Children, adolescents, and adults									
Feitz et al. [43]	1994	To investigate the long-term psychosexual and socioeconomic development of patients born with bladder exstrophy	BE Male: mean age 29 years (17–55) Female: mean age 32 years (20–51) 11 (50%) males	The Netherlands	• Standardized personal interview (1 h) with an investigator • Symptom Check List-90	No patients lost to follow-up reported 100% response rate	22	Yes, reference values as normative data, but no statistically significant analyses performed	Hospital
Diseth et al. [44]	1998	To report somatic outcome, mental health and psychosocial adjustment in adolescents with bladder exstrophy and epispadias, and assessed parental experiences	BEEC Median age 14.5 years (11–20) 17 (77%)	Norway	• VAS to assess satisfaction with genital appraisal • Interview regarding experiences with erection, ejaculation, masturbation, intercourse, and thoughts of establishing a close sexual relationship, family and having children in the future, psychiatric and psychosocial assessments • Child Assessment Schedule • Child Behavior Checklist • Children's Global Assessment Scale • Parental Account of Children's (maternal warmth and criticism towards the index child) • A global assessment of chronic family difficulties • Parent interviews with questions regarding emotional and practical aspects of treatment procedures and medical follow-up	7% patients lost to follow-up Of 29 patients, 2 with severe associated anomalies (anorectal anomalies and multiple handicaps) were excluded from the study and another had emigrated 85% response rate	22	Yes, normative reference values	Not reported
Wilson et al. [17]	2004	To determine the factors that control quality of life as perceived by adolescent patients with bladder exstrophy, and to compare their views using standard instruments	BE Mean age 19 years (16–21) 11 (69%) males	United Kingdom	• Semi-structured interview (60–90 min) was designed to explore each participant's experiences phenomenological analysis • Culture Free Self-Esteem Inventory-2 • The Brief Symptom Inventory	71% patients lost to follow-up: 20 patients lived too far away to attend for interview, had been transferred to other units, or were lost to follow-up of any other reason 18 of remaining 24 patients (75%) agreed to participate 89% response rate	16	Yes, normative reference values	NR

Table 2 (continued)

Study (reference)	Publication year	Objective of the study	Population diagnosis, age, and male distribution	Country	Health-related quality-of-life assessment and additional measures	Lost to follow-up and response rates (number, %)	Sample size	External control/reference group	Location for data collection
Ebert et al. [45]	2005	To report the psychosocial and psychosexual development of children and adolescents with the exstrophy–epispadias complex after complete functional repair using the Erlangen single-stage technique	BEEC Average age of 14.6 years (6–28) In the psychosexual development paper males had a mean age of 18.2 years (15–27) and 9 were female with mean age 19.4 years (15–28) Male distribution NR for study sample	Germany	• 1 Self-designed questionnaire about their individual urological, social and psychosocial situation, including health status, urinary continence, clean intermittent catheterization, urinary tract infections, number of hospitalizations and procedures, planned operations, current medication and allergies, as well as school and job, sports and hobbies, peer relations, self-esteem, and coping strategies • 1 Self-designed questionnaire concerning sexual history	No patients lost to follow-up out reported 81% response rate to the general questionnaire, 76% psychosexual development	100 medical records, 81 patients regarding general questionnaire, 41 adolescents regarding psychosexual development	No control group or normative references used	
Lee et al. [46]	2005	To identify problems in the long-term psychosocial and developmental outcome specific to patients with the bladder exstrophy–epispadias complex	BEEC Age group 0–4 years: 43 patients (35.2) 5–13 years: 47 patients (38.5) 14–20 years: 17 patients (13.9) > 20 years: 15 patients (12.3) 75 (61%) males	Germany	• Self-developed semi-structured questionnaire on functional and psychosocial developmental outcome and quality of life with bladder exstrophy–epispadias complex	No patients lost to follow-up reported: 208 contacted patients 59% response rate	122	No control group or normative references used	Mail
Jochault-Ritz et al. [47]	2010	To report characteristics of bladder exstrophy reconstruction and compare HRQOL between different age groups, children vs adolescents and adolescents vs adults	BE Adults mean 26.3 years Adolescents mean 15.3 years Children mean 7.7 (overall range 8–47) 23 (63.9%) adult males 9 (50%)adolescent males 9 (52.9%) children with male gender	France	• SF-36 (adults and adolescents) • VSP-A & VSP-AE (adolescents and children) • AUQUIE (6–12 years old)	47% patients lost to follow-up: 134 eligible patients Response rate not reported/not applicable	71 patients: 36 adults 18 adolescents 17 children	Yes normative reference values	Postal questionnaires/mailed

Table 2 (continued)

Study (reference)	Publication year	Objective of the study	Population diagnosis, age, and male distribution	Country	Health-related quality-of-life assessment and additional measures	Lost to follow-up and response rates (number, %)	Sample size	External control/reference group	Location for data collection
Pennison et al. [48]	2014	To compare HRQOL in patients with bladder exstrophy to that in patients with kidney stones, and correlate body image to HRQOL	BE 8–25 years 17(71%) males	USA	• PedsQL 4.0 generic score scales • Urological Body Image Questionnaire	72% patients lost to follow-up: of 83 patients 10 due to limited English, 4 due to other medical conditions, 33 couldn't be contacted, 9 patients refused participation (two patients died, not included in calculations of patients lost to follow-up) 96% response rate	24	Patients with kidney stone ($n=24$) and healthy norms/reference values	Telephone except two collections on email
Amesty et al. [49]	2015	To evaluate the results of female epispadias treatment in terms of continence, sexuality, and HRQOL	Isolated epispadias Mean 20.3 years (range 5–39) No males	Spain	• SF-36 • International Consultation on Incontinence Questionnaire • Potenziani-14-IO-QOL-2000	2% patients lost to follow-up 56% response rate (5/9 patients responded to the HRQOL questionnaires)	9	Yes, normative reference values	Telephone/Postal questionnaires
Taskinen et al. [50]	2015	To evaluate HRQOL and mental health aspects of adult patients with bladder exstrophy–epispadia, using validated questionnaires and compare results with national reference population To evaluate if bladder augmentation and clean intermittent catheterization program produced better outcomes, than accepting minor incontinence	BEEC Median 27 years (15–52) 22 (69%) males	Finland	• SF-RAND-36 scores • Symptom Checklist 90 • Satisfaction with appearance of genitals (developed by authors)	1 address was not found and was lost to follow-up: (4 patients died, not included in the analysis) 62 patients received the questionnaires 53% response rate	33	Yes, normative reference values	Postal questionnaires/Mailed

Table 2 (continued)

Study (reference)	Publication year	Objective of the study	Population diagnosis, age, and male distribution	Country	Health-related quality-of-life assessment and additional measures	Lost to follow-up and response rates (number, %)	Sample size	External control/reference group	Location for data collection
Deans et al. [51]	2015	To investigate sexual function and HRQOL in adolescent and adult women with classic bladder exstrophy	BE Mean 32 years (17–46) No males	Australia	• EuroQOL-5D questionnaire • Female Sexual Function Index • Vaginal perception questionnaire	16% patients lost to follow-up: of 52 females patients, 2 patients moved abroad, 5 patients had been lost to follow-up, 8 patients died (not included in lost to follow-up calculations) 44 received the questionnaires 64% response rate 57% (25 responded to the HRQOL questionnaire)	28	Yes, normative reference values	NR
da Cruz et al. [52]	2016	To study the long-term outcome of patients with BE regarding quality of life comparing males and females	BE Mean 22.35 years (15–48) 29 (67%) males	Brazil	• SF-36	55% patients lost to follow-up: of 96 patients, 51 were successfully contacted 43 agreed to participate in the study 100% response rate	43	No control group or normative reference values used	Outclinic visit
Adults									
Catti et al. [38]	2005	To analyze the impact of bladder and cloacal exstrophy and reconstructive surgery on the HRQOL of adult women over 18 years	BEEC Median 26.5 years (19–41) of the eligible patients (not study sample) No males	France	• Questionnaire developed by gynecologist, child psychiatrist, and pediatric urologist	No patients lost to follow-up: all 23 patients received questionnaires 74% response rate	17	No control or reference group used, and no statistically significant comparison analysis performed	Postal questionnaires/Mailed
Wittmeyer et al. [39]	2010	To evaluate HRQOL in adults with bladder exstrophy–epispadia complex to improve patient and parent counseling	BEEC Mean 30.5 years (19.5–49.5) 16 (64%) males	France	• SF-36 • Local questionnaire evaluating functional and social aspects	44% patients lost to follow-up: of 47 patients, 3 patients declined 2 did not return, 15 couldn't be contacted (2 patients died, was not included in this analysis) 88% response rate	25	Yes, normative reference values	Postal questionnaires/Mailed

Table 2 (continued)

Study (reference)	Publication year	Objective of the study	Population diagnosis, age, and male distribution	Country	Health-related quality-of-life assessment and additional measures	Lost to follow-up and response rates (number, %)	Sample size	External control/reference group	Location for data collection
Gupta et al. [41]	2013	To examine long-term quality of life, urinary continence, and sexual function outcomes in patients diagnosed with bladder	BE 27–37 years in the eligible number of patients (not study sample) 15 (71%) males	United Kingdom	• SF-36 • The International Consultation on Incontinence Questionnaire • The International Index of Erectile Function questionnaire	No patients lost to follow-up reported 29–32% response rate (depending on questionnaire)	21	Reference group used, but no statistically significant analysis presented	Home/Postal
Bujons et al. [40]	2016	To evaluate the HRQOL of adult females with bladder exstrophy–epispadia complex, including urinary incontinence, sexual function, and general health	BEEC Mean 26 years (18–50) No males	Spain	• SF-36 • Pelvic Organ Prolapse/Urinary Incontinence • Sexual Questionnaire, PISQ-12 • International Consultation on Incontinence Modular Questionnaire, ICIQ-SF • POTENZIANI-14	42% patients lost to follow-up: of 33 eligible patients, 19 agreed to participate 100% response rate	19	Yes, normative reference values	Email
Traceviciute et al. [42]	2018	To investigate sexual function and quality of life in adult male individuals with exstrophy–epispadias complex	BEEC Median 26 years (22–38) 100% males	Germany	• The International Index of Erectile Function questionnaire • The Cologne Assessment of Erectile Dysfunction • SF-36 • A self-designed semi-structured questionnaire	56% patients lost to follow-up: 29 patients did not sign the informed consent ($n=1$), cloacal exstrophy ($n=1$) Response rate 19/20 95%	19	Yes reference population of normative values used	Home

AUQUIE AUto-QUestionnaire Imagé de l'Enfant for children, *BE* bladder exstrophy, *BEEC* bladder exstrophy–epispadias complex, *CE* cloacal exstrophy, *HRQOL* health-related quality of life, *NR* not reported, *SF 36* short-form survey 36, *VSP-A* Vécu et Santé Perçue de l'Adolescent, *VSP-AE* Vécu et Santé Perçue de l'Enfant

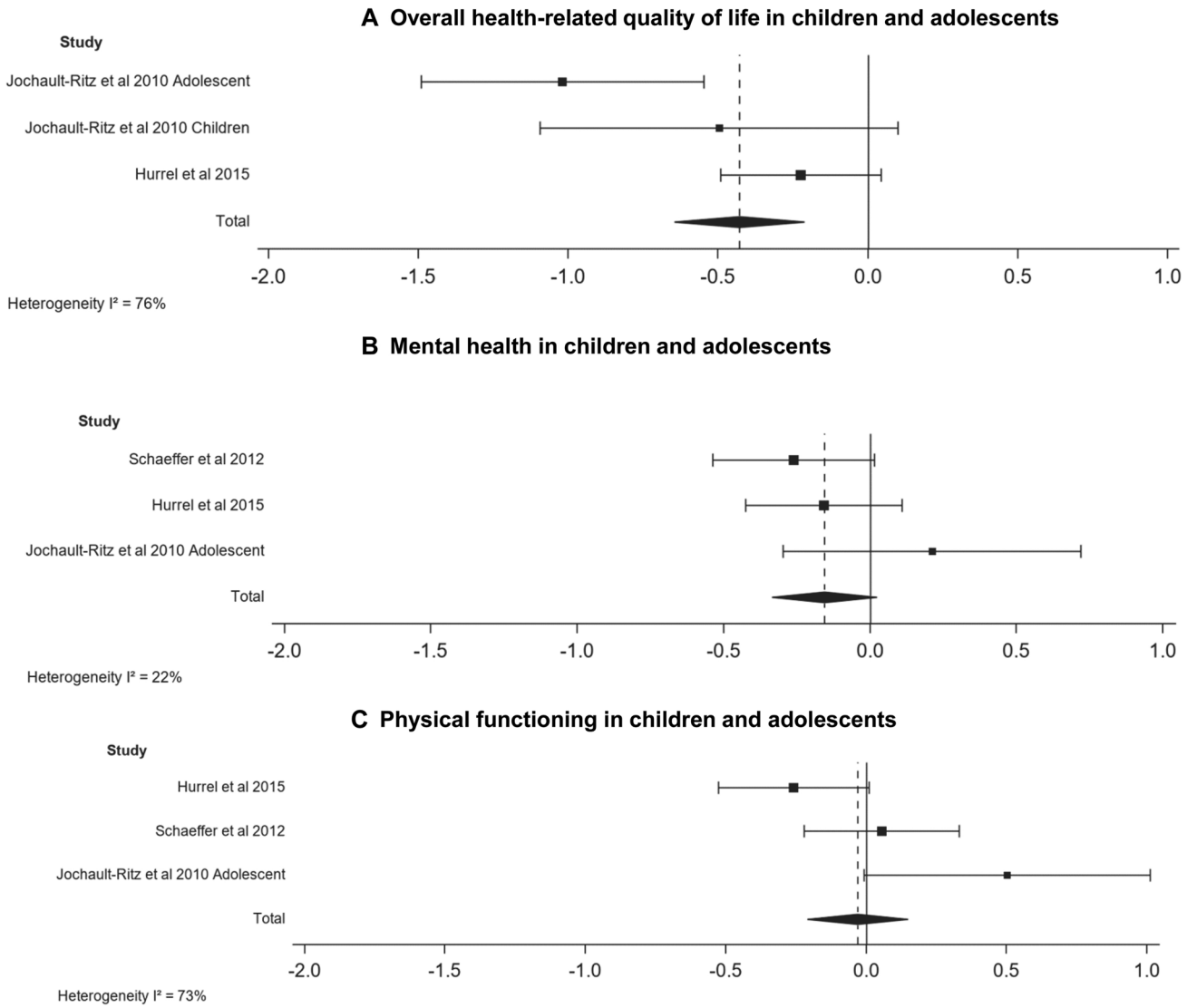

Fig. 2 Forest plots of the child or adult self-reports from patients with a condition within the bladder exstrophy–epispadias complex compared to healthy references; **a** overall HRQOL in children and adolescents, **b** mental health in children and adolescents, and **c** physical functioning in children and adolescents, **d** mental health in adults, **e** physical functioning in adults, **f** social functioning in adults. The pooled estimate of the effect of a condition within the bladder exstrophy–epispadias complex indicates worse health-related quality of life, effect sizes small or less than small using Cohen's criteria for interpretation with ES > 0.2 small, > 0.5 moderate, and > 0.8 large

Physical and general health

Three studies [33, 34, 37] described worse general health and one study worse physical functioning [35] in BE/BEEC children compared to healthy norms. In one study [34], physical HRQOL was better compared to children with KS. Children with isolated E had improved physical outcomes compared to BE children [35]. Urinary incontinence was associated with worse general health and bodily pain in BEEC patients [34] in child report, but not parent report [33].

In integrated age population studies, BE patients scored lower on physical health dimensions compared to general norms [47]. In other studies, patients with isolated E [49] and BE [51] had similar scores on physical health [49], mobility or pain [51], and young BE cohorts [47, 48] and male BEEC patients [50] had better physical health/functioning. In one study [43], 41% of BE individuals played sports, 14% of whom experienced physical problems. In 54% of BE patients who were not exercising physically, it was due to handicap. In another study [45], only 5% of BEEC patients following failed reconstruction believed they had poor health. In one [50] of the two studies [50, 52] BE/BEEC females had worse physical functioning, general

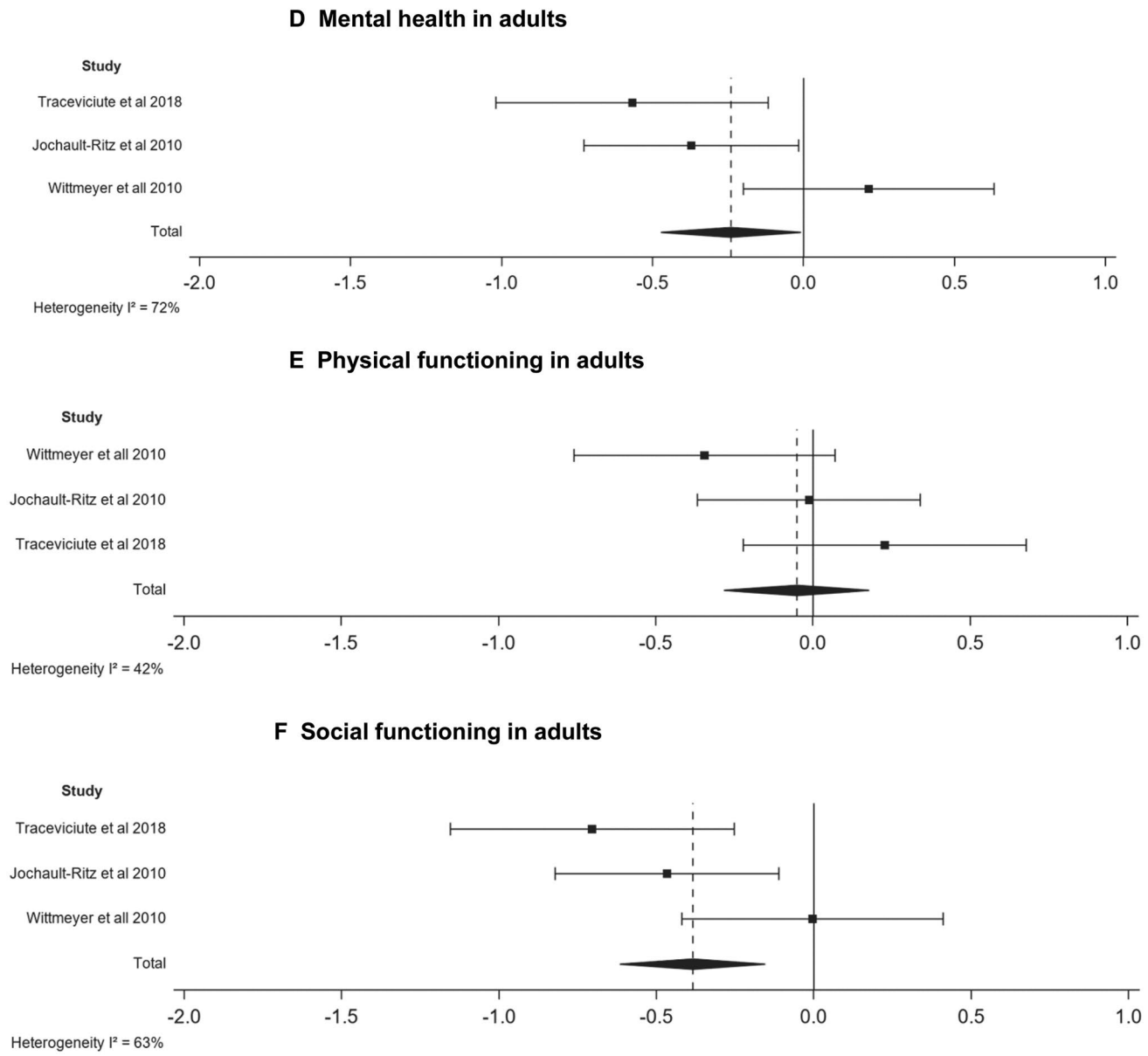

Fig. 2 (continued)

health, and bodily pain compared to males. Worse general health was associated with use of diapers in BEEC individuals, but not to the number of anesthesias [50]. Better physical functioning was found in BE adolescents compared to adults [47].

BE/BEEC adults had worse general health compared to healthy norms [39, 41], and their physical functioning was impaired in two studies [39, 40], not affected in one study [42], and better in another study [41]. In one study [39], 64% of BEEC adults complained of urinary infections, genital prolapse, and fatigability. In BEEC adults, physical functioning was better in reconstructed patients with urinary voiding vs those with CIC, and UD was associated to less activity limitations [39]. In BEEC patients [42], male dissatisfaction with genital appearance was related to worse physical and general health, medication intake with worse physical health and energy/fatigue, but no associations were found regarding reconstruction method, smoking, or alcohol consumption.

Mental health, psychological, and psychosocial functioning

In two studies, BE/BEEC children had worse scores of mental health [34], psychosocial health [35], and emotional functioning [35] compared to healthy references. Behavior problems were present in 27% of BE children. From school

Table 3 Presentation of findings in self-reported health-related quality of life among patients with bladder exstrophy–epispadias complex compared to healthy norms in studies eligible for the meta-analysis

Study (reference)	HRQOL in patients with a BEEC condition			HRQOL in healthy references			Cohens' d (95% CI)	*p* value	Weight (%)
	N	Mean	SD	*N*	Mean	SD			
Children and adolescents_overall HRQOL									
Jochault-Ritz et al. [47], children	11	61.10	10.30	664	67.50	12.90	−0.50 (−1.09; 0.10)	0.10	13.2
Jochault-Ritz et al. [47], adolescents	18	54.40	10.70	664	67.50	12.90	−1.02 (−1.50; −0.55)	<0.0001	21.2
Hurrel et al. [35]	54	80.98	18.84	5480	83.84	12.65	−0.22 (−0.49;0.04)	0.10	65.6
Children and adolescents_mental HRQOL									
Schaeffer et al. [34]	57	74.80	13.28	444	78.20	13.00	−0.26 (−0.54;0.02)	0.064	42.4
Hurrel et al. [35]	54	79.63	19.14	5480	81.87	14.09	−0.16 (−0.43; 0.11)	0.25	45.1
Jochault-Ritz et al. [47], adolescents	16	72.20	16.80	209	68.50	17.60	0.21 (−0.30; 0.72)	0.42	12.5
Children and adolescents_physical HRQOL									
Schaeffer et al. [34]	57	97.1	5.78	444	96.80	5.4	0.055 (−0.22; 0.33)	0.70	42.5
Hurrel et al. [35]	54	84.0	23.05	5480	87.53	13.5	−0.26 (−0.53; 0.01)	0.058	45.0
Jochault-Ritz et al. [47], adolescents	16	94.7	5.90	209	84.40	21.2	0.50 (−0.01;1.01)	0.054	12.4
Adults_mental HRQOL									
Traceviciute et al. [42]	19	66.5	16.2	6964	75.2	15.3	−0.57 (−1.02; −0.12)	0.013	26.4
Jochault-Ritz et al. [47], adults	36	61.7	21.9	209	68.5	17.6	−0.37 (−0.73; −0.017)	0.040	42.5
Wittmeyer et al. [39]	25	72.5	25.3	209	68.5	17.6	0.22 (−0.12; 0.63)	0.31	31.1
Adults_physical HRQOL									
Wittmeyer et al [39]	25	76.6	33.9	209	84.5	21.2	−0.35 (−0.76; 0.07)	0.10	30.9
Jochault-Ritz et al. [47], adults	36	84.1	24.9	209	84.4	21.2	−0.014 (−0.37; 0.34)	0.94	42.7
Traceviciute et al. [42]	19	92.4	14.4	6964	88.2	18.5	0.23 (−0.22; 0.68)	0.32	26.4
Adults_social HRQOL									
Traceviciute et al. [42]	19	75.7	20.6	6964	88.6	18.3	−0.70 (−1.16; −0.25)	0.0022	26.5
Jochault-Ritz et al. [47]	36	70.8	30.3	209	81.5	21.4	−0.47 (−0.82; −0.11)	0.010	42.3
Wittmeyer et al. [39]	25	80.5	29.1	209	80.6	21.4	−0.00 (−0.42; 0.41)	0.98	31.2

BEEC bladder exstrophy–epispadias complex, *CI* confidence interval, *HRQOL* health-related quality of life

age, BE children felt different, depressed, and were ashamed for their genitalia [37]. In another study, 32% of BEEC children had signs of depression or anxiety and 31% scored within borderline or abnormal ranges of the Strengths and Difficulties Questionnaire (SDQ), corresponding to 35% in parent report [35]. In other studies, BE/BEEC children had similar mental health [33] or improved emotional role functioning and behavior [34] compared to healthy children, and their self-esteem was good [37]. Of factors associated with poor mental health, child age correlated positively with the SDQ scales "total difficulties", "emotional symptoms, conduct problems", and "peer problems". Conversely, a negative relationship was observed between child age and "prosocial behavior." Child age also correlated positively with a borderline level of anxiety. Males had worse SDQ scores on "conduct difficulties", "hyperactivity", "impact of difficulties" compared to females, and BE children had poorer psychosocial outcomes compared to those with isolated E. Incontinence was related to impaired mental health, behavior, and self-esteem in BEEC children in child report [34], but not in parent report [33]. CE children described more psychosocial problems than their parents [36].

Six combined age population studies reported impaired psychological and/or psychosocial health in BE [17, 47] or BEEC populations [44–46, 50]. In one study [44], 50% of BEEC patients, significantly more compared to controls, had psychiatric diagnosis of mostly emotional and internalizing character. More psychoticism was also found in BEEC patients compared to general controls [50]. The BE adolescents' wish to feel normal was strong [17]. In BEEC individuals, feelings of being disadvantaged [46] were present in 43% of 5–13 year olds, 69% of 14–20 year olds, or 88% of > 20 year olds. In patients > 13 years, males (66%) and females (50%) believed peers to be happier [46]. Self-esteem was "frequently to always" affected in 24% of BEEC patients [45]. Four studies [44, 49, 51, 52] reported similar mental health in patients with isolated E [49], BE [51, 52], or BEEC [44] compared to healthy norms, and two studies [47, 48]

described better scores on mental HRQOL dimensions [47, 48] and self-esteem [47] in BE adolescents or young adults.

Factors associated with poor mental health, psychosocial functioning [44], or experiences of disadvantages [46] in children and young people [44] or adolescents and adults [47, 50, 52] were urinary incontinence [44, 46, 47, 50, 52], fecal incontinence [44], CIC [46], or bullying [17, 46]. In five studies [44, 46–48, 52], severity of genital malformations, satisfaction with genital appearance, pleasure in sexual activity influenced mental health and psychosocial functioning. BE adolescents' belief of a close sexual relationship was the only predictor of psychosocial functioning [44]. In BE females, sexual function or vaginal perception influenced psychological well-being [34]. Two [46, 47] of the four [44, 46, 47, 52] studies associated older age to poorer psychological outcomes in BE/BEEC patients. Patients with isolated E were less affected by somatization than BE patients [50]. Other studies found poorer mental health outcomes in BEEC females [50] or no gender association [44, 52]. In BE/BEEC patients, mental health was not related to the number of anesthesias/surgeries [50], but to the family HRQOL scale [47], and parental warmth interacted with mental health/psychosocial functioning in BEEC youngsters [44].

One study showed worse mental health and emotional role in BEEC adults compared to healthy references [40], contrasting to other two studies [41, 42]. Catti et al. [38] showed that 41% of BEEC women had psychological distress, characterized as difficult in puberty by 24%. In BEEC adults, urinary incontinence was related to impaired mental health dimensions, and better outcomes to UD. Mental health was not influenced by gender, number of surgeries, scar cosmesis, sexual life, or renal function [39].

Social and school functioning

BEEC children had lower mean values in social and school functioning compared to healthy references [35], 50% of BE children were teased by peers and 47% restricted in social life. All children considered it positive to inform schoolmates about BE [37]. In two studies, social functioning was not impaired in CE [36] or BEEC children [34], but the children's family activities were reduced [33]. Children with isolated E had better school functioning and less peer problems compared to BE children [35]. Adjusted for child gender and diagnosis, a borderline negative relationship was found between age and PedsQL social functioning and between age and PedsQL school functioning [35].

Six integrated age population studies [17, 43–47] showed a negative impact of BE/BEEC on friendships, loneliness, or spare time hobbies. Accordingly, 12% of BEEC patients aged > 6 years denied close friendships [46], 59% stated that peer contacts were influenced by exstrophy [45], and 68–100% of BE/BEEC individuals experienced bullying [17, 44]. BE adolescents were worried to be treated badly if they told people about exstrophy [17]. Undressing or showering in a public dressing room were avoided by 90% of males and 44% of females with BEEC. In > 25% of subjects, BEEC was hidden from peers and in 16% none outside the family knew about their condition [45]. While sports was frequently or occasionally played by 65–92% [45, 46], 52% of 6–28-year-old BEEC individuals did not participate in parties, discos, or movies [45]. Feitz et al. [43] described a lack of friends in BE patients close enough to discuss their problems with during puberty and Wilson et al. [17] stated BE adolescents' wish to talk to someone about their worries. In one study [44], 72% of BEEC individuals had no difficulties to communicate with parents or friends about their problems, and friend relationships were better in BE adolescents compared to BE children and general norms [47]. Parents' support was needed; however, adolescents wanted to make own decisions supported by a professional [17], though medical staff relations were worse in adolescents compared to children [47]. In four more studies, patients with isolated E [49], BE [48, 52], or BEEC [50] had either comparable [49, 50, 52] or better [48] social HRQOL compared to healthy norms. BE adolescents, but not children, had impaired scholar work [47], and young BE adults improved school//work HRQOL [48] compared to general norms. In BE patients, male gender was associated with few close friend relationships [46]. BEEC patients' worry about friends discovering the condition, worry and thoughts of being less likely to have romantic relationships [46], and incontinence or bladder augmentation [50] were negatively related to social functioning. However, adolescent age [47] or gender [52] did not affect social HRQOL.

Four studies showed comparable social HRQOL between BE/BEEC adults [39–42] and healthy references. In one study [38], 76% of BEEC females were satisfied with social life, 35% felt limited especially in sports and traveling, and 18% were unsatisfied with their professional lives [38]. Urinary incontinence negatively influenced social HRQOL in BE [38] or BEEC adults [39], but was not affected by gender, surgical procedures, scar cosmesis, school, sexual life, fertility, or renal function [39, 42].

Body perception and sexual health/functioning

Table 4 summarizes study findings regarding body perception and sexual health/functioning among patients with a BEEC condition.

Table 4 Overview of study findings on body perception, and sexual health/functioning in patients with conditions of the bladder exstrophy–epispadias complex

Studies (reference)	Body perception	Sexual health and functioning
Integrated age populations		
Diseth et al. [44]	• 59% of BEEC adolescents indicated dissatisfaction with genital appearance and function • 23% of BEEC adolescents believed their genital malformations had influenced thoughts of establishing a close sexual relationship	• 73% of BEEC adolescents reported dating • 55% of BEEC adolescents regularly masturbated • 94% of BEEC boys had erection • 59% of BEEC boys had ejaculation • 32% of BEEC adolescents reported worry about ability to establish a family and have children
Ebert et al. [45]	• 33% of BEEC females and 22% of males found their genital appearance acceptable • 94% of BEEC males had complaints of penile size • 31% BEEC males and 22% females rated "poor to very bad" satisfaction with reconstruction • 38% of the BEEC patients did not comment on genital appearance	• 71% of BEEC adolescents reported dating • 68% of BEEC patients never or rarely practiced masturbation • 97% of BEEC males reported erection • 84% of BEEC males reported ejaculation • 58% of BEEC adolescents had anxiety concerning their sexual relationships • 52% of BEEC adolescents had anxiety concerning partnerships
Wilson et al. [17]	• For BE adolescents, lower abdominal scars and the absence of an umbilicus were important body issues • For girls, there was a particular issue with clothes, and worries about continence could alter the choice of clothing • For adolescent boys, changing rooms were a main problem due to the risk of exposing their genitals	• 100% of BE adolescents described insecurity and worrying concerning their sexual function • Adolescents' sexual activity took place within an established relationship
Jochault-Ritz et al. [47]		• 78% of BE adults and 53% of adolescents had sexual interest, when concerned • 72% of BE adults and 53% had sexual activity • 72% of BE adults had pleasure in sexual activity
Lee et al. [46]		• Patients' experience with intercourse was positive for both partners in 33%, no such confirmation was reported in 8%, and 58% of patients gave no answer
Amesty et al. [49]		• Four of five females with isolated epispadias responded to have good self-confidence and satisfaction in their sexual relationships
Da Cruz et al. [52]	• 71% of BE females and 54% of BE males described cosmetic satisfaction • 90% of BE males had complaints of small penile length	• 64% of women and 69% of men with BE related to sexual activity • 76% of BE males were satisfied with ejaculation
Feitz et al. [43]	• 36% of female with BE were hampered in sexual activity due to genital and physical appearance • 27% of all patients thought BE had caused broken relationships	• 95% of BE patients began masturbation at normal age • 63% of the BE men were satisfied with erection • 54% of BE men and 80% of BE women were satisfied with orgasm
Deans et al. [51]	• 65% of BE women perceive their vagina abnormal • 42% of BE women perceived the angle of the vagina as 'not right' • 40% of BE women felt that a partner would notice that they were different	• BE females had lower scores on all subscales and overall sexual function on the Female Sexual Function Index compared with healthy norms • Poorer scores in the EuroQOL-5D anxiety/depression domain and poorer scores in the Female Sexual Function Index scores on sexual arousal, sexual satisfaction, and the overall Female Sexual Function Index score correlated, suggesting a relationship between sexual function and overall psychological well-being

Table 4 (continued)

Studies (reference)	Body perception	Sexual health and functioning
Adult population only		
Bujons et al. [40]		• 84% of BEEC females experienced sexual activity • 42% reported having dyspareunia • BEEC females had severe sexual dysfunction according to Pelvic Organ Prolapse • Urinary Incontinence Sexual Function Questionnaire. This related to urinary incontinence, lack of clitoral sensitivity, dyspareunia due to introital stenosis, genital prolapse, and abnormal vaginal perception
Traceviciute et al. [42]		• 89% of BEEC men experienced sexual activity • 37% of BEEC men had erection always or often hard enough for penetration • 42% of BEEC men had erection always or often sufficient for the duration of intercourse • 63% of BEEC men always or often experienced orgasm • 32% of BEEC men would feel content or excellent if their current sex life did not change • According to the International Index of Erectile Function questionnaire, scores of erectile function, orgasmic function, sexual desire, overall satisfaction showed mild/moderate dysfunction, and intercourse satisfaction moderate dysfunction
Catti et al. [38]	• In BEEC females, most patients were unsatisfied with their external genitalia's cosmesis because of scars and abnormal pubic hair disposition, which could limit their body image, self-esteem, libido, and sexual acts	• 67% of BEEC females experienced sexual activity • 47% of the sexually active patients considered there were problems in their sexual life due to urinary incontinence, reduction or lack of clitoral sensitivity, dyspareunia due to introital stenosis, genital prolapse, abnormal vaginal position limiting sexual act to specific positions only, and excessive vaginal dryness requiring lubrication • 35% of BEEC females said they were completely satisfied with their sexual lives and reached orgasms 100% of BEEC women stressed the importance of their partners' understanding for BE and 92% regarded their partner's reaction to BE as good
Wittmeyer et al. [39]	• 6% of BEEC men thought their penis to be of normal size	• 67% of BEEC females experienced sexual activity • 22% of BEEC women experienced dyspareunia during sexual intercourse • 11% of BEEC women refused sexual intercourse due to genital prolapse • 75% of BEEC men experienced sexual activity • 100% of BEEC men experienced erection • 69% of BEEC men had ability to ejaculate

Table 4 (continued)

Studies (reference)	Body perception	Sexual health and functioning
Gupta et al. [41]		• 53% of BE men experienced erection • 67% of patients who reported no erectile dysfunction, felt complete satisfaction during intercourse • 47% of BE men reported their orgasmic function to be mild to moderately dysfunctional • 67% of BE men reported their sexual desire to be mild to moderately dysfunctional • 47% of BE men had mild to moderately dysfunctional orgasmic function • With 29% response rate for the International Index of Erectile Function, sexual function in BE males showed mild to moderate dysfunction across all dimensions

BE bladder exstrophy, *BEEC* bladder exstrophy–epispadias complex

Discussion

This literature review found 21 articles describing cross-sectional HRQOL assessments in patients of the BEEC spectrum, as of May 2018. HRQOL in patients with BEEC may be negatively impacted, particularly considering mental and social HRQOL. In adolescents and adults, sexual health/functioning or body perception impairments may be present. Urinary incontinence and genital function/appearance were the most consistent factors associated with HRQOL restrictions. However, the study populations and HRQOL assessments are heterogeneous, and HRQOL findings differently described.

Article characteristics

A notable proportion of studies included different ages of the BE/BEEC patients, particularly overlapping adolescence and adulthood. Although this approach collects a larger study sample, the HRQOL evaluation may fail to reflect relevant findings of different psycho-developmental stages [96, 97]. This was pointed out already in 1999 by Diseth et al. [98]. Age may influence the individual's perception of HRQOL [28, 99, 100]. Children's and adolescents' lives are embedded within contexts of family, peer relationships, and school. The understanding of their illness develops with maturity, which should be considered in HRQOL assessments [28, 99, 100]. Furthermore, six reviewed HRQOL studies [36, 38, 40, 42, 49, 51] focused on females or males. Important psychological findings in BEEC patients may be uncovered when age and gender are considered [101]. In this review, HRQOL differed [35, 46, 50] and were comparable between patient gender [39, 44, 52]. Moreover, the majority were European studies including small study samples; nevertheless, few multi-center studies were identified. Additionally, a significant proportion of patients were frequently lost to follow-up, which may further bias the HRQOL observations [48, 102]. Only 5/21 studies provided sufficient HRQOL data for a meta-analysis, and I^2 statistics revealed heterogeneity among the studies, which should be considered in relation to the reported findings. Furthermore, surgical/clinical characteristics of the study sample are needed to understand HRQOL in BEEC patients, but were occasionally incompletely reported. Particularly, this regarded surgical treatments in children [33–36], osteotomy or not [40, 44, 47], and failed exstrophy closure [45, 48]. The failed closure is a major complication with significant implications on the long-term outcome of the urinary tract [103]. Additionally, staged, complete primary repair and UD were heterogeneously performed in the study samples. This limits generalizability of the HRQOL findings.

HRQOL was differently assessed and provided varying profiles of information, but also made interpretation of HRQOL complex [98]. Altogether 22/32 questionnaires were available for review. Several authors used descriptive and/or self-designed questionnaires [38, 39, 45, 46, 50]. Generic measurements permit the advantage of comparison of HRQOL with general norms and other disease groups, while condition-specific questionnaires provide more clinically sensitive information. The advantages of a condition-specific HRQOL instrument are also improved content validity and a standardized methodology to reach statistical power in the HRQOL evaluation of a rare condition [104, 105]. In disagreement with current standards [28, 105], several of the reviewed questionnaires lacked involvement of the target population in the establishment of content validity. Body perception and sexual health/functioning in adolescences and adults may be BEEC-specific HRQOL aspects [106]. The importance of a BEEC-specific HRQOL instrument has been addressed earlier [33, 35, 45] and such an instrument could be used in research and clinical practice [22–25].

BEEC children reported more HRQOL problems than their parents [35, 36]. While proxy reports provide complementary information about children's HRQOL, the self-report is of primary importance [28, 107].

HRQOL outcomes

The few studies included in the meta-analysis demonstrated worse HRQOL for patients with BE/BEEC, although ESs were often small. Altogether, this study suggests that BE/BEEC children may have impaired overall HRQOL, and reduced general and mental health. In adults, overall HRQOL was not assessed. In older BE/BEEC individuals, primarily psychological and social HRQOL seem negatively affected. Bullying, loneliness, communication problems about BE, and social restrictions were described [17, 43–46]. Incontinence affected HRQOL aspects across patient ages [17, 34, 38–41, 44–47, 49, 50, 52]. Similar to Lloyd et al. [108] definitions of continence in BE/BEEC patients varied, but urinary incontinence rates were similar to earlier studies [7–15]. Genital function/appearance may particularly influence psychological HRQOL [17, 44, 46–48, 52]. In congruence with malformation severity, isolated E was associated with better outcomes compared to BE [35, 50]. The number of surgical procedures were mostly not related to HRQOL [36, 39, 42, 50], perhaps because surgical treatments aim to relief the patient's symptom burden. Moreover, higher age and male gender may predispose a negatively affected mental HRQOL in BE/BEEC patients [35, 45–47], which is in line with other psychological studies of this patient group [101, 109].

Interestingly, HRQOL was also improved in BE/BEEC patients compared to other references, which could be explained by these patients' coping strategies [17, 19, 101]. Coping may become more advanced with increased child maturity [110]. However, one study [101] observed a decreased adaptive competence among BEEC patients with increased age. In turn, BE/BEEC patients were described to conceal their condition. Avoidance is generally related to poor psychosocial adjustment [111]. This suggests that coping should be measured jointly with HRQOL in BEEC patients, and that better HRQOL in BEEC patients may be otherwise explained. It could relate to the HRQOL questions, and their appropriateness for this rare condition [105, 112–114].

Study limitations and strengths

This study lacks reports of HRQOL in eight interventional studies of BEEC conditions [115–122], and fertility and child birth outcomes in BEEC adults [106], but is strengthened by frameworks, predefined protocols, multiple researcher involvement, and comprehensiveness.

Conclusions and recommendations

Children of the BEEC conditions may have impaired overall HRQOL, as well as impaired general and mental health. Adolescences and adults seem especially to have reduced mental and social HRQOL. Urinary incontinence, genital dysfunction/dissatisfaction with genital appearance, and higher patient age may define BEEC patients at risk for HRQOL impairments. However, HRQOL is differently reported. Definite conclusions cannot be drawn from existing studies, due to small study samples, significant proportion of patients being lost to follow-up, integration of different patient ages, lack of control group, and heterogeneous HRQOL measurements.

Future research should determine to what degree HRQOL is affected in BEEC patients, and should include longitudinal studies, cross-cultural multi-center approaches, and a careful documentation of surgical/clinical population characteristics. Knowledge of HRQOL in patients with isolated E or CE, and of BEEC children, adolescences, and adults is specifically warranted. HRQOL evaluations should consider patient gender, culture, coping, child-proxy agreements, and strategies to increase study participation. Further studies are recommended to employ established generic or domain-specific HRQOL instruments, and to develop a standardized, international,

and multidimensional HRQOL measurement specifically for BEEC patients. This would advance knowledge of the impact of BEEC in the patients' lives, and provide health care organizations with a valid assessment for communication, monitoring, and improvement of patient health in clinical practice, as well as researchers with possibilities to improve treatment evaluations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human and animal participants This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Ebert, A. K., Reutter, H., Ludwig, M., & Rosch, W. H. (2009). The exstrophy-epispadias complex. *Orphanet Journal of Rare Diseases, 4*, 23. https://doi.org/10.1186/1750-1172-4-23.
2. Jayachandran, D., Bythell, M., Platt, M. W., & Rankin, J. (2011). Register based study of bladder exstrophy-epispadias complex: Prevalence, associated anomalies, prenatal diagnosis and survival. *Journal of Urology, 186*(5), 2056–2060.
3. Pierre, K., Borer, J., Phelps, A., & Chow, J. S. (2014). Bladder exstrophy: current management and postoperative imaging. *Pediatric Radiology, 44*(7), 768–786 (**quiz 765–767**).
4. Dickson, A. P. (2014). The management of bladder exstrophy: The Manchester experience. *Journal of Pediatric Surgery, 49*(2), 244–250.
5. Wild, A. T., Sponseller, P. D., Stec, A. A., & Gearhart, J. P. (2011). The role of osteotomy in surgical repair of bladder exstrophy. *Seminars in Pediatric Surgery, 20*(2), 71–78.
6. Siffel, C., Correa, A., Amar, E., Bakker, M. K., Bermejo-Sanchez, E., Bianca, S., et al. (2011). Bladder exstrophy: An epidemiologic study from the International Clearinghouse for Birth Defects Surveillance and Research, and an overview of the literature. *American Journal of Medical Genetics. Part C, 157*(4), 321–332. https://doi.org/10.1002/ajmg.c.30316.
7. Shoukry, A. I., Ziada, A. M., Morsi, H. A., Habib, E. I., Aref, A., Badawy, H. A., et al. (2009). Outcome of complete primary bladder exstrophy repair: Single-center experience. *Journal of Pediatric Urology, 5*(6), 496–499.
8. Purves, J. T., Baird, A. D., & Gearhart, J. P. (2008). The modern staged repair of bladder exstrophy in the female: A contemporary series. *Journal of Pediatric Urology, 4*(2), 150–153.
9. Shnorhavorian, M., Grady, R. W., Andersen, A., Joyner, B. D., & Mitchell, M. E. (2008). Long-term followup of complete primary repair of exstrophy: The Seattle experience. *Journal of Urology, 180*(4 Suppl), 1615–1619 (**discussion 1619–1620**).
10. Ellison, J. S., Shnorhavorian, M., Willihnganz-Lawson, K., Grady, R., & Merguerian, P. A. (2016). A critical appraisal of continence in bladder exstrophy: Long-term outcomes of the complete primary repair. *Journal of Pediatric Urology, 12*(4), 205.e201–205.e207.
11. Arab, H. O., Helmy, T. E., Abdelhalim, A., Soltan, M., Dawaba, M. E., & Hafez, A. T. (2018). Complete primary repair of bladder exstrophy: Critical analysis of the long-term outcome. *Urology, 117*, 131–136.
12. Surer, I., Baker, L. A., Jeffs, R. D., & Gearhart, J. P. (2001). Modified Young-Dees-Leadbetter bladder neck reconstruction in patients with successful primary bladder closure elsewhere: A single institution experience. *Journal of Urology, 165*(6 Pt 2), 2438–2440.
13. Hammouda, H. M., & Kotb, H. (2004). Complete primary repair of bladder exstrophy: Initial experience with 33 cases. *Journal of Urology, 172*(4 Pt 1), 1441–1444.
14. Shaw, M. B., Rink, R. C., Kaefer, M., Cain, M. P., & Casale, A. J. (2004). Continence and classic bladder exstrophy treated with staged repair. *Journal of Urology, 172*(4 Pt 1), 1450–1453.
15. Gargollo, P., Hendren, W. H., Diamond, D. A., Pennison, M., Grant, R., Rosoklija, I., Retik, A. B., & Borer, J. G. (2011). Bladder neck reconstruction is often necessary after complete primary repair of exstrophy. *Journal of Urology, 185*(6 Suppl), 2563–2571.
16. Pennison, M. C., Mednick, L., Grant, R., Price, D., Rosoklija, I., Huang, L., Ziniel, S., & Borer, J. G. (2013). A survey to assess body and self-image in individuals with bladder exstrophy: A call for psychosocial support. *Journal of Urology, 190*(4 Suppl), 1572–1576.
17. Wilson, C., Christie, D., & Woodhouse, C. R. J. (2004). The ambitions of adolescents born with exstrophy: A structured survey. *BJU International, 94*(4), 607–612.
18. Park, W., Zwink, N., Rosch, W. H., Schmiedeke, E., Stein, R., Schmidt, D., et al. (2015). Sexual function in adult patients with classic bladder exstrophy: A multicenter study. *Journal of Pediatric Urology, 11*(3), 125.e121–125.e126.
19. Wilson, C. J., Pistrang, N., Woodhouse, C. R., & Christie, D. (2007). The psychosocial impact of bladder exstrophy in adolescence. *Journal of Adolescent Health, 41*(5), 504–508.
20. Gobet, R., Weber, D., Horst, M., Yamamoto, S., & Fischer, J. (2009). Long-term followup (37 to 69 years) in patients with bladder exstrophy treated with ureterosigmoidostomy: psychosocial and psychosexual outcomes. *Journal of Urology, 182*(4 Suppl), 1819–1823.
21. Suominen, J. S., Santtila, P., & Taskinen, S. (2015). Sexual function in patients operated on for bladder exstrophy and epispadias. *Journal of Urology, 194*(1), 195–199.
22. Greenhalgh, J. (2009). The applications of PROs in clinical practice: What are they, do they work, and why? *Quality of Life Research, 18*(1), 115–123.
23. Black, N., Burke, L., Forrest, C. B., Sieberer, U. H., Ahmed, S., Valderas, J. M., et al. (2016). Patient-reported outcomes: Pathways to better health, better services, and better societies. *Quality of Life Research, 25*(5), 1103–1112.
24. Sharma, P., Dunn, R. L., Wei, J. T., Montie, J. E., & Gilbert, S. M. (2016). Evaluation of point-of-care PRO assessment in clinic settings: Integration, parallel-forms reliability, and patient acceptability of electronic QOL measures during clinic visits. *Quality of Life Research, 25*(3), 575–583.
25. Santana, M. J., & Feeny, D. (2014). Framework to assess the effects of using patient-reported outcome measures in chronic care management. *Quality of Life Research, 23*(5), 1505–1513.
26. Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine, 6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097.
27. Guyatt, G. H., Feeny, D. H., & Patrick, D. L. (1993). Measuring health-related quality of life. *Annals of Internal Medicine, 118*(8), 622–629.

28. Matza, L. S., Patrick, D. L., Riley, A. W., Alexander, J. J., Rajmil, L., Pleil, A. M., et al. (2013). Pediatric patient-reported outcome instruments for research to support medical product labeling: Report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. *Value in Health, 16*(4), 461–479.
29. Aaronson, N., Alonso, J., Burnam, A., Lohr, K. N., Patrick, D. L., Perrin, E., et al. (2002). Assessing health status and quality-of-life instruments: Attributes and review criteria. *Quality of Life Research, 11*(3), 193–205.
30. Terwee, C. B., Bot, S. D., de Boer, M. R., van der Windt, D. A., Knol, D. L., Dekker, J., et al. (2007). Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of Clinical Epidemiology, 60*(1), 34–42.
31. Sullivan, G. M., & Feinn, R. (2012). Using Effect Size-or why the P value is not enough. *The Journal of Graduate Medical Education, 4*(3), 279–282.
32. Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal, 327*(7414), 557–560.
33. Dodson, J. L., Furth, S. L., Yenokyan, G., Alcorn, K., Diener-West, M., Wu, A. W., et al. (2010). Parent perspectives of health related quality of life for adolescents with bladder exstrophy-epispadias as measured by the child health questionnaire-parent form 50. *Journal of Urology, 184*(4 Suppl), 1656–1661.
34. Schaeffer, A. J., Yenokyan, G., Alcorn, K., Furth, S. L., Diener-West, M., Wu, A. W., et al. (2012). Health related quality of life in adolescents with bladder exstrophy-epispadias as measured by the Child Health Questionnaire-Child Form 87. *Journal of Urology, 188*(5), 1924–1929.
35. Hurrell, R. A., Fullwood, C., Keys, J., Dickson, A. P., Fishwick, J., Whitnall, B., et al. (2015). Psychosocial screening at paediatric BEEC clinics: A pilot evaluation study. *Journal of Pediatric Urology, 11*(2), 79.e71–79.e76.
36. Baker Towell, D. M., & Towell, A. D. (2003). A preliminary investigation into quality of life, psychological distress and social competence in children with cloacal exstrophy. *Journal of Urology, 169*(5), 1850–1853.
37. Stjernqvist, K., & Kockum, C. C. (1999). Bladder exstrophy: Psychological impact during childhood. *Journal of Urology, 162*(6), 2125–2129.
38. Catti, M., Paccalin, C., Rudigoz, R. C., & Mouriquand, P. (2006). Quality of life for adult women born with bladder and cloacal exstrophy: A long-term follow up. *Journal of Pediatric Urology, 2*(1), 16–22.
39. Wittmeyer, V., Aubry, E., Liard-Zmuda, A., Grise, P., Ravasse, P., Ricard, J., et al. (2010). Quality of life in adults with bladder exstrophy-epispadias complex. *Journal of Urology, 184*(6), 2389–2394.
40. Bujons, A., Lopategui, D. M., Rodriguez, N., Centeno, C., Caffaratti, J., & Villavicencio, H. (2016). Quality of life in female patients with bladder exstrophy-epispadias complex: Long-term follow-up. *Journal of Pediatric Urology, 12*(4), 210.e211–210.e216.
41. Gupta, A. D., Goel, S. K., Woodhouse, C. R., & Wood, D. (2014). Examining long-term outcomes of bladder exstrophy: A 20-year follow-up. *BJU International, 113*(1), 137–141.
42. Traceviciute, J., Zwink, N., Jenetzky, E., Reutter, H., Hirsch, K., Stein, R., et al. (2018). Sexual function and quality of life in adult male individuals with exstrophy-epispadias complex—A survey of the German CURE-Network. *Urology, 112*, 215–221.
43. Feitz, W. F., Van Grunsven, E. J., Froeling, F. M., & de Vries, J. D. (1994). Outcome analysis of the psychosexual and socio-economical development of adult patients born with bladder exstrophy. *Journal of Urology, 152*(5 Pt 1), 1417–1419.
44. Diseth, T. H., Bjordal, R., Schultz, A., Stange, M., & Emblem, R. (1998). Somatic function, mental health and psychosocial functioning in 22 adolescents with bladder exstrophy and epispadias. *Journal of Urology, 159*(5), 1684–1689.
45. Ebert, A., Scheuering, S., Schott, G., & Roesch, W. H. (2005). Psychosocial and psychosexual development in childhood and adolescence within the exstrophy-epispadias complex. *Journal of Urology, 174*(3), 1094–1098.
46. Lee, C., Reutter, H. M., Grasser, M. F., Fisch, M., & Noeker, M. (2006). Gender-associated differences in the psychosocial and developmental outcome in patients affected with the bladder exstrophy-epispadias complex. *BJU International, 97*(2), 349–353.
47. Jochault-Ritz, S., Mercier, M., & Aubert, D. (2010). Short and long-term quality of life after reconstruction of bladder exstrophy in infancy: Preliminary results of the QUALEX (QUAlity of Life of bladder EXstrophy) study. *Journal of Pediatric Surgery, 45*(8), 1693–1700.
48. Pennison, M. C., Mednick, L., Rosoklija, I., Grant, R., Price, D., Huang, L., et al. (2014). Health related quality of life in patients with bladder exstrophy: A call for targeted interventions. *Journal of Urology, 191*(5 Suppl), 1553–1557.
49. Amesty, M. V., Chocarro, G., Lobato, R., Monsalve, S., Martinez-Urrutia, M. J., Lopez-Pereira, P. C., et al. (2016). Quality of life in female epispadias. *European Journal of Pediatric Surgery, 26*(3), e1. https://doi.org/10.1055/s-0035-1569065.
50. Taskinen, S., Suominen, J. S., & Mattila, A. K. (2015). Health-related quality of life and mental health in adolescents and adults operated for bladder exstrophy and epispadias. *Urology, 85*(6), 1515–1519.
51. Deans, R., Liao, L. M., Wood, D., Woodhouse, C., & Creighton, S. M. (2015). Sexual function and health-related quality of life in women with classic bladder exstrophy. *BJU International, 115*(4), 633–638.
52. da Cruz, J. A., de Mattos, B., Srougi, M., Nguyen, H., Bonan, R., Denes, F., et al. (2016). Quality of life in young adult patients treated for bladder exstrophy. *Central European Journal of Urology, 69*(2), 221–224.
53. Landgfuf, J. M., & Abetz, L. N. (1997). Functional status and well-being of children representing three cultural groups: Initial self-reports using the chq-cf87. *Psychology & Health, 12*(6), 839–854.
54. Landgraf, J. M., Maunsell, E., Speechley, K. N., Bullinger, M., Campbell, S., Abetz, L., et al. (1998). Canadian-French, German and UK versions of the Child Health Questionnaire: Methodology and preliminary item scaling results. *Quality of Life Research, 7*(5), 433–445.
55. Waters, E. B., Salmon, L. A., Wake, M., Wright, M., & Hesketh, K. D. (2001). The health and well-being of adolescents: A school-based population study of the self-report Child Health Questionnaire. *Journal of Adolescent Health, 29*(2), 140–149.
56. Graham, P., Stevenson, J., & Flynn, D. (1997). A new measure of health-related quality of life for children: Preliminary findings. *Psychology & Health, 12*(5), 655–665.
57. EuroQol G. (1990). EuroQol—New facility for the measurement of health-related quality of life. *Health Policy, 16*(3), 199–208.
58. Brooks, R. (1996). EuroQol: The current state of play. *Health Policy, 37*(1), 53–72.
59. Janssen, M. F., Pickard, A. S., Golicki, D., Gudex, C., Niewada, M., Scalone, L., et al. (2013). Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: A multi-country study. *Quality of Life Research, 22*(7), 1717–1727.
60. Payakachat, N., Ali, M. M., & Tilford, J. M. (2015). Can the EQ-5D detect meaningful change? A systematic review. *Pharmacoeconomics, 33*(11), 1137–1154.

61. Rabin, R., Gudex, C., Selai, C., & Herdman, M. (2014). From translation to version management: A history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. *Value in Health, 17*(1), 70–76.
62. Varni, J. W., Seid, M., & Kurtin, P. S. (2001). PedsQL 4.0: Reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Medical Care, 39*(8), 800–812.
63. Varni, J. W., Burwinkle, T. M., Seid, M., & Skarr, D. (2003). The PedsQL 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. *Ambulatory Pediatrics, 3*(6), 329–341.
64. Feeny, D., Furlong, W., Barr, R. D., Torrance, G. W., Rosenbaum, P., & Weitzman, S. (1992). A comprehensive multiattribute system for classifying the health status of survivors of childhood cancer. *Journal of Clinical Oncology, 10*(6), 923–928.
65. Torrance, G. W., Feeny, D. H., Furlong, W. J., Barr, R. D., Zhang, Y., & Wang, Q. (1996). Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. *Medical Care, 34*(7), 702–722.
66. Simeoni, M. C., Auquier, P., Antoniotti, S., Sapin, C., & San Marco, J. L. (2000). Validation of a French health-related quality of life instrument for adolescents: The VSP-A. *Quality of Life Research, 9*(4), 393–403.
67. Sapin, C., Antoniotti, S., Simeoni, M. C., Clement, A., El Khammar, M., & Auquier, P. (2004). Shortening the VSP-A: Preliminary development of the VSP-A12, a 12-item short-form. *Quality of Life Research, 13*(1), 235–241.
68. Ware, J. E. Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*(6), 473–483.
69. McHorney, C. A., Ware, J. E. Jr., & Raczek, A. E. (1993). The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care, 31*(3), 247–263.
70. McHorney, C. A., Ware, J. E. Jr., Lu, J. F., & Sherbourne, C. D. (1994). The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care, 32*(1), 40–66.
71. Derogatis, L. R., & Melisaratos, N. (1983). The brief symptom inventory: An introductory report. *Psychological Medicine, 13*(3), 595–605.
72. Boulet, J., & Boss, M. W. (1991). Reliability and validity of the brief symptom inventory. *Psychological Assessment, 3*(3), 433–437.
73. Derogatis, R. L. (2017). Symptom checklist-90-revised, brief symptom inventory, and BSI-18. In E. M. Maruish (Ed.), *Handbook of psychological assessment in primary care settings*. New York: Routledge.
74. Hodges, K., McKnew, D., Cytryn, L., Stern, L., & Kline, J. (1982). The Child Assessment Schedule (CAS) Diagnostic Interview: A report on reliability and validity. *Journal of the American Academy of Child Psychiatry, 21*(5), 468–473.
75. Hodges, K. (1993). Structured interviews for assessing children. *Journal of Child Psychology and Psychiatry, 34*(1), 49–68.
76. Shaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., et al. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry, 40*(11), 1228–1231.
77. Achenbach, T. M. & Rescorla, L. A. (2018). Manual for the ASEBA preschool forms & profiles: Child behavior checklist for ages 1 1/2 to 5, language development survey, caregiver-teacher report form. Achenbach system of empirically based assessment. Retrieved August 19, 2018, from http://www.aseba.org/ordering/ASEBA%20Reliability%20&%20Validity-Pre-school%20.pdf.
78. Achenbach, T. M. & Rescorla, L. A. (2018). Manual for the ASEBA school-age forms & profiles: Child behavior checklist for ages 6–18, teacher-report form, youth self-report. Achenbach system of empirically based assessment. Retrieved August 19, 2018, from http://www.aseba.org/ordering/ASEBA%20Reliability%20and%20Validity-School%20Age.pdf.
79. Ouvinen-Birgerstam, P. (1985). *"I Think I Am" manual*. Stockholm: Psykologiförlaget AB.
80. Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica, 67*(6), 361–370.
81. Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale—A review of validation data and clinical results. *Journal of Psychosomatic Research, 42*(1), 17–41.
82. Snaith, R. P. (2003). The Hospital Anxiety And Depression Scale. *Health and Quality of Life Outcomes, 1*, 29.
83. O'Connor, S., Ferguson, E., Carney, T., House, E., & O'Connor, R. C. (2016). The development and evaluation of the paediatric index of emotional distress (PI-ED). *Social Psychiatry and Psychiatric Epidemiology, 51*(1), 15–26.
84. Derogatis, L. R., Lipman, R. S., & Covi, L. (1973). SCL-90: An outpatient psychiatric rating scale-preliminary report. *Psychopharmacology Bulletin, 9*(1), 13–28.
85. Derogatis, L. R., Rickels, K., & Rock, A. F. (1976). The SCL-90 and the MMPI: A step in the validation of a new self-report scale. *The British Journal of Psychiatry, 128*, 280–289.
86. Carpenter, K. M., & Hittner, J. B. (1995). Dimensional characteristics of the SCL-90-R: Evaluation of gender differences in dually diagnosed inpatients. *Journal of Clinical Psychology, 51*(3), 383–390.
87. Skuse, D. H., James, R. S., Bishop, D. V., Coppin, B., Dalton, P., Aamodt-Leeper, G., et al. (1997). Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature, 387*(6634), 705–708.
88. Goodman, R. (1997). The Strengths and Difficulties Questionnaire: A research note. *Journal of Child Psychology and Psychiatry, 38*(5), 581–586.
89. Goodman, R., Meltzer, H., & Bailey, V. (1998). The Strengths and Difficulties Questionnaire: A pilot study on the validity of the self-report version. *European Child & Adolescent Psychiatry, 7*(3), 125–130.
90. Goodman, R. (2001). Psychometric properties of the Strengths and Difficulties Questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(11), 1337–1345.
91. Goodman, R., Ford, T., Simmons, H., Gatward, R., & Meltzer, H. (2003). Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. *International Review of Psychiatry, 15*(1–2), 166–172.
92. Rosen, R., Brown, C., Heiman, J., Leiblum, S., Meston, C., Shabsigh, R., et al. (2000). The Female Sexual Function Index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. *Journal of Sex & Marital Therapy, 26*(2), 191–208.
93. Rosen, R. C., Riley, A., Wagner, G., Osterloh, I. H., Kirkpatrick, J., & Mishra, A. (1997). The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology, 49*(6), 822–830.
94. Rogers, R. G., Kammerer-Doak, D., Villarreal, A., Coates, K., & Qualls, C. (2001). A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse. *American Journal of Obstetrics & Gynecology, 184*(4), 552–558.
95. Ismail-Pratt, I. S., Bikoo, M., Liao, L. M., Conway, G. S., & Creighton, S. M. (2007). Normalization of the vagina by dilator treatment alone in Complete Androgen Insensitivity Syndrome and Mayer-Rokitansky-Kuster-Hauser Syndrome. *Human Reproduction, 22*(7), 2020–2024.

96. World Health Organization. Adolescent development. World Health Organization, maternal, newborn, child and adolescent health. Retrieved August 19, 2018, from http://www.who.int/maternal_child_adolescent/topics/adolescence/development/en/.
97. Huang, I. C., Revicki, D. A., & Schwartz, C. E. (2014). Measuring pediatric patient-reported outcomes: Good progress but a long way to go. *Quality of Life Research, 23*(3), 747–750.
98. Diseth, T. H., Emblem, R., & Schultz, A. (1999). Mental health, psychosocial functioning, and quality of life in patients with bladder exstrophy and epispadias—An overview. *World Journal of Urology, 17*(4), 239–248.
99. Matza, L. S., Swensen, A. R., Flood, E. M., Secnik, K., & Leidy, N. K. (2004). Assessment of health-related quality of life in children: A review of conceptual, methodological, and regulatory issues. *Value in Health, 7*(1), 79–92.
100. Bullinger, M., Schmidt, S., Petersen, C., & Ravens-Sieberer, U. (2006). Quality of life—Evaluation criteria for children with chronic conditions in medical care. *Journal of Public Health, 14*(6), 343–355.
101. Hankinson, J. C., Eldridge, M. A., Ostrander, R., Shah, B., Reynolds, E. K., Perry-Parrish, C., et al. (2014). Emotional and behavioral functioning in children with bladder exstrophy-epispadias complex: A developmental perspective. *Journal of Pediatric Urology, 10*(1), 136–141.
102. Haddad, E., Sancaktutar, A. A., Palmer, B. W., Aston, C., & Kropp, B. P. (2018). Who, where, and why are patients lost to follow-up? A 20-year study of bladder exstrophy patients at a single institution. *Journal of Pediatric Urology, 4*(3), 276e1–276.e6. https://doi.org/10.1016/j.jpurol.2017.12.022.
103. Novak, T. E. (2011). Failed exstrophy closure. *Seminars in Pediatric Surgery, 20*(2), 97–101.
104. Rajmil, L., Perestelo-Perez, L., & Herdman, M. (2010). Quality of life and rare diseases. *Advances in Experimental Medicine and Biology, 686*, 251–272.
105. Benjamin, K., Vernon, M. K., Patrick, D. L., Perfetto, E., Nestler-Parr, S., & Burke, L. (2017). Patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials: An ISPOR COA emerging good practices task force report. *Value in Health, 20*(7), 838–855.
106. Baird, A. D. (2011). Exstrophy in the adolescent and young adult population. *Seminars in Pediatric Surgery, 20*(2), 109–112.
107. Eiser, C., & Morse, R. (2001). Can parents rate their child's health-related quality of life? Results of a systematic review. *Quality of Life Research, 10*(4), 347–357.
108. Lloyd, J. C., Spano, S. M., Ross, S. S., Wiener, J. S., & Routh, J. C. (2012). How dry is dry? A review of definitions of continence in the contemporary exstrophy/epispadias literature. *Journal of Urology, 188*(5), 1900–1904.
109. Reiner, W. G., Gearhart, J. P., & Kropp, B. (2008). Suicide and suicidal ideation in classic exstrophy. *Journal of Urology, 180*(4 Suppl), 1661–1663 (**discussion 1663–1664**).
110. Skinner, E. A., & Zimmer-Gembeck, M. J. (2007). The development of coping. *Annual Review of Psychology, 58*, 119–144.
111. Compas, B. E., Jaser, S. S., Dunn, M. J., & Rodriguez, E. M. (2012). Coping with chronic illness in childhood and adolescence. *Annual Review of Clinical Psychology, 8*, 455–480.
112. Slade, A., Isa, F., Kyte, D., Pankhurst, T., Kerecuk, L., Ferguson, J., et al. (2018). Patient reported outcome measures in rare diseases: A narrative review. *Orphanet Journal of Rare Diseases, 13*(1), 61. https://doi.org/10.1186/s13023-018-0810-x.
113. Knauper, B., & Turner, P. A. (2003). Measuring health: Improving the validity of health assessments. *Quality of Life Research, 12*(Suppl 1), 81–89.
114. Connell, J., Carlton, J., Grundy, A., Taylor Buck, E., Keetharuth, A. D., Ricketts, T., et al. (2018). The importance of content and face validity in instrument development: Lessons learnt from service users when developing the Recovering Quality of Life measure (ReQoL). *Quality of Life Research, 27*(7), 1893–1902.
115. Messina, M., Molinaro, F., Ferrara, F., Angotti, R., Bulotta, A. L., Di Maggio, G., et al. (2016). Continence and quality of life with the modified Heitz-Boyer-Hovelacque rectal bladder for children with urinary incontinence following bladder exstrophy. *Journal of Pediatric Urology, 12*(3), 174.e171–174.e176.
116. Elmi, A., Kajbafzadeh, A. M., Tourchi, A., Talab, S. S., & Esfahani, S. A. (2011). Safety, efficacy and health related quality of life of autologous myoblast transplantation for treatment of urinary incontinence in children with bladder exstrophy-epispadias complex. *Journal of Urology, 186*(5), 2021–2026.
117. Kurbet, S. B., Prashanth, G. P., Patil, M. V., & Mane, S. (2013). A retrospective analysis of early experience with modified complete primary repair of exstrophy bladder (CPRE) in neonates and children. *Indian Journal of Plastic Surgery, 46*(3), 549–554.
118. Kanojia, R. P., Rao, K. L., Menon, P., Agarwal, S., Bawa, M., Mahajan, J. K., et al. (2014). Recto sigmoid bladder reservoir for patients with exstrophy: Three dimensional evaluation for outcome analysis. *Journal of Pediatric Urology, 10*(6), 1176–1180.
119. Kanojia, R. P., Agarwal, S., Rathod, K. K., Bawa, M., Menon, P., Mahajan, J. K., et al. (2013). Quantified outcome for patients with bladder exstrophy. *Journal of Pediatric Urology, 9*(3), 298–302.
120. Nerli, R. B., Shirol, S. S., Guntaka, A., Patil, S., & Hiremath, M. B. (2012). Genital reconstruction in exstrophy patients. *Indian Journal of Urology, 28*(3), 280–285.
121. Ricketts, S., Hunter-Smith, D. J., & Coombs, C. J. (2011). Quality of life after penile reconstruction using the radial forearm flap in adult bladder exstrophy patients—Technique and outcomes. *ANZ Journal of Surgery, 81*(1–2), 52–55.
122. Everett, R. G., Lue, K. M., Reddy, S. S., Friedlander, D. A., Alexander, C. E., Young, E. E., Abdelwahab, M., Gandhi, N. M., Wright, E. J., & Gearhart, J. P. (2017). Patient-reported impact of pelvic organ prolapse on continence and sexual function in women with exstrophy-epispadias complex. *Female Pelvic Medicine & Reconstructive Surgery, 23*(6), 377–381.