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SYSTEMATIC REVIEW

Health State Utility Values in Juvenile Idiopathic Arthritis: What is the Evidence?

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Abstract

Objectives The objectives of this systematic review were to identify health state utility values (HSUV) of children and adults with juvenile idiopathic arthritis in the literature and to assess whether HSUV were appropriately reported and could be used to inform parameter inputs for a model-based cost-utility analysis to inform decision making.

Methods MEDLINE, EMBASE, PsycINFO, EconLit and CINAHL databases were searched in July 2019. Inclusion criteria were studies using preference-based instruments, targeting children or adults with juvenile idiopathic arthritis, and in the English language. The quality of studies was assessed using a modified checklist that included relevant sources of bias and assessment of quality of HSUV valuation and measurement. A descriptive analysis was conducted, including assessment on reporting of population characteristics and stratification of HSUV by potential health states or population subgroup.

Results From 620 identified articles, ten reported HSUV. Seven studies reported HSUV of children with juvenile idiopathic arthritis, and three of adults with a history of juvenile idiopathic arthritis. Population disease activity status and drug treatment were reported in less than half of the studies. Six (out of ten) studies stratified HSUV results for at least one of the potential health state categories, but they represent very specific situations or interventions (e.g. patients receiving different types of physiotherapy or treated with etanercept over time).

Conclusions We have identified critical gaps in the literature reporting HSUV in patients with juvenile idiopathic arthritis including a lack of HSUV measures for distinct health states, particularly in adults with a history of juvenile idiopathic arthritis. The current reported HSUV data in juvenile idiopathic arthritis are insufficient for a full cost-utility analysis with a short or lifetime horizon.

1 Background

Juvenile idiopathic arthritis (JIA) is an umbrella term that encompasses all forms of arthritis, without another cause, with onset before the age of 16 years that persists for more than 6 weeks. It is considered one of the most common chronic childhood disorders, affecting approximately 1 in 1000 children [1, 2]. Costs associated with JIA can pose a large burden on the healthcare system including medical visits (e.g. clinic visits, medical day care unit visits), radiology and laboratory testing, hospitalisations and medications. There is a significant burden on families with out-of-pocket expenses and loss of productivity [3].

In many cases, JIA will remain active during adulthood and require ongoing disease-modifying antirheumatic drug treatment, which results in impaired quality of life and reduced physical functioning [4, 5]. As timely JIA diagnosis, care and treatment are crucial to avoid long-term impairment, novel interventions and early treatment strategies are currently being assessed [6]. With limited healthcare budgets, there is a need for assessing the cost effectiveness of these interventions using a cost-utility analysis (CUA) to inform reimbursement decision making [7]. Cost-utility analyses require the measurement of health state utility values (HSUV) to calculate the quality-adjusted life-years.

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Key Points

This systematic review is the first study to provide an overview of existing health state utility value (HSUV) evidence in juvenile idiopathic arthritis and discuss whether these estimates are appropriately reported to populate model-based economic evaluations.

Our review showed that the evidence on HSUV in juvenile idiopathic arthritis is still limited, only ten studies reporting HSUV were identified in this review. These studies stratified HSUV by very specific situations or interventions that limit the use of the data to populate a cost-utility analysis.

The current reported HSUV of adults with history of juvenile idiopathic arthritis is insufficient to inform a model-based cost-utility analysis with a lifetime horizon.

When developing a model-based CUA, HSUV need to be obtained from the literature when they are not available from clinical trial data, it is not feasible to conduct a study to collect this information, or when clinical trial data are available, but it is necessary to expand the analysis beyond the trial time horizon [8]. In such a circumstance, a number of issues may arise: HSUVs might not match the health states within the model, data quality might be poor or data might not be appropriately reported to permit its use in model-based economic evaluations [9]. It is important to highlight that although the need for appropriate HSUVs is crucial when developing model-based economic evaluations, all other parameters estimated from multiple data sources and other model assumptions also contribute to uncertainty of the final outcomes [10]. To mitigate potential biases in parameter estimates, best research practice recommendations have been published by the International Society for Pharmacoeconomics and Outcomes Research Modelling Task Force [11].

As summarised in the International Society for Pharmacoeconomics and Outcomes Research Good Practices for Outcomes Research Task Force Report on Identification, Review, and Use of Health State Utilities in Cost-Effectiveness Models and other relevant literature in systematic reviews of HSUVs, there are several key considerations to assess the appropriateness of HSUV for use in a model-based CUA [9, 12]. First, it is important to verify whether the characteristics of the population are similar to the characteristics of the population that the model intends to represent [9]. These characteristics may include age, sex, disease status, disease stage or use of specific drugs. Second, HSUV might be needed for several distinct health states in a CUA, which might be stratified by stage or severity of disease, disease status, comorbidities, age, sex or adverse events. Another significant consideration when evaluating data appropriateness is the extent to which the measure used in a study is valid and sensitive to changes in the domains of health likely to be affected by the condition. Other considerations to assess data appropriateness are specific to the guidance determined by the intended audience. For example, guidelines for an economic evaluation from a health technology assessment agency may recommend a particular preference-based questionnaire (e.g. EQ-5D) or the use of specific valuation techniques such as time trade-off (TTO) or standard gamble (SG) as opposed to other techniques such as a visual analogue scale [9].

Previously published cost-effectiveness analyses in JIA raised the issue of limited data on HSUV [13]. As a result, studies have reported health consequences using intermediate outcomes, and HSUV derived from an adult population [13, 14]. A systematic review summarising a broad range of childhood HSUV, conducted prior to 2015, showed that there are some studies measuring HSUV in children with JIA [15]. However, it is still unclear to what extent these studies appropriately report data that can be used to populate a model-based CUA. Critically, this systematic review did not include studies that evaluate HSUV of adults with a history of JIA or during transition to adulthood. For chronic conditions associated with on-going medical management such as JIA, it is essential to consider modelling lifetime horizons and, therefore, retrieving HSUV of adults with a history of JIA is particularly relevant. This systematic review aims to identify studies measuring HSUV of patients with JIA across their lifespan, including children, adults, and adolescents transitioning between pediatric and adult care, and to assess whether these HSUV are appropriate to inform a model-based CUA.

2 Methods

2.1 Information Sources

A literature search to identify all published studies of interest was conducted in July 2019. The electronic databases searched included MEDLINE (1966-present), EMBASE (1947–present), PsycINFO (1806–present), EconLit (1969–present) and CINAHL (1937–present). The search strategy combined relevant MeSH terms and other keywords related to HSUV and JIA (Appendix 1 of the Electronic Supplementary Material [ESM]). In addition, reference lists from the identified publications and other relevant reviews identified in the search were screened to ascertain other pertinent studies.

2.2 Eligibility Criteria

Studies were assessed for eligibility based on the following criteria: (1) primary studies reporting HSUV data of patients with JIA (including children, adolescents and adults), (2) studies measuring HSUV using direct valuation methods (i.e. TTO, SG or conjoint analysis such as discrete choice experiments), or preference-based multi-attribute questionnaires including EQ-5D (EQ-5D-3L, EQ-5D-5L, EQ-5D-Y), Health Utilities Index (HUI, HUI2 or HUI3), Short Form 6-dimensions, quality of well-being scale, and assessment of quality of life, and (3) studies published in English.

Reviews, editorials, letters, guidelines, conference abstracts, commentaries, or responses to a previous study were excluded. Studies were also excluded if they included patients with JIA but did not report results separately for this population.

2.3 Data Collection Process

Titles and abstracts were independently screened by two reviewers (L.G. and C.R.) and any disagreement was resolved by consensus. Articles identified for full-text review were evaluated for inclusion independently, and any disagreement was resolved by consensus. Articles included were then summarised in an Excel spreadsheet in duplicate by two reviewers (L.G. and R.L.), who listed the authors, year of publication, country, study design, inclusion criteria, target population, intervention, population characteristics (e.g. age, sex), type of respondents (self vs proxy), number of respondents, type of valuation method, instrument used, the tariff set used (for preference-based multi-attribute questionnaires), whether the HSUV results are stratified by potential health states and quality assessment.

2.4 Assessing Appropriateness of Reported Health State Utility Values for Populating Model-Based Economic Evaluations

To evaluate the appropriateness of reported HSUV for populating model-based economic evaluations, we followed three steps. First, we assessed if studies reported key population characteristics that allow evaluation of whether the study population is similar to the modelled population. The population characteristics assessed included age, sex, JIA subtype, summary of disease activity or disease status (which can be measured using the Childhood Health Assessment Questionnaire [CHAQ], Juvenile Arthritis Disease Activity Score, Wallace criteria, or American College of Rheumatology responses), and description of medications.

Second, we developed a list of potential health states and population subgroups from published cost-effectiveness analyses in JIA and other health economic models developed in rheumatoid arthritis [13, 14, 16, 17]. We then assessed whether studies reported HSUV within these categories. The potential health states included:

1. health states related to disease activity or disease status (active disease, refractory disease, remission and flares), which can be measured using the CHAQ, Juvenile Arthritis Disease Activity Score, Wallace criteria or American College of Rheumatology responses;
2. health states related to treatment such as treatment response (i.e. response, no-response), treatment response to a specific treatment type (e.g. classified by drug class such as non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs or by specific drug agent) or treatment status (on treatment, off treatment);
3. health states related to other intervention effects (e.g. pre/post joint replacement, pre/post exercise programme); and
4. health states related to associated conditions (e.g. presence of uveitis, malignancies).

Population subgroups that might be considered are different age groups, sex, or JIA subtype (e.g. systemic, non-systemic). Finally, we also identified whether authors examined or raised concerns regarding the sensitivity of the preference-based health-related quality-of-life instrument in comparison with other clinical measures.

2.5 Quality Assessment

The quality of studies was assessed using a modified version of a quality assessment checklist adapted by Ara et al., as there is no validated checklist to assess studies that report HSUV [18]. This checklist assesses the most relevant aspects of study designs and direct/indirect HSUV valuation to determine if studies' estimates are free from known sources of bias (e.g. selection bias, measurement bias) and whether utility values are measured and valued appropriately.

First, we assessed the likelihood of bias including dimensions such as response rate, loss of follow-up and missing data. One challenge in developing a checklist to assess the quality of studies that report HSUV is that studies can have distinct study designs and types of valuation methods. Therefore, some of the checklist criteria are not applicable to all studies designs (e.g. loss to follow-up is only applicable to longitudinal studies and randomised controlled trials [RCTs]). Based on the information reported by the study for each of the items, we assessed the overall likelihood of bias (e.g. "are response rates reported, and if so, are the rates likely to be a threat to the validity of the estimated HSUV for the health states?"). If the study did not provide enough information to allow the item's bias assessment, the likelihood of bias was categorised as "can't tell". Each

question could be completed with: high, low, can't tell and not applicable.

The assessment of valuation methods was divided into two categories: direct valuation methods and multi-attribute questionnaires. Details about the questions assessed for each category are reported in the original checklist [18]. Each question could be completed with: yes, no, can't tell and not applicable. Quality assessment was performed by two reviewers independently (L.G. and R.L.) and disagreements were resolved by a third investigator (G.C.).

2.6 Data Synthesis

Characteristics of included studies were presented descriptively. The evaluation of appropriateness for using reported HSUV in model-based economic evaluations was presented as the percentage of studies that described key population characteristics and presented HSUV for each potential health state and/or population subgroup. Quality assessment was summarised as the number of studies that fell in each of the response categories.

3 Results

A total of 620 abstracts were retrieved from the database searches, and five were retrieved during a manual hand search. The percentage of agreement among the two reviewers with respect to title and abstract screening was 93% with a Cohen's kappa of 0.82. After duplicate removal and title and abstract screening, 39 abstracts were selected for full-text screening (Fig. 1). Among those, 13 articles matched the inclusion criteria. These 13 articles originated from ten unique studies because of multiple publications from the same cohort data. Reasons for excluding studies at the full-text screening included the lack of use of preference-based questionnaires ($n=12$), studies that did not report HSUV results separately for patients with JIA ($n=9$) and studies that administered the preference-based questionnaire (i.e. EQ-5D) but did not report HSUV ($n=5$). Instead, in these studies, results were described as the percentage of patients who answered each level of the questionnaire or by graphs (without numeric values).

3.1 Study Characteristics

The ten studies included in this review were published from 1999 to 2019. The age group targeted by the articles varied widely: seven studies (70%) included only patients with JIA aged younger or equal to 19 years, while two studies (20%) targeted only adult patients with JIA (aged ≥ 18 years), and one study did not have age restrictions, but only reported HSUV for respondents aged ≥ 18 years. The most frequent study design was cross-sectional ($n=4$), followed by longitudinal ($n=3$) and RCT ($n=3$).

The characteristics of the studies are reported in Table 1. All HSUV were valued by the general public, except for the Brunner et al. [19] study, which elicited HSUV directly from patients. Detailed characteristics of the studies, including HSUV results, are available in Appendix 2 of the ESM.

Among the studies ($n=7$) that reported HSUV of children and/or adolescents (aged younger than 19 years), four used HUI-3, two used EQ-5D (EQ-5D-3L and EQ-5D-Y), and one used a modified SG. Three studies reported only proxy-reported HSUV, one study reported self-reported HSUV, and two studies reported both self- and proxy-reported HSUV. The self-reported mode of administration was generally used in studies targeting patients aged above 12 years. The sample sizes in these studies were fewer than 72 patients per study. Other study characteristics are described in Appendix 2 of the ESM.

All three studies that reported HSUV of adults (aged older than 18 years) with a history of JIA were cross-sectional cohorts that used the EQ-5D questionnaire. The sample sizes varied widely from 35 to 2594 respondents. Detailed study characteristics are further reported in Appendix 3 of the ESM.

3.2 Appropriateness for Using Reported Health State Utility Values in Model-Based Economic Evaluations

Population characteristics reported by the included studies are described in Table 2. All studies described the population age (ten out of ten studies) and the majority of studies reported the population sex (eight out of ten studies). However, disease activity/disease status was reported in five out of ten studies, and drug treatment was reported in four out of ten studies.

Regarding reporting results by potential health states, six out of ten studies stratified for at least one of the potential health state categories or population subgroups (Table 3). One study (out of ten) reported HSUV of patients with a polyarticular course treated with etanercept over a period of 27 months [20–22]. Health states related to interventions were reported by three RCTs [23–25]. These studies evaluated non-pharmacological (i.e. combination of hydrotherapy and land-based physiotherapy [23], and a multidisciplinary foot care programme [24]) and pharmacological (i.e. adalimumab and methotrexate vs methotrexate alone for the treatment of uveitis [25]) interventions in children and adolescents with JIA. In the non-pharmacological RCTs [23, 24], the EQ-5D's HSUV were very similar among intervention and control groups while condition-specific measures were not and the authors raised the concern that the EQ-5D

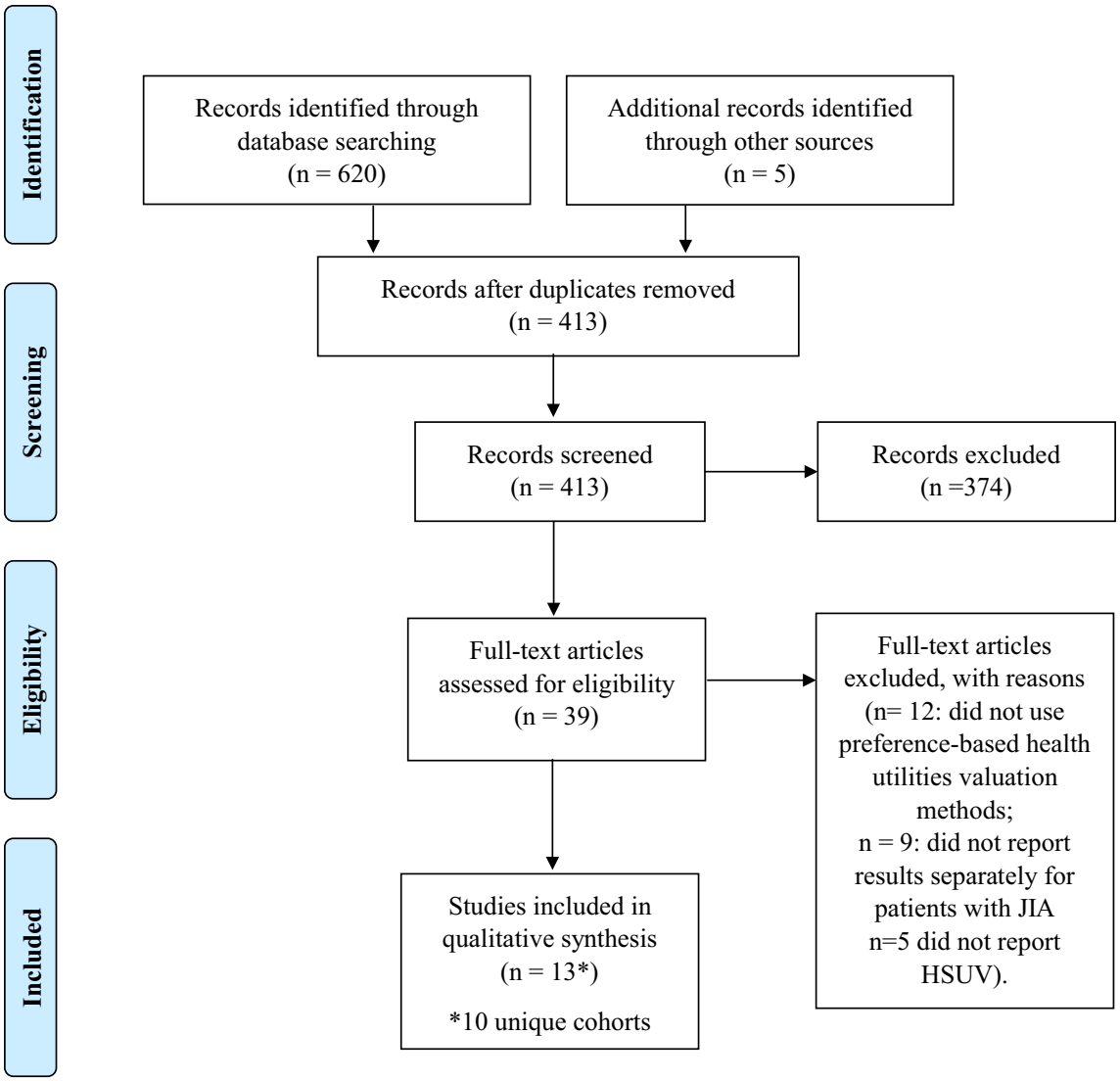

Fig. 1 PRISMA flow diagram

questionnaire might have not been sufficiently sensitive to capture the impact of these interventions.

Barth et al. [26] reported HSUV for the overall cohort and specifically for patients receiving drug treatment (however, drug treatment type was not specified). Finally, Haasnoot et al. [27] stratified HSUV measured by EQ-5D-3L among patients with and without uveitis. The authors discussed that health-related quality of life measured using EQ-5D scores in that population do not seem to be influenced by the presence of uveitis [27]. These effects, however, were captured by other condition-specific instruments. Only one study, by Brunner et al., [19] stratified HSUV based on disease activity measured using disease activity states defined by CHAQ (absent, mild, mild/moderate, moderate). However, the HSUV measured by the modified SG was not sensitive to changes among different CHAQ categories. None of the studies reported HSUV for health states related to treatment response or across different population subgroups.

The remaining four studies did not report HSUV stratified by potential health states or population subgroups [26, 28–31]. These studies presented the mean or median HSUV associated with a broad and heterogeneous population, or did not present sufficient information to evaluate whether the cohort was a homogenous population subgroup.

3.3 Quality Assessment

The quality assessment is summarised in Figs. 2 and 3. The likelihood of bias due to response rate issues was considered high in four out of ten studies. We could not evaluate the likelihood of response rate and missing data bias because

Table 1 Study characteristics grouped by targeted age group, sorted by year

Study, year	Country	Study type	Inclusion criteria	Intervention	Instrument	Respondent	Valuation method (country)	Number of respondents
Patients with JIA aged ≤ 19 years								
Mittmann et al., 1999 [28]	Canada	Cross-sectional	Household residents in all Canadian provinces over the age of 12 years	NA	HUI-3	Self-reported	SG (Canada)	20[a]
Brunner et al., 2004 [19]	USA	Longitudinal	Patients aged ≤ 18 years with symptoms of chronic arthritis, irrespective of a specific underlying diagnosis, for more than 3 months	NA	Modified SG	Self-reported and proxy reported	NA	58 parents and 31 children (age ≥ 12 years)
Epps et al., 2005 [23]	UK	RCT	Age 4–19 years, diagnosed with JIA for more than 3 months, onset before age 16 years, stable medication with at least one active joint	Hydrotherapy and land-based physiotherapy vs land-based physiotherapy only	EQ-5D-3L	Proxy reported	TTO (UK)	72
Petrou et al., 2009 [29]	England and Scotland	Cross-sectional	Families of children in the UK with disability or severe illness included in the "disability survey 2000", age 5–16 years	NA	HUI-3	Proxy reported	SG (Canada)	21
Prince et al., 2010, 2011 [20, 22]; Anink et al., 2015 [21]	The Netherlands	Longitudinal	Patients with a polyarticular course of the disease and the response to the maximum tolerated dose of methotrexate is not sufficient	Therapy with etanercept	HUI-3	Proxy reported	SG (Canada)	49

Table 1 (continued)

Study, year	Country	Study type	Inclusion criteria	Intervention	Instrument	Respondent	Valuation method (country)	Number of respondents
Hendry et al., 2013 [24]	UK	RCT	Patients with JIA with documented arthritis in the foot including small joints, documented foot arthritis in one or more large joints, and/or current widespread polyarthritis involving large and small foot joints	Multidisciplinary foot care intervention vs standard of care	EQ-5D-Y and EQ-5D-3L	Self-reported and proxy reported	ND	44
Ramanan et al., 2019 [25]	UK	RCT	Children and adolescents (aged 2–18 years) with JIA, active anterior uveitis, who did not respond to methotrexate and did not receive DMARDs in the 4 weeks prior to screening	Treatment with adalimumab and methotrexate vs methotrexate alone	HUI-3	Proxy reported and interview administered	SG (Canada)	90
Patients with JIA aged ≥ 16 years								
Kuhlmann et al., 2016 [30]; Angelis et al., 2016 [31][b]	Germany, Italy, Spain, France, UK, Bulgaria, Sweden	Cross-sectional	Patients diagnosed with JIA who received outpatient care and were living in the community	NA	EQ-5D[c]	Self-reported	TTO (Germany, Sweden and UK)	Total: 161 respondents, age ≥ 18 years: 35[b]
Barth et al., 2016 [26]	Germany	Cross-sectional	Patients with rheumatic disease who had been admitted to the German Centre for Rheumatology in Children and Adolescents between 1952 and 2010 and aged > 18 years	NA	EQ-5D-3L	Self-reported	VAS and TTO (Germany)	2592

Table 1 (continued)

Study, year	Country	Study type	Inclusion criteria	Intervention	Instrument	Respondent	Valuation method (country)	Number of respondents
Haasnoot et al., 2017 [27]	The Netherlands	Cross-sectional	Patients with a history of JIA with or without anterior uveitis, aged > 18 years, who visited the ophthalmology department and/or rheumatology department of the University Medical Center of Utrecht	NA	EQ-5D-3L	Self-reported	TTO (the Netherlands)	81

DMARD disease-modifying anti-rheumatic drug, *HUI-3* Health Utility Instrument version 3, *HSUV* health state utility values, *JIA* juvenile idiopathic arthritis, *NA* not applicable, *ND* not described, *RCT* randomised clinical trial, *SG* standard gamble, *TTO* time trade-off, *VAS* visual analogue scale

[a]Respondents with arthritis aged between 12 and 19 years

[b]Study did not present age limitation in its inclusion criteria, but only reported HSUV for age ≥ 18 years

[c]Inconsistency between version of questionnaire reported on abstract (5L), and version reported in the methods (3L)

of limited reported information in two and six out of the ten studies, respectively.

Regarding the appropriate use of valuation methods (Fig. 3), one study used a modified version of SG as a direct valuation method. The modified SG did not anchor 1 as equivalent to full health and 0 as dead, but instead 0 was equivalent to "lifelong severe arthritis, requiring use of wheelchair and help with activities of daily living for the rest of the child's natural life". The majority of studies that used a preference-based multi-attribute questionnaire ($n = 7$ out of 9) reported appropriate details on the questionnaire version used, and whether it was used for the age group for which it was designed. Only one study did not describe which tariff set was used. The quality assessment details for each of the studies are described in Appendix 4 of the ESM.

4 Discussion

This systematic review is the first study that provides an overview of existing HSUV evidence in JIA and discusses whether these estimates are appropriately reported to populate a model-based CUA. Our review showed that evidence on HSUV in JIA is still very limited, only ten studies reported HSUV in the current literature. Reporting on population characteristics was poor in at least seven of the ten studies regarding details on JIA subtype, disease severity, disease status and treatment regime. The implication of this finding is that poor reporting hinders the evaluation of whether the study population is similar to the population being represented by the model. In addition, we observed that very few studies reported HSUV among distinct health states to allow their use in health economic models. Critically, there is also a lack of reporting of HSUV for distinct health states in adults with a history of JIA, limiting the development of models with longer time horizons.

Studies that could potentially be used to populate in a model-based CUA include the longitudinal cohort by Prince et al. that evaluated HSUV over time in a homogenous population of children with a polyarticular JIA course receiving etanercept. This study described detailed population characteristics and is considered appropriate to inform a model evaluating specific etanercept treatment-response health states [20, 22]. This study, however, did not measure HSUV in a comparator group to provide information around the difference between on-treatment vs off-treatment states, which would then need to be determined elsewhere. Other studies with potential to inform health economic models are the three clinical trials [23–25]. However, despite reporting detailed population characteristics and HSUV results for intervention groups, they also represent a very specific population and interventions that raise concerns regarding

Table 2 Evaluation of reporting regarding relevant population characteristics used to assess appropriateness, sorted by year

Study, year	Age descriptives	Sex descriptives	JIA subtype	Disease activity/ disease status	Drug treatment
Mittmann et al., 1999 [28]	+[a]	–	–	–	–
Brunner et al., 2004 [19]	+	+	–	+	–
Epps et al., 2005 [23]	+	+	+	+	+
Petrou et al., 2009 [29]	+	–	–	–	–
Prince et al., 2010, 2011 [20, 22]; Anink et al., 2015 [21]	+	+	+	+	+
Hendry et al., 2013 [24]	+	+	+	+	+
Kuhlmann et al., 2016 [30]; Angelis et al., 2016 [31]	+	+	+	–	–
Barth et al., 2016 [26]	+[a]	+	–	–	–[b]
Haasnoot et al., 2017 [27]	+	+	+	–	–[b]
Ramanan et al., 2019 [25]	+	+	+	+	+
Number of studies that reported this information (out of 10 studies)	10	8	6	5	4

DMARDs disease-modifying antirheumatic drugs, *HSUV* health state utility values, *JIA* juvenile idiopathic arthritis, *NSAIDs* non-steroidal anti-inflammatory drugs, + indicates that the study reported information, – indicates that the study did not report information

[a]Study reported only the age range (i.e. there was no other measure of frequency such as mean or median)

[b]Details on treatment type were not described (i.e. did not specify whether treatment was NSAIDs, DMARDs or others)

Table 3 Evaluation of reporting health state utility values (HSUV) by potential health states and/or population subgroups, sorted by year

Study, year	Disease activity	Treatment response	Treatment status	Intervention related	Associated conditions	Any population subgroup
Mittmann et al., 1999 [28]	–	–	–	–	–	–
Brunner et al., 2004 [19]	+	–	–	–	–	–
Epps et al., 2005 [23]	–	–	–	+	–	–
Petrou et al., 2009 [29]	–	–	–	–	–	–
Prince et al., 2010, 2011 [20, 22]; Anink et al., 2015 [21]	–	+	–	–	–	–
Hendry et al., 2013 [24]	–	–	–	+	–	–
Kuhlmann et al., 2016 [30]; Angelis et al. 2016 [31]	–	–	–	–	–	–
Barth et al., 2016 [26]	–	–	+[a]	–	–	–
Haasnoot et al., 2017 [27]	–	–	–	–	+	–
Ramanan et al., 2019 [25]	–	–	–	+	–	–
Number of studies that reported this information (out of 10 studies)	1	2	1	3	1	0

+ Indicates that the study reported HSUV related to that potential health state category, – indicates that the study did not report HSUV related to that potential health state category

[a]Study reported HSUV of patients receiving drug treatment (type of drug treatment not specified); however, failed to report HSUV of patients not receiving treatment

EQ-5D lacking sensitivity for detecting differences in HSUV for the exercise programmes.

The questionnaire's lack of sensitivity related to other clinical measures was also a concern raised in another two studies: the first reported HSUV for distinct disease activity in children using SG and the second reported HSUV for adults with history of JIA with and without uveitis using EQ-5D-3L. The issue regarding EQ-5D-3L's lack of responsiveness to health changes is not exclusive to JIA. A systematic review found that the EQ-5D-3L presented mixed evidence of responsiveness for half of the studies reviewed, which included multiple conditions [32]. The authors suggest using condition-specific measures in addition to EQ-5D to ensure appropriate estimates of effectiveness.

Another issue identified that could prevent the use of HSUV in a model-based CUA is that in some of the studies, health states are not well characterised (i.e. one study reported HSUV for patients receiving treatment but did not specify the type of treatment). These findings show the current HSUV evidence in JIA that could be considered

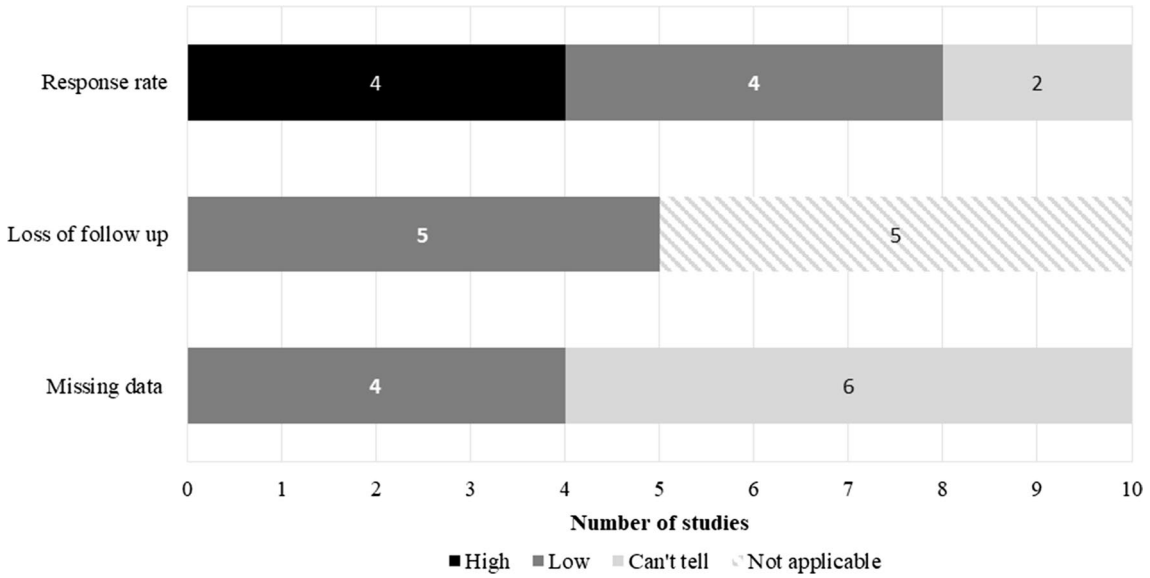

Fig. 2 Description of the likelihood of bias evaluation by the dimensions of quality assessment checklist (response rate, loss to follow-up (if applicable), and missing data)

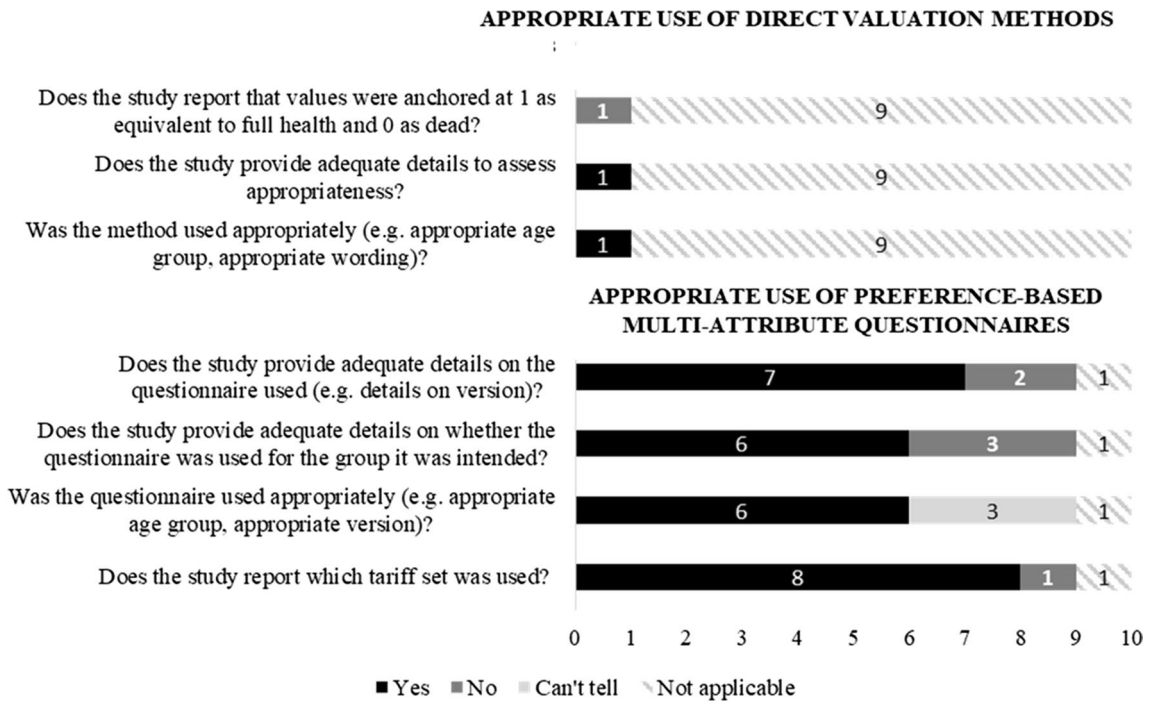

Fig. 3 Number of studies satisfying appropriateness criterion for use of direct valuation methods or preference-based multi-attribute questionnaires

appropriate to populate model-based economic evaluations is limited.

To populate model-based economic evaluations, in addition to evaluating the appropriateness and relevance of reporting on patient population characteristics and health states, it is crucial to assess the quality of the evidence. Our findings showed that a quality assessment can be challenging because study characteristics, such as response rates or missing data, are not always described in sufficient detail. The use of biased or low-quality evidence can lead to high analysis uncertainty or over/underestimation of quality-adjusted life-year gains, which can impact decision making.

Health state utility values are usually estimated using direct valuation methods (e.g. TTO, SG) or preference-based multi-attribute questionnaires (e.g. EQ-5D). In the absence of a direct valuation, it is possible to derive HSUV by mapping algorithms from disease-specific questionnaires (e.g. Child Health Assessment Questionnaire) onto generic preference-based measures [33]. Typically, direct values are preferred to values that are mapped from disease-specific quality-of-life questionnaires when developing model-based economic evaluations, as the use of mapping can lead to increased uncertainty and error around the estimates of HSUV [18]. Although this systematic review was focused specifically on identifying studies measuring direct or indirect HSUV, we have not observed any studies mapping disease-specific questionnaires to HSUV in JIA during title and abstract screening.

In the studies identified, EQ-5D and HUI questionnaires were the only two types of preference-based multi-attribute questionnaires used to measure HSUV in JIA. While HUI-3 was most commonly used to measure HSUV in children with JIA, EQ-5D was the questionnaire of choice in adults with a history of JIA. This difference can be explained by the fact that the HUI-3 questionnaire was designed to be used in a broad age range (≥ 5 years) and with the same multi-attribute weights to calculate HUI scores independently of age group [34]. Conversely, the EQ-5D version adapted for children and adolescents (EQ-5D-Y) was published and validated only in 2010 [35]. Although we observed an increase in the number of studies using EQ-5D-Y over time, value sets for EQ-5D-Y are still unavailable. Research has suggested that the adult version of EQ-5D-3L value sets is inappropriate to be used for children and adolescents [36]. Even though the structure of the two questionnaires is very similar, a multinational study showed that health states are valued differently when they are described as applying to a child rather than for an adult [37].

We also noted that the EQ-5D-3L was used in all studies, including studies published after the 5L EQ-5D version was introduced in 2009. Possible explanations for choosing the EQ-5D-3L over the 5L are the lack of availability of country-specific EQ-5D-5L value sets when the study was conducted, lack of validation of the updated version in the population of interest or simply because the 3L version has been a well-established version of EQ-5D.

The EQ-5D-5L version was introduced in 2009 with the intent to improve sensitivity and reduce ceiling effects found in the 3L version [38]. A recent systematic review that included 20 studies comparing EQ-5D-5L and EQ-5D-3L measurement properties indicated that the 5L version demonstrated advantages in terms of ceiling effects, distributional properties and how the descriptive system is used [39]. Specifically, in the rheumatology field, studies in patients with arthritis undergoing hip and knee replacements suggests that EQ-5D-5L has evidence of superior construct validity, informativity and discriminatory power, especially for the mobility dimension [40, 41]. Moving forward, as the body of evidence around the advantages (or not) of using EQ-5D-5L grows, there is potential to explore the use of this version of the instrument when measuring HSUV in JIA.

All the valuation methods used by the multi-attribute questionnaires elicited preferences from the general population. The HUI-3 health states were valuated using value sets derived from the SG method, while country-specific TTO value sets were used in studies that used EQ-5D. Only one study elicited HSUV directly from children with JIA and their parents using a modified SG technique. The issue regarding whose preferences should be measured was widely discussed in the health economics literature. If the intent of the analysis is to inform societal resource allocation using a societal decision-making framework, then it would be usually preferred to elicit preferences of a representative sample of the population rather than use individual preferences of people's own health [42].

This review has limitations. The search strategy used would not capture articles that did not refer to any of the HSUV valuation methods either in the title, abstract or keywords. To mitigate this limitation, we also hand searched articles' references and searched the grey literature (i.e. Google Scholar and EuroQoL websites) using JIA-related terms in July 2019. No additional studies were identified through this strategy.

5 Conclusions

We have identified critical gaps in the literature reporting HSUV in patients with JIA including a lack of detail regarding the population characteristics and measures for distinct health states. These issues can produce discrepancies in the results generated, which can undermine policy decisions informed by cost per quality-adjusted life-year [43]. Based on our findings, there is a need for improvement in the quality of data reported and in the differentiation of HSUV among JIA health states. The current reported HSUV data in JIA are insufficient to fully inform cost-effectiveness models with a short or lifetime horizon. Rigorous HSUV assessment and reporting are needed to inform model-based CUAs in JIA.

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Data Availability The detailed information regarding search strategy, data extracted from included studies and quality assessment of individual studies are available in the Electronic Supplementary Material.

Compliance with Ethical Standards

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Conflict of interest Luiza R. Grazziotin, Gillian Currie, Michelle M. A. Kip, Maarten J. IJzerman, Marinka Twilt, Raymond Lee, and Deborah A. Marshall have no conflicts of interest that are directly relevant to the content of this article.

References

1. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet. 2011;377(9783):2138–49. https://doi.org/10.1016/s0140-6736(11)60244-4.
2. Shiff NJ, Oen K, Kroeker K, Lix LM. Trends in population-based incidence and prevalence of juvenile idiopathic arthritis in Manitoba, Canada. Arthritis Care Res. 2019;71(3):413–8. https://doi.org/10.1002/acr.23606.
3. Kip MMA, Currie G, Marshall DA, Grazziotin Lago L, Twilt M, Vastert SJ, et al. Seeking the state of the art in standardized measurement of health care resource use and costs in juvenile idiopathic arthritis: a scoping review. Pediatr Rheumatol Online J. 2019;17(1):20. https://doi.org/10.1186/s12969-019-0321-x.
4. Tollisen A, Selvaag AM, Aulie HA, Lilleby V, Aasland A, Lerdal A, et al. Physical functioning, pain, and health-related quality of life in adults with juvenile idiopathic arthritis: a longitudinal 30-year followup study. Arthritis Care Res. 2018;70(5):741–9. https://doi.org/10.1002/acr.23327.
5. Oliveira-Ramos F, Eusebio M, Mourao AF, Furtado C, Campanilho-Marques R, et al. Juvenile idiopathic arthritis in adulthood: fulfilment of classification criteria for adult rheumatic diseases, long-term outcomes and predictors of inactive disease, functional status and damage. RMD Open. 2016;2(2):e000304. https://doi.org/10.1136/rmdopen-2016-000304.
6. Albers HM, Wessels JA, van der Straaten RJ, Brinkman DM, Suijlekom-Smit LW, Kamphuis SS, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. Arthritis Rheum. 2009;61(1):46–51. https://doi.org/10.1002/art.24087.
7. Otten MH, Anink J, Prince FH, Twilt M, Vastert SJ, ten Cate R, et al. Trends in prescription of biological agents and outcomes of juvenile idiopathic arthritis: results of the Dutch National Arthritis and Biologics in Children Register. Ann Rheum Dis. 2015;74(7):1379–86. https://doi.org/10.1136/annrheumdis-2013-204641.
8. Brazier J. Valuing health states for use in cost-effectiveness analysis. Pharmacoeconomics. 2008;26(9):769–79. https://doi.org/10.2165/00019053-200826090-00007.
9. Brazier J, Ara R, Azzabi I, Busschbach J, Chevrou-Severac H, Crawford B, et al. Identification, review, and use of health state utilities in cost-effectiveness models: an ISPOR Good Practices for Outcomes Research Task Force Report. Value Health. 2019;22(3):267–75. https://doi.org/10.1016/j.jval.2019.01.004.
10. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. Med Decis Mak. 2012;32(5):678–89. https://doi.org/10.1177/0272989x12454941.
11. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices: overview. A report of the ISPOR-SMDM Modeling Good Research Practices Task Force: 1. Value Health. 2012;15(6):796–803. https://doi.org/10.1016/j.jval.2012.06.012.
12. Petrou S, Kwon J, Madan J. A practical guide to conducting a systematic review and meta-analysis of health state utility values. Pharmacoeconomics. 2018;36(9):1043–61. https://doi.org/10.1007/s40273-018-0670-1.
13. Luca NJ, Burnett HF, Ungar WJ, Moretti ME, Beukelman T, Feldman BM, et al. Cost-effectiveness analysis of first-line treatment with biologic agents in polyarticular juvenile idiopathic arthritis. Arthritis Care Res. 2016;68(12):1803–11.
14. Ungar WJ, Costa V, Hancock-Howard R, Feldman BM, Laxer RM. Cost-effectiveness of biologics in polyarticular-course juvenile idiopathic arthritis patients unresponsive to disease-modifying antirheumatic drugs. Arthritis Care Res. 2011;63(1):111–9.
15. Kwon J, Kim SW, Ungar WJ, Tsiplova K, Madan J, Petrou S. A systematic review and meta-analysis of childhood health utilities. Med Decis Mak. 2018;38(3):277–305. https://doi.org/10.1177/0272989x17732990.
16. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20(34):1–222.
17. Bansback N, Ara R, Karnon J, Anis A. Economic evaluations in rheumatoid arthritis: a critical review of measures used to define health States. Pharmacoeconomics. 2008;26(5):395–408. https://doi.org/10.2165/00019053-200826050-00004.
18. Ara R, Brazier J, Peasgood T, Paisley S. The identification, review and synthesis of health state utility values from the literature. Pharmacoeconomics. 2017;35(Suppl. 1):43–55. https://doi.org/10.1007/s40273-017-0547-8.
19. Brunner HI, Klein-Gitelman MS, Miller MJ, Trombley M, Baldwin N, Kress A, et al. Health of children with chronic arthritis: relationship of different measures and the quality of parent proxy reporting. Arthritis Rheum. 2004;51(5):763–73.
20. Prince FH, de Bekker-Grob EW, Twilt M, van Rossum MA, Hoppenreijs EP, ten Cate R, et al. An analysis of the costs and treatment success of etanercept in juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children Register. Rheumatology. 2011;50(6):1131–6.
21. Anink J, Prince FH, Dijkstra M, Otten MH, Twilt M, ten Cate R, et al. Long-term quality of life and functional outcome of patients with juvenile idiopathic arthritis in the biologic era: a longitudinal follow-up study in the Dutch Arthritis and Biologicals in Children Register. Rheumatology. 2015;54(11):1964–9.

22. Prince FH, Geerdink LM, Borsboom GJ, Twilt M, van Rossum MA, Hoppenreijs EP, et al. Major improvements in health-related quality of life during the use of etanercept in patients with previously refractory juvenile idiopathic arthritis. Ann Rheum Dis. 2010;69(1):138–42.
23. Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, et al. Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis. Health Technol Assess. 2005;9(39):iii–iv, ix–x, 1–59.
24. Hendry GJ, Watt GF, Brandon M, Friel L, Turner DE, Lorgelly PK, et al. The effectiveness of a multidisciplinary foot care program for children and adolescents with juvenile idiopathic arthritis: an exploratory trial. J Rehabil Med. 2013;45(5):467–76. https://doi.org/10.2340/16501977-1130.
25. Ramanan AV, Dick AD, Jones AP, Hughes DA, McKay A, Rosala-Hallas A, et al. Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT. Health Technol Assess. 2019;23(15):1–140. https://doi.org/10.3310/hta23150.
26. Barth S, Haas JP, Schlichtiger J, Molz J, Bisdorff B, Michels H, et al. Long-term health-related quality of life in German patients with juvenile idiopathic arthritis in comparison to German general population. PLoS ONE. 2016;11(4):e0153267.
27. Haasnoot AJW, Sint Jago NFM, Tekstra J, de Boer JH. Impact of uveitis on quality of life in adult patients with juvenile idiopathic arthritis. Arthritis Care Res. 2017;69(12):1895–902.
28. Mittmann N, Trakas K, Risebrough N, Liu BA. Utility scores for chronic conditions in a community-dwelling population. Pharmacoeconomics. 1999;15(4):369–76. https://doi.org/10.2165/00019053-199915040-00004.
29. Petrou S, Kupek E. Estimating preference-based Health Utilities Index Mark 3 utility scores for childhood conditions in England and Scotland. Med Decis Mak. 2009;29(3):291–303. https://doi.org/10.1177/0272989x08327398.
30. Kuhlmann A, Schmidt T, Treskova M, López-Bastida J, Linertová R, Oliva-Moreno J, et al. Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe. Eur J Health Econ. 2016;17:79–877. https://doi.org/10.1007/s10198-016-0786-1.
31. Angelis A, Kanavos P, Lopez-Bastida J, Linertova R, Serrano-Aguilar P. Socioeconomic costs and health-related quality of life in juvenile idiopathic arthritis: a cost-of-illness study in the United Kingdom. BMC Musculoskelet Disord. 2016;17:321.
32. Payakachat N, Ali MM, Tilford JM. Can the EQ-5D detect meaningful change? A systematic review. Pharmacoeconomics. 2015;33(11):1137–54. https://doi.org/10.1007/s40273-015-0295-6.
33. Ara R, Rowen D, Mukuria C. The use of mapping to estimate health state utility values. Pharmacoeconomics. 2017;35(Suppl. 1):57–66. https://doi.org/10.1007/s40273-017-0548-7.
34. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. Med Care. 2002;40(2):113–28.
35. Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res. 2010;19(6):875–86. https://doi.org/10.1007/s11136-010-9648-y.
36. Rowen D, Rivero-Arias O, Devlin N, Ratcliffe J. Review of valuation methods of preference-based measures of health for economic evaluation in child and adolescent populations: where are we now and where are we going? Pharmacoeconomics. 2020;38(4):325–40. https://doi.org/10.1007/s40273-019-00873-7.
37. Kind P, Klose K, Gusi N, Olivares PR, Greiner W. Can adult weights be used to value child health states? Testing the influence of perspective in valuing EQ-5D-Y. Qual Life Res. 2015;24(10):2519–39. https://doi.org/10.1007/s11136-015-0971-1.
38. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36. https://doi.org/10.1007/s11136-011-9903-x.
39. Buchholz I, Janssen MF, Kohlmann T, Feng Y-S. A systematic review of studies comparing the measurement properties of the three-level and five-level versions of the EQ-5D. Pharmacoeconomics. 2018;36(6):645–61. https://doi.org/10.1007/s40273-018-0642-5.
40. Conner-Spady BL, Marshall DA, Bohm E, Dunbar MJ, Loucks L, Al Khudairy A, et al. Reliability and validity of the EQ-5D-5L compared to the EQ-5D-3L in patients with osteoarthritis referred for hip and knee replacement. Qual Life Res. 2015;24(7):1775–844. https://doi.org/10.1007/s11136-014-0910-6.
41. Jin X, Al Sayah F, Ohinmaa A, Marshall DA, Smith C, Johnson JA. The EQ-5D-5L is superior to the -3L version in measuring health-related quality of life in patients awaiting THA or TKA. Clin Orthop Relat Res. 2019;477(7):1632–44. https://doi.org/10.1097/corr.0000000000000662.
42. Weinstein MC, Torrance G, McGuire A. QALYs: the basics. Value Health. 2009;12(Suppl. 1):S5–9. https://doi.org/10.1111/j.1524-4733.2009.00515.x.
43. Ara R, Brazier J, Zouraq IA. The use of health state utility values in decision models. Pharmacoeconomics. 2017;35(Suppl. 1):77–88. https://doi.org/10.1007/s40273-017-0550-0.

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