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Preference-Based Health-Related Quality-of-Life Outcomes in Children with Autism Spectrum Disorders

A Comparison of Generic Instruments

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Abstract

Background: Cost-effectiveness analysis of pharmaceutical and other treatments for children with autism spectrum disorders (ASDs) has the potential to improve access to services by demonstrating the value of treatment to public and private payers, but methods for measuring QALYs in children are under-studied. No cost-effectiveness analyses have been undertaken in this population using the cost-per-QALY metric.

Objective: This study describes health-related quality-of-life (HR-QOL) outcomes in children with ASDs and compares the sensitivity of two generic preference-based instruments relative to ASD-related conditions and symptoms.

Methods: The study design was cross-sectional with prospectively collected outcome data that were correlated with retrospectively assessed clinical information. Subjects were recruited from two sites of the Autism Treatment Network (ATN) in the US: a developmental centre in Little Rock, Arkansas, and an outpatient psychiatric clinic at Columbia University Medical Center in New York. Children that met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for an ASD by a multidisciplinary team evaluation were asked to participate in a clinical registry. Families of children with an ASD that agreed to be contacted about participation in

future research studies as part of the ATN formed the sampling frame for the study. Families were included if the child with the ASD was between 4 and 17 years of age and the family caregiver spoke English. Eligible families were contacted by mail to see if they would be interested in participating in the study with 150 completing surveys. HR-QOL outcomes were described using the Health Utilities Index (HUI) 3 and the Quality of Well-Being Self-Administered (QWB-SA) scale obtained by proxy via the family caregiver.

Results: Children were diagnosed as having autistic disorder (76%), pervasive developmental disorder-not otherwise specified [PDD-NOS] (15%), and Asperger's disorder (9%). Average HUI3 and QWB-SA scores were 0.68 (SD 0.21, range 0.07–1) and 0.59 (SD 0.16, range 0.18–1), respectively. The HUI3 score was significantly correlated with clinical variables including adaptive behaviour ($\rho = 0.52$; $p < 0.001$) and cognitive functioning ($\rho = 0.36$; $p < 0.001$). The QWB-SA score had weak correlation with adaptive behaviour ($\rho = 0.25$; $p < 0.001$) and cognitive functioning ($\rho = 0.17$; $p < 0.005$). Change scores for the HUI3 were larger than the QWB-SA for all clinical measures. Scores for the HUI3 increased 0.21 points (95% CI 0.14, 0.29) across the first to the third quartile of the cognitive functioning measure compared with 0.05 (95% CI –0.01, 0.11) for the QWB-SA. Adjusted R^2 values also were higher for the HUI3 compared with the QWB-SA across all clinical measures.

Conclusions: The HUI3 was more sensitive to clinical measures used to characterize children with autism compared with the QWB-SA score. The findings provide a benchmark to compare scores obtained by alternative methods and instruments. Researchers should consider incorporating the HUI3 in clinical trials and other longitudinal research studies to build the evidence base for describing the cost effectiveness of services provided to this important population.

Key points for decision makers

- Information on QALY scores in children with autism spectrum disorders (ASDs) is scant
- Currently, it is unclear which instruments are able to measure the health-related quality of life (HR-QOL) of these children reliably
- We find that the Health Utilities Index 3 is relatively sensitive to variations in clinical measures in this target group
- Thirty percent of children with ASDs have severe problems with language use and understanding, resulting in a large decrement in HR-QOL

Introduction

Autism spectrum disorders (ASDs) are characterized by impairments in social skills, communication, and cognitive and behavioural functioning.[1-4] Children with ASDs can exhibit severe tantrums, non-compliance, destructiveness and self-injury.[5-7] They may require less sleep and have

frequent awakenings during the night.[8-11] Successful pharmaceutical and other interventions for children with ASDs thus have the potential to improve their quality-of-life (QOL) outcomes, yet we know little about the relative impact of different ASD-related impairments on general health-related QOL (HR-QOL). In addition, given the varied symptoms that are common among children with ASDs, there is need for evidence on the cost effectiveness of ASD interventions to assist with prioritizing services. Only one study has examined HR-QOL outcomes for children with ASDs across the complete spectrum of disorders and in relation to ASD severity and common behavioural characteristics. Kuhlthau et al.[12] measured HR-QOL outcomes for children enrolled in the Autism Treatment Network (ATN) using the Pediatric Quality of Life Inventory™ (PedsQL™) questionnaire. Survey responses to the PedsQL™ were linked with clinical data describing the child's cognitive ability, adaptive functioning, ASD-related symptoms, and behavioural problems. Findings from the study showed HR-QOL deficits in all domains of health including physical, psychosocial, emotional, social and school functioning relative to healthy children. In addition, ASD-related symptoms were associated with decrements in HR-QOL.[12]

Evidence of associations between ASD-related symptoms and HR-QOL suggests that effective treatments for children with ASDs have the potential to reduce associated symptoms and improve HR-QOL for the child. Such associations also permit targeting or development of interventions for specific behavioural characteristics that might produce the greatest gains in HR-QOL, although such evidence would require appropriate confirmation. Interventions could be prioritized using cost-effectiveness analysis and other relevant criteria, which would permit a more rational allocation of resources by informing public and private payers of the value of services.[13] Despite the importance of developing treatment protocols for children with ASDs that can optimally reduce ASD-related symptoms and improve HR-QOL, no studies have reported on the cost effectiveness of ASD services using a cost-utility or cost-per-QALY framework.

The lack of information on cost effectiveness may be related to the limited information available that identifies *preference-based* HR-QOL outcomes in children with ASDs. Preference-based HR-QOL outcomes are valued on a 0–1 scale where 0 represents death and 1 represents perfect health. Preference-based HR-QOL outcomes need to be combined with life-years in order to calculate QALYs, which are commonly viewed as the preferred metric for cost-effectiveness analysis.[14] When cost-effectiveness analyses are conducted with QALYs, they, in principle, permit standardized comparisons with other mental and physical conditions as well as conditions affecting different age groups.[15] Different interventions targeted at different impairments associated with a condition (e.g. behavioural problems, sleep issues and communication issues – all of which are common for children with ASDs) can thus be compared in terms of their efficiency expressed as costs per QALY gained. Measurement of preference-based HR-QOL outcomes in the context of child health conditions, however, has typically lagged behind adult conditions.[16-18] Measuring preference-based HR-QOL in children raises a number of methodological issues, including the need to use proxy respondents such as parents.[19,20] We are aware of only two small case series that report preference-based HR-QOL outcomes in children with ASDs.[21,22] Both studies of children with ASDs used the Health Utilities Index (HUI) 3 instrument to describe HR-QOL outcomes with the child's caregiver as a proxy respondent. Information on the clinical characteristics of the child was not included in these descriptions so it is not possible to relate differences in ASD-specific outcomes to differences in QALY scores.

This paper seeks to explore further the validity of generic preference-based instruments to describe HR-QOL in relation to disease-specific health outcomes for children with ASDs. A number of studies have examined the sensitivity of different generic instruments to describe preference-based HR-QOL in relation to disease-specific health outcomes in adult conditions including schizophrenia,[23,24] substance-use disorders,[25] and other physical[26,27] and mental health conditions.[28]

Studies test the sensitivity of different instruments because the choice of instrument has the potential to influence estimated cost-effectiveness ratios.[29] As different instruments have different domain structures, some instruments may be better suited for economic evaluations of a given condition relative to other instruments.[30] While the literature on the 'comparative effectiveness' of different instruments to measure QALYs in different adult conditions is large and growing,[30] few studies have compared instruments for conditions affecting children.[31,32]

Thus, the current study had two main objectives: (i) to evaluate the construct validity of two instruments for describing preference-based HR-QOL in children with ASDs; and (ii) to identify the magnitude of potential QALY gains from treatment based on relationships between clinical variables and the HR-QOL instruments. Information on construct validity is necessary to determine whether some generic instruments may be considered better suited for measuring HR-QOL scores in children with ASDs relative to others. For this study, we compared the HUI3 with the Quality of Well-Being Self-Administered (QWB-SA) scale. The HUI3 has been used in a number of studies involving children[33,34] as well as autism.[21,22] The QWB-SA was used for comparison in this study because it has been shown to work well in mental health conditions in adult populations.[23,35] We provide an indication of the magnitude of changes in relation to clinical parameters using both instruments to inform future cost-effectiveness analyses of ASD interventions.

Methods

Participants and Study Design

The study used a cross-sectional and prospective design to obtain outcome measures that were correlated with retrospectively captured clinical data. Participants for the study were recruited through two sites of the ATN in the US funded by Autism Speaks (an autism advocacy organization): a developmental centre in Little Rock, Arkansas, and an outpatient psychiatric clinic at Columbia University Medical Center in New York. At these two clinical sites, children suspected of having an ASD completed a multidisciplinary evaluation that included diagnostic, cognitive, behavioural and physical assessments. Children that met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for an ASD were asked to participate in a clinical registry. The clinical registry contains information on ASD-related symptoms and severity, cognitive functioning, and other clinical information as described in the 'Clinical Measures' section. Families of children with an ASD that agreed to be contacted about participation in future research studies as part of the ATN formed the sampling frame for the study. Families were included if the child with the ASD was between 4 and 17 years of age and the family caregiver spoke English. Eligible families were contacted by mail to see if they would be interested in participating in the study.

Eligible families were sent a packet that contained a recruitment letter, consent forms, and instruments to measure preference-based HR-QOL outcomes for the child and the caregiver. The information sheet requested that the primary caregiver of the child complete the survey. The survey contained two separate packets that were clearly labelled 'caregiver items about caregiver' and 'caregiver items about child'. In this study, we consider only the caregiver responses about the child's health. Families were contacted up to three times by mail or phone (follow-up calls) to get the surveys returned. Families that signed Health Insurance Portability and Accountability Act (HIPAA) forms, consent/assent forms, and returned the surveys were provided a $US25 gift certificate. Survey instruments were formatted so that data could be scanned into SPSS (SPSS Inc., Chicago, IL, USA) using Remark Classic OMR® (optimal mark recognition) software (Gravic, Inc., Malvern, PA, USA). Remark automatically flags fields that include multiple responses or are left blank. Data from the returned surveys were then merged with clinical information from the ATN. The study was approved by the institutional review boards at Columbia University and the University of Arkansas for Medical Sciences.

Instruments

Two generic preference-based HR-QOL instruments, the HUI3[36] and the QWB-SA,[37,38] were selected for this study. These instruments are widely used in economic evaluations for patients with different conditions, although the QWB-SA has been used less frequently in children despite being recommended as a generic instrument for use in cost-effectiveness analysis by the US Panel on Cost Effectiveness in Health and Medicine.[39] Studies in children that used the QWB-SA to measure preference weights reached mixed conclusions concerning its sensitivity.[40,41] Tilford et al.[42] generated preference scores for children with traumatic brain injuries using the QWB-SA and Smith-Olinde et al.[32] compared scores for the HUI3 and QWB-SA in children with hearing loss. While there was evidence of sensitivity to clinical outcomes in both of these studies, the HUI3 appeared to be the better choice for studying outcomes in children with hearing loss.

The HUI3 describes an individual's health in terms of eight attributes: vision, hearing, speech, ambulation, dexterity, cognition, emotion and pain, with five or six levels per attribute. Caregivers were asked to report on the health states of the child over a 3-day period to be consistent with the QWB-SA described below. A multiplicative scoring function is used to calculate the HUI3 index; the values range from –0.36 (some health states are considered worse than dead) to 1 (perfect health state). The HUI has strong theoretical and empirical foundations and employs a multiattribute utility function based on standard gamble weights obtained from a community sample.[36]

The QWB-SA is a self-administered preference-weighted measure combining three scales of functioning (mobility, physical activity and social activity including completion of role expectation) with a measure of symptoms and problems (58 symptom/problem complexes [CPX]) to produce a point-in-time expression of well-being that ranges from 0 (for death) to 1.0 (for asymptomatic full function). The CPX scale includes two conditions (sexuality and hangovers) that are not applicable to children of all ages, and thus were not included in the survey. Caregivers were asked to report their child's health on the four subscales over the 3-day recall period. Preference weights for the QWB-SA health states were derived from a representative sample of the community using categorical rating scales. Because the QWB-SA uses visual analogue scales in determining weights, many investigators do not consider it to represent a utility value.[43] We used the QWB-SA in this study because of prior concerns that instruments other than the QWB-SA were insensitive to mental health outcomes in adult populations[44] and deemed it necessary to test it in a mental health condition affecting children.

Clinical Measures

To test the construct validity of the preference-based HR-QOL instruments, we assessed their correlations with ASD-specific diagnostic instruments, behavioural measures, symptoms and measures of cognitive functioning. All of the clinical measures were obtained at the time of the child's first visit to the ATN site. For most of the children, clinical data were obtained within 1 year of the survey data. Approximately 90% of the clinical data were obtained within 2 years of obtaining the survey data.

All children had a clinical diagnosis of ASD meeting DSM-IV text revision (DSM-IV-TR) criteria (e.g. autistic disorder, pervasive developmental disorder-not otherwise specified [PDD-NOS] or Asperger's disorder) and confirmed by scores meeting or exceeding cut-offs for classification with ASD on the Autism Diagnostic Observation Schedule (ADOS). The ADOS is a semi-structured autism observation measure that has become the gold standard for assessing autistic behaviour and is administered as part of the ATN initial comprehensive evaluation. An overall measure of autism severity was constructed from scores on the ADOS following recent work by Gotham et al.[45] The ADOS-calibrated severity score provides a metric to quantify ASD severity with relative independence from the child's age and IQ. The score ranges from 1 to 10 with scores of 1–3 indicating a non-spectrum classification on the ADOS and scores of 4 and above indicating greater severity of autism on the ADOS.

Adaptive skills are an aspect of a child's development that is a major factor in future prognosis concerning the ability to function successfully and independently.[46] We measured adaptive skills using the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II).[47] The Vineland-II consists of four major adaptive domains: communication, socialization, daily living skills, and motor skills (age <6 years), which contribute to a single adaptive behaviour composite score. The Vineland-II is a valid and reliable individually administered semi-structured caregiver interview designed to measure adaptive behaviour in individuals from birth to age 90 years. The Vineland-II interview form is scored by the clinician assigning 0 to behaviours that are never performed by the individual, 1 to behaviours that are sometimes or partially performed by the individual, and 2 to behaviours that are usually performed by the individual. The Vineland-II has proven to be sensitive to changes in development over time. The composite and domain scores are expressed as standard scores with a mean of 100 and standard deviation (SD) of 15. The Vineland-II adaptive behaviour composite score was used in this study, with higher scores indicative of better adaptive functioning.

Cognitive functioning for children with ASDs can range from low to high across any level of ASD symptom severity[48,49] and may produce an independent effect on HR-QOL after controlling for ASD symptom severity.[45] Cognitive functioning was determined based on results of an individually administered, formal test of general cognitive abilities. We used one of three cognitive tests, chosen on the age of the child and clinical preferences of the ATN clinician involved in the initial assessments. All three cognitive measures yield an overall composite score that is expressed as a standard score with a mean of 100 and an SD of 15 to describe an individual's cognitive ability and are comparable measures of general intelligence. The tools are the Stanford-Binet Intelligence Scales, Fifth Edition, Abbreviated Battery; the Mullen Scales of Early Learning, American Guidance Service [AGS] Edition; and the Bayley Scales of Infant Development, Third Edition.

The Stanford-Binet is an individually administered formal test of intelligence used with individuals as young as 2 years and yields an IQ value. The Mullen is an individually administered comprehensive measure of cognitive functioning for children from birth through 68 months of age and yields a cognitive composite score, the early learning composite. The Bayley is an individually administered comprehensive measure of cognitive functioning for children from birth through 42 months of age and produces a cognitive score. The Stanford-Binet was used the most often, followed by the Mullen. To differentiate children with intellectual disability or significant delay, we used a cut-off of 69 on each of the cognitive instruments, as this cut-off corresponds to scores at or below the second percentile rank and two or more SDs below the mean compared with same-age peers.

The ATN assessment battery includes information on a number of ASD-specific symptoms (e.g. social interactions, sensory issues, and self-stimulatory and repetitive behaviours) as well as number of associated behaviour symptoms (e.g. aggression, hyperactivity and sleep disturbances) to characterize the child's behavioural adjustment. Some of the symptoms are parent reported on an ATN custom parent report form designed to capture parents' concerns about the child's behaviour and the extent to which the behaviour has been experienced as a problem from the parents' perspective. Other symptoms are clinician reported using a diagnostic checklist and aimed at assessing the presence or absence of the core symptoms of ASD. We provide data on both sets of symptoms as reported by parents and clinicians to assist with the identification of conditions or behavioural adjustment patterns that might have large impacts on preference-based HR-QOL.

We hypothesized that increasing impairment associated with an ASD would result in lower HR-QOL scores from the two instruments. Therefore, to test whether an instrument is sensitive to clinical outcomes, we expected a statistically significant negative relationship between the HR-QOL scores and the ADOS severity scale and significant positive relationships between the HR-QOL scores

Table I. Demographic characteristics of children with autism spectrum disorders and their caregivers (n = 150)

Characteristics	n (%)[a]
Children	
Age, mean years (SD) [range]	8.6 (3.3) [4–17]
Male	128 (85.3)
Ethnicity/race	
Caucasian	118 (78.7)
African American	13 (8.7)
Hispanic	10 (6.7)
Other race	9 (5.9)
Child's birth order[b]	
1st born	73 (49.0)
2nd born	44 (29.5)
3rd born	20 (13.4)
Other	12 (8.1)
Highest grade completed[b]	
Preschool	34 (22.8)
Kindergarten	32 (21.5)
1st–2nd grade	30 (20.1)
3rd–5th grade	21 (14.1)
6th–8th grade	13 (8.7)
9th–10th grade	9 (6.0)
Other	10 (6.7)
School type[b]	
General public school	71 (47.7)
Special education school	31 (20.8)
Private school	16 (10.7)
Special public school	15 (10.1)
Home school	4 (2.7)
Vocational public school	1 (0.7)
Other	11 (7.4)
Caregivers	
Female	133 (88.7)
Education[b]	
High school or lower	15 (10.0)
Some college or higher	134 (90.0)
Marital status	
Married	110 (73.3)
Divorced	19 (12.7)
Never married	13 (8.7)
Separated	6 (4.0)
Widowed	2 (1.3)
Family income[c]	
Less than $US20 000	21 (14.6)
$US20 000–35 000	22 (15.3)
$US35 000–60 000	26 (18.1)
$US60 000–100 000	28 (19.4)
Above $US100 000	47 (32.6)

a Unless otherwise indicated.

b Missing one observation.

c Missing six observations.

SD = standard deviation.

and the cognitive functioning scales and the Vineland-II scales. We were unable to state *a priori* what symptoms are more likely to be associated with HR-QOL scores, but we expected overall that the presence of ASD-related symptoms would decrease HR-QOL scores.

Statistical Analysis

Preference-based HR-QOL scores were calculated from the HUI3 and the QWB-SA instruments according to their scoring manuals. Associations among the two preference-based HR-QOL instruments and clinical measures were tested using ordinary least squares (OLS) regression analysis and Spearman correlation coefficients. We explored if there was any difference among the HR-QOL scores by severity, adaptive behaviour, cognitive functioning and other symptoms. OLS regression was used because there was little evidence of ceiling or floor effects in the HR-QOL scores. Restricted cubic splines with three knots were used in the analysis in order to relax assumptions of linearity. Restricted cubic splines allow continuous data to fit the OLS model without assuming a linear relation.[50] All regression analyses controlled for age and gender. Other demographic variables had no measurable impact on the estimated coefficients, and thus were not included. To test the predictive accuracy of the models, an adjusted R^2 was calculated and validated using 150 bootstrap samples to address the potential for model over-fitting. All statistical analyses were performed using SAS 9.2 (SAS Institute Cary, NC, USA) and the open source R (version 2.11.1) statistical computing language (R Development Core Team, Vienna, Austria). The regression modelling

strategies (RMS) library in R was used to construct regression models.

Results

Data collection for the study began in March 2010 at the Little Rock ATN site and August 2010 at the Columbia New York ATN site. Data collected through April 2011, the time the article was written, were used for this report with 150 total surveys returned (88 returned from Little Rock and 62 from Columbia). The response rate for Little Rock was 59% out of 149 eligible participants and 46% out of 135 eligible participants at Columbia. Ten percent of families diagnosed with an ASD through the ATN in Little Rock and 5% of families in New York elected not to participate in the registry and could not be contacted for this study.

Table I provides demographic characteristics of enrolled children and their families. Children ranged in age from 4 to 17 years with a mean age of 8.6 (SD 3.3) years. Consistent with the condition, the vast majority of children in the sample were male (85.3%). The sample contained a higher proportion of Caucasian children (78.7%) relative to African-American (8.7%) and Hispanic children (6.7%) than would be expected on the basis of the US population and the populations of New York and Arkansas. Population-based surveys typically find similar racial distributions for children with autism and the study area.[51] In most cases, the survey respondent was the mother of the child with the ASD. At the time of the survey, 73.3% of caregivers reported being married with 25.4% reporting being divorced, separated or never married.

Percentage distribution of responses on HUI3 and QWB-SA are presented in tables II and III. The speech and cognition domains appear to contribute the most to the HUI3 scores and some contributions were made by the emotion and pain domains (table II). Examination of the distribution of health states in the speech domain indicates that 20.7% of the children had level 1 speech (able to be understood completely when speaking with strangers or friends), whereas 10.0% of caregivers reported that their child was unable to be understood when speaking to other people (or unable to speak at all). Similarly, 22.0% of caregivers reported level 1 cognition (able to remember most things, think clearly and solve day-to-day problems) and 45.3% reported having a little difficulty with these tasks. The percentage of missing responses increased with the emotion, cognition and pain domains, which are more subjective measures of HR-QOL. This pattern of response is consistent with prior reports of using caregivers as proxy respondents for child health outcomes,[52] although more recent evidence is mixed.[53]

Table III provides the percentage of responses for specific items of the QWB-SA CPX scale based on whether the child experienced the problem on any day over the 3-day recall period and the associated disutility weight for that problem. Examination of tables II and III indicates similarities and differences in responses to the QWB-SA items relative to the HUI3. In particular, for both instruments, speech problems represent the condition with the highest percentage of problem responses, with 54.1% of caregivers reporting their child had been stuttering/unable to speak

Table II. Percentage distribution of responses for children with autism spectrum disorders on the Health Utilities Index 3

Level	Attributes (%)							
	Vision	Hearing	Speech	Ambulation	Dexterity	Emotion	Cognition	Pain
1	85.3	96.0	20.7	93.3	84.0	61.3	22.0	74.7
2	10.0	0.7	35.3	3.3	8.7	31.3	45.3	20.0
3	1.3	0.0	18.7	1.3	0.0	4.0	5.3	2.0
4	1.3	0.7	14.7	0.7	6.7	1.3	17.3	1.3
5	0.7	0.0	10.0	0.7	0.0	0.0	6.7	0.0
6	0.0	0.0		0.0	0.0		1.3	
Missing	1.3	2.7	0.7	0.7	0.7	2.0	2.0	2.0

Table III. Percentage distribution of responses for children with autism spectrum disorders on the Quality of Well-Being Self-Administered scale[a]

Item no.	QWB-SA item	Yes (%)	Decrement
1b	Stuttering/unable to speak clearly?[b]	54.1	0.358
1d	Any deformity of face, fingers, etc.?	2.0	0.408
1e	General fatigue, tiredness or weakness?	20.7	0.256
1f	Problem with unwanted weight gain or loss?	15.3	0.233
1g	Problem with being underweight or overweight?	20.7	0.225
1h	Problems chewing food adequately?	18.0	0.204
1j	Noticeable skin problems?[c]	8.7	0.187
1k	Eye glasses/contacts?	18.0	0.066
2c	Headache?	7.3	0.189
2d	Dizziness/earache/ringing ears?	4.0	0.299
2e	Difficulty hearing, or discharge/bleeding from ear?	2.7	0.350
2f	Stuffy/runny nose/bleeding of nose?	25.3	0.178
2j	Coughing/wheezing?	16.0	0.386
2m	Abdominal pain/nausea/heartburn/vomiting?	12.0	0.260
2n	Difficulty with bowel movements/diarrhoea/constipation/rectal bleeding/black tar-like stools/pain or discomfort in the rectal area?	14.0	0.278
2s	Pain/stiffness/cramps/weakness/numbness in the neck or back?	3.3	0.318
2t	Pain/stiffness/cramps/weakness/numbness in the hips or sides?	2.0	0.365
2u	Pain/stiffness/cramps/weakness/numbness in the joints or muscles of extremities?	5.3	0.318
3a	Trouble falling asleep/staying asleep?	34.7	0.296
3b	Feeling nervous/shaky?	14.0	0.286
3c	Feeling upset/downhearted/blue?	26.7	0.327
3d	Excessive worry/anxiety?	28.7	0.324
3e	Loss of control over events in life?	16.0	0.430
3f	Feeling lonely/isolated?	13.3	0.311
3g	Frustration/irritation/losing temper?	52.0	0.378
3j	Confusion/memory loss?	26.0	0.559
3k	Recurring thoughts/images?	20.0	0.255
3l	Take any medication?	46.7	0.160
3m	Medically prescribed diet?	9.3	0.201
3n	Appetite loss/overeating?	16.7	0.223

a Percentage of parents indicating at least one occurrence of selected health symptoms/problems from the QWB-SA and the associated decrement in preference score of their children with ASDs.

b Missing two observations.

c Missing one observation.

ASD = autism spectrum disorder; **QWB-SA** = Quality of Well-Being Self-Administered scale.

clearly over the 3-day period. A significant percentage of children exhibited confusion/memory loss (26.0%), as well as other mental health conditions such as trouble falling asleep/staying asleep (34.7%), frustration/irritation/losing temper (52.0%) and excessive worrying/anxiety (28.7%). Because only the symptoms experienced by the child with the highest disutility weight over the 3-day recall period is included in the calculation of the QWB-SA score, confusion and memory loss (0.559) represent an important contributor to the overall QWB-SA score for a significant number of children.

Table IV provides mean HR-QOL scores by diagnosis. The mean score for the HUI3 averaged

Table IV. Mean preference-weighted scores by autism spectrum disorder diagnosis

Preference-weighted scores	HUI3		QWB-SA	
	n	Mean (SD) [range]	n	Mean (SD) [range]
Full sample	146	0.66 (0.23) [–0.03–1.0]	150	0.59 (0.16) [0.18–1.0]
Autistic disorder	110	0.64 (0.23) [0.07–1.0]	114	0.58 (0.16) [0.18–1.0]
PDD-NOS	23	0.70 (0.24) [–0.03–0.93]	23	0.62 (0.18) [0.27–1.0]
Asperger's disorder	13	0.79 (0.16) [0.57–1.0][a]	13	0.62 (0.15) [0.36–0.89]

a The HUI3 scores among children with Asperger's disorder were significantly higher than those among the children with autistic disorder ($p = 0.026$).

HUI = Health Utilities Index 3; **PDD-NOS** = pervasive developmental disorder-not otherwise specified; **QWB-SA** = Quality of Well-Being Self-Administered scale; **SD** = standard deviation.

0.66 (SD 0.23) with a range from –0.03 to 1.0. The QWB-SA score averaged 0.59 (SD 0.16) with a range from 0.18 to 1.0. Mean scores for the HUI3 increased for children with PDD-NOS relative to autistic disorder (0.70 vs 0.64; $p = 0.283$) and Asperger's disorder (0.79 vs 0.64; $p = 0.026$). In contrast, mean scores for the QWB-SA were similar for both children with PDD-NOS and children with Asperger's disorder (0.62) and were not significantly different from QWB-SA scores for children with autistic disorder.

Table V describes the clinical measures in relation to the HR-QOL summary scores for the child using Spearman correlation. The ADOS severity score ranged from 2 to 10 with a mean of 7.2 (SD 1.8). It had insignificant correlations with both the HUI3 and the QWB-SA scores. The Vineland-II adaptive behaviour composite score averaged 67.4 (SD 11.2) and had significant moderate correlation with the HUI3 ($\rho = 0.521$; $p < 0.001$). Other Vineland-II domain scores were also significantly correlated with the HUI3 scores, especially the communication, daily living skills and motor skills domains. The QWB-SA scores were weakly correlated with the Vineland-II composite and domain scores. Their correlations, however, were statistically significant except for the Vineland-II motor skill domain. The cognitive ability scores (based on the Stanford-Binet, Mullen or Bayley Scales) had statistically significant correlations with the HUI3 score ($\rho = 0.359$; $p < 0.001$) and weak correlation with the QWB-SA score ($\rho = 0.166$; $p < 0.05$).

Table VI and figure 1 provide parent-rated and clinician-rated symptoms associated with ASDs in relation to the HUI3 and QWB-SA scores. We report HR-QOL scores for the child unadjusted for age and gender following a recent suggestion by Russell.[54] To avoid problems with multiplicity, the significance level α of 0.05 was corrected

Table V. Clinical characteristics and correlations with health-related quality-of-life summary scores

Variables	n	Mean (SD)	Spearman correlations	
			HUI3	QWB-SA
ADOS calibrated severity score	146	7.2 (1.8)	–0.143	0.068
Vineland-II				
Communication	140	71.1 (15.3)	0.475**	0.212**
Daily living skills	140	69.7 (12.7)	0.485**	0.248**
Socialization	140	66.9 (11.3)	0.373**	0.200**
Motor skills	84	73.9 (11.1)	0.552**	0.053
Composite score	140	67.4 (11.2)	0.521**	0.247**
Cognitive functioning[a]	146	75.6 (24.4)	0.359**	0.166*

a Cognition scores are based on the Stanford-Binet Intelligence Scales, Fifth Edition, Abbreviated Battery (n = 140) or either the Mullen Scales or the Bayley Scales (n = 6).

ADOS = Autism Diagnostic Observation Schedule; **HUI3** = Health Utilities Index 3; **QWB-SA** = Quality of Well-Being Self-Administered scale; **SD** = standard deviation; **Vineland-II** = Vineland Adaptive Behavior Scales, Second Edition; * $p < 0.05$, ** $p < 0.001$.

Table VI. Parent-reported autism spectrum disorder-related symptoms in relation to health-related quality-of-life scores

Symptoms	HUI3 (n = 136)				QWB-SA (n = 140)			
	n (%)	Mean	SD	p-Value	n (%)	Mean	SD	p-Value
Language use and understanding								
No problem	21 (15)	0.84	0.09	<0.01[a]	21 (15)	0.69	0.16	<0.01[a]
Mild problem	25 (18)	0.74	0.14		25 (18)	0.60	0.13	
Moderate problem	49 (36)	0.70	0.19		49 (35)	0.60	0.17	
Severe problem	41 (30)	0.51	0.25		45 (32)	0.51	0.13	
Compulsive behaviours								
No problem	41 (30)	0.72	0.19	0.04	41 (29)	0.63	0.16	0.02
Mild problem	36 (26)	0.69	0.23		36 (26)	0.58	0.13	
Moderate problem	38 (28)	0.64	0.24		39 (28)	0.58	0.15	
Severe problem	21 (15)	0.61	0.23		24 (17)	0.53	0.19	
Anxiety								
No problem	29 (21)	0.72	0.23	0.01[a]	30 (21)	0.66	0.15	0.01[a]
Mild problem	34 (25)	0.69	0.21		35 (25)	0.55	0.16	
Moderate problem	46 (34)	0.65	0.24		47 (34)	0.58	0.15	
Severe problem	27 (20)	0.63	0.19		28 (20)	0.56	0.17	
Sensory issues								
No problem	28 (21)	0.70	0.25	0.03	28 (20)	0.67	0.18	0.03
Mild problem	35 (26)	0.70	0.22		35 (25)	0.58	0.15	
Moderate problem	48 (35)	0.65	0.20		49 (35)	0.55	0.14	
Severe problem	25 (18)	0.62	0.23		28 (20)	0.56	0.14	
Sleep disturbance								
No problem	63 (46)	0.71	0.22	<0.01[a]	64 (46)	0.64	0.16	<0.01[a]
Mild problem	28 (21)	0.73	0.15		29 (21)	0.55	0.18	
Moderate problem	26 (19)	0.55	0.26		27 (19)	0.53	0.12	
Severe problem	19 (14)	0.61	0.20		20 (14)	0.53	0.11	
Aggression								
No problem	75 (55)	0.69	0.21	0.12	75 (54)	0.61	0.17	0.03
Mild problem	30 (22)	0.69	0.22		32 (23)	0.57	0.14	
Moderate problem	11 (8)	0.50	0.29		12 (9)	0.49	0.14	
Severe problem	20 (15)	0.66	0.22		21 (15)	0.55	0.14	
Hyperactivity								
No problem	21 (15)	0.73	0.26	<0.01[a]	23 (16)	0.59	0.21	0.03
Mild problem	36 (26)	0.72	0.20		36 (26)	0.61	0.15	
Moderate problem	46 (34)	0.66	0.21		46 (33)	0.61	0.14	
Severe problem	33 (24)	0.59	0.23		35 (25)	0.52	0.15	
Attention span								
No problem	10 (7)	0.82	0.14	<0.01[a]	10 (7)	0.72	0.18	<0.01[a]
Mild problem	29 (21)	0.72	0.19		30 (21)	0.64	0.16	
Moderate problem	47 (35)	0.69	0.24		48 (34)	0.57	0.16	
Severe problem	50 (37)	0.60	0.22		52 (37)	0.55	0.14	
Mood swings								
No problem	50 (37)	0.69	0.22	0.31	50 (36)	0.62	0.14	0.03
Mild problem	43 (32)	0.66	0.24		44 (31)	0.58	0.18	
Moderate problem	28 (21)	0.65	0.22		29 (21)	0.54	0.14	
Severe problem	15 (11)	0.67	0.21		17 (12)	0.57	0.17	

Continued next page

Table VI. Contd

Symptoms	HUI3 (n = 136)				QWB-SA (n = 140)			
	n (%)	Mean	SD	p-Value	n (%)	Mean	SD	p-Value
Eating habits								
No problem	31 (23)	0.70	0.24	0.01[a]	32 (23)	0.61	0.16	0.12
Mild problem	27 (20)	0.72	0.17		28 (20)	0.58	0.13	
Moderate problem	43 (32)	0.68	0.20		44 (31)	0.61	0.15	
Severe problem	35 (26)	0.59	0.26		36 (26)	0.54	0.18	
Social interactions								
No problem	19 (14)	0.71	0.26	0.03	19 (14)	0.62	0.12	0.23
Mild problem	25 (18)	0.67	0.26		25 (18)	0.56	0.17	
Moderate problem	52 (38)	0.68	0.21		53 (38)	0.60	0.18	
Severe problem	40 (29)	0.64	0.19		43 (31)	0.57	0.14	
Self-stimulatory and repetitive behaviours								
No problem	36 (26)	0.78	0.16	<0.01[a]	36 (26)	0.61	0.15	0.05
Mild problem	34 (25)	0.75	0.15		34 (24)	0.63	0.15	
Moderate problem	35 (26)	0.58	0.25		36 (26)	0.54	0.16	
Severe problem	31 (23)	0.57	0.23		34 (24)	0.57	0.16	
Self-injurious behaviour								
No problem	89 (65)	0.71	0.21	<0.01[a]	90 (64)	0.61	0.17	0.07
Mild problem	23 (17)	0.61	0.25		24 (17)	0.56	0.12	
Moderate problem	12 (9)	0.57	0.20		13 (9)	0.58	0.14	
Severe problem	12 (9)	0.62	0.21		13 (9)	0.49	0.14	
Has lost or seems to be losing skills that he/she previously had								
No problem	103 (76)	0.70	0.21	<0.01[a]	103 (74)	0.61	0.16	<0.01[a]
Mild problem	21 (16)	0.64	0.19		24 (17)	0.55	0.15	
Moderate problem	6 (4)	0.43	0.26		6 (4)	0.47	0.20	
Severe problem	5 (4)	0.49	0.26		6 (4)	0.46	0.10	

a Statistically significant difference among the group, adjusted using Tukey, Ciminera and Heyse's adjustment for multiple comparisons.

HUI3 = Health Utilities Index 3; **QWB-SA** = Quality of Well-Being Self-Administered scale; **SD** = standard deviation.

using the Tukey, Ciminera and Heyse adjustment.[55] For table VI, 14 outcomes were analysed using an adjusted significance level of 0.014. The p-values correspond to the Spearman correlation coefficients between the ordinal variable symptoms and the two HR-QOL scores. In particular, we investigated whether there was a trend between symptom severity and the HR-QOL scores.

Table VI provides an indication of the extent of the different symptoms and exploratory findings on the magnitude of the HR-QOL scores in relation to the extent of the problem. For example, in table VI only 15% of children did not have problems with language use and understanding, and for these children HR-QOL scores for both the HUI3 and QWB-SA were elevated relative to children with mild problems (18%), moderate problems (35%) or severe problems (33%). The HUI3 score changed from 0.84 (SD 0.09) for children that did not have language use and understanding problems to 0.51 (SD 0.25) for children with severe language use and understanding problems ($p < 0.01$). For the QWB-SA, the mean score for the children without this symptom was 0.69 (SD 0.16) and 0.51 (SD 0.13) for the children with severe problems ($p < 0.01$). Other symptoms with large changes in HR-QOL scores included attention span, hyperactivity, self-stimulatory and repetitive behaviours, and loss of or losing skills they previously had. The last symptom (loss of skills) had a low prevalence with only 4% of children having severe problems and another 4% having moderate problems. However, in both problem states and for both the HUI3 and the

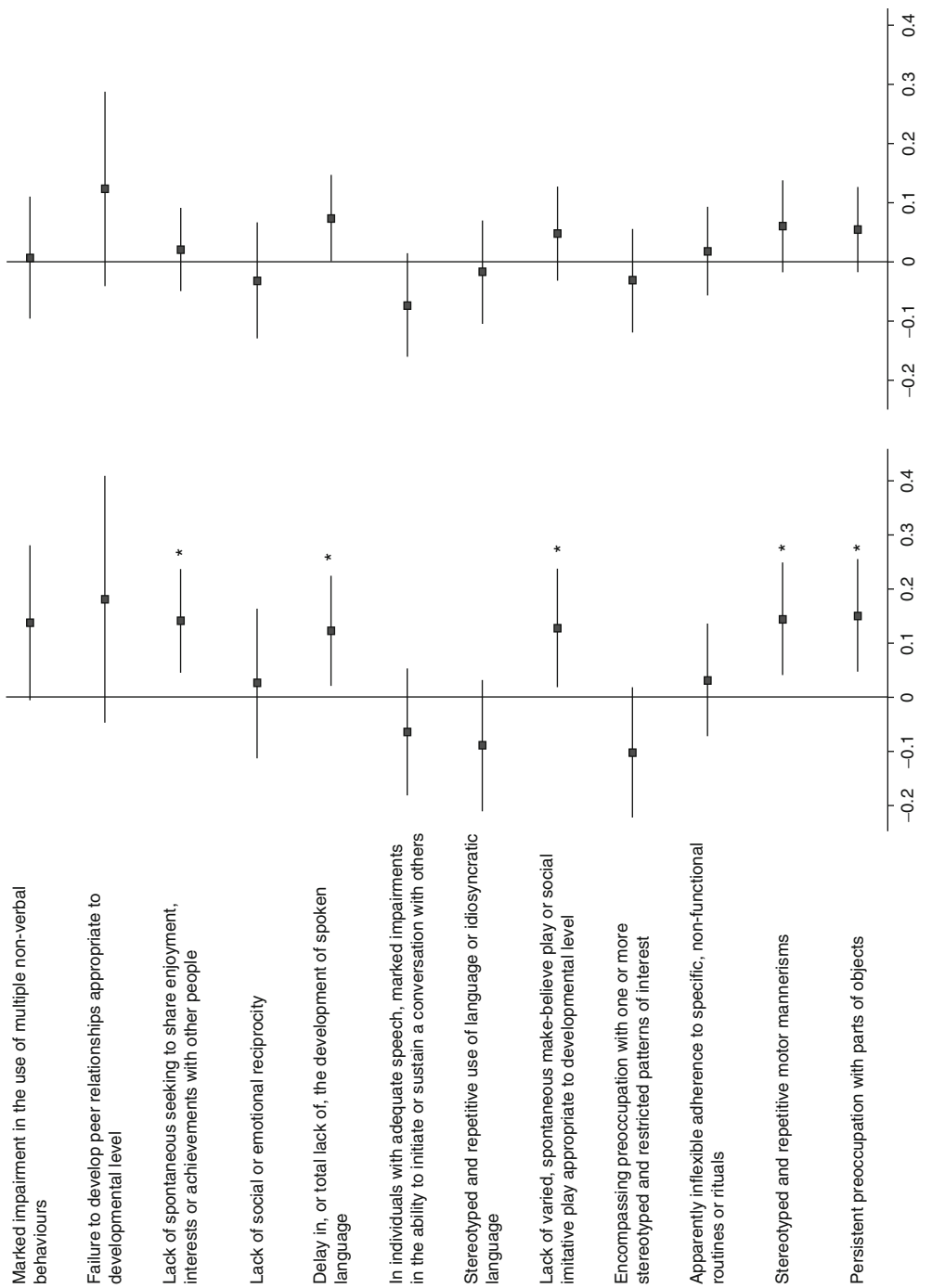

Fig. 1. Clinician-rated symptoms associated with autism spectrum disorders in relation to the preference-weighted scores. **HUI3** = Health Utilities Index 3; **QWB-SA** = Quality of Well-Being Self-Administered scale; * $p < 0.014$.

Table VII. Ordinary least squares regression of clinical measures and preference-weighted scores

Measure	Q1–Q3	HUI3				QWB-SA			
		n	Effect and 95% CI	p-Value	Adjusted R^{2a}	n	Effect and 95% CI	p-Value	Adjusted R^{2a}
ADOS calibrated severity score	6–8	141	–0.04 (–0.08, 0.00)	0.12	–0.02	145	0.00 (–0.03, 0.03)	0.88	–0.05
Vineland-II									
Communication	61–79	136	0.16 (0.12, 0.20)	<0.01	0.26	139	0.05 (0.02, 0.08)	0.01	0.02
Daily living skills	62–78	136	0.16 (0.12, 0.20)	<0.01	0.27	139	0.05 (0.02, 0.09)	0.01	0.00
Socialization	59–75	136	0.15 (0.10, 0.20)	<0.01	0.15	139	0.05 (0.01, 0.09)	0.02	0.02
Composite score	60–76	136	0.19 (0.14, 0.23)	<0.01	0.32	139	0.06 (0.03, 0.10)	0.01	0.03
Cognitive functioning[b]	52–94	141	0.21 (0.14, 0.29)	<0.01	0.14	145	0.05 (–0.01, 0.11)	0.23	–0.03

a Calculated using 150 bootstrap samples for the model over-fitting potential, controlled for age and gender.

b Cognition scores are based on the Stanford-Binet Intelligence Scales, Fifth Edition, Abbreviated Battery (n = 140) or either the Mullen Scales or the Bayley Scales (n = 6).

ADOS = Autism Diagnostic Observation Schedule; **CI** = confidence interval; **HUI3** = Health Utilities Index 3; **Q1** = 25th percentile; **Q3** = 75th percentile; **QWB-SA** = Quality of Well-Being Self-Administered scale; **Vineland-II** = Vineland Adaptive Behavior Scales, Second Edition.

QWB-SA, HR-QOL scores ranged towards the lower end of the distribution of overall scores (0.43–0.49).

Figure 1 reports clinician-rated symptoms as to whether the problems are present or absent in relation to the HUI3 and QWB-SA scores. For figure 1, because 12 outcomes were analysed, confidence interval plots for the HUI3 and QWB-SA are presented using the adjusted significance level of 0.015. In general, the pattern of change scores for the HUI3 and the QWB-SA associated with symptoms that were present in the child relative to children without symptoms was similar. However, for the QWB-SA, no significant differences in HR-QOL scores were found among the clinician-reported ASD symptoms. In contrast, there were five clinician-reported symptoms where the HUI3 score differed significantly, including a lack of spontaneous seeking to share enjoyment, etc.; a delay in or total lack of spoken language; a lack of play for developmental level; stereotyped and repetitive motor mannerisms; and persistent preoccupation with parts of objects. Similar to the parent-rated symptoms, the changes in scores for the HUI3 tended to be larger relative to the QWB-SA for a number of symptoms. For example, for the 38% of children who were identified as having a persistent preoccupation with parts of objects, mean values for the HUI3 score changed by 0.15 points compared with 0.06 with the QWB-SA.

Table VII reports OLS regression coefficients and adjusted R^2 values from an analysis of the two instruments in relation to the clinical measures as the clinical measure changes from the first to third quartile of their distribution. Effects for all predictors are presented as regression coefficients and indicate the change in HR-QOL scores (HUI3 or QWB-SA) as the value of the clinical variable changes from the 25th percentile (Q1) to the 75th percentile (Q3).[50] The findings in table VI indicate that the HUI3 has better explanatory power in all of the estimated models relative to the QWB-SA based on adjusted R^2 values. The R^2 for the regression analysis using the Vineland-II composite score had the highest adjusted R^2 for both the HUI3 (0.32) and the QWB-SA (0.03). Other components of the Vineland-II

also had adjusted R^2 values that were higher than the ADOS severity score. The ADOS severity score was negatively associated with the HUI3 as expected although not significant. The QWB-SA did not have the expected sign or significance with the ADOS severity score. The ADOS severity score model performed poorly in terms of adjusted R^2 when either the QWB-SA or the HUI3 was used as the dependent variable. In general, the coefficients from the HUI3 were larger than the QWB-SA.

Discussion

Information on the cost effectiveness of pharmaceutical and other treatment services for children with autism is lacking. One reason for the lack of information may be the limited data on preference-based HR-QOL outcomes associated with ASD-related conditions and their validity. Data on preference-based HR-QOL outcomes are necessary for calculating QALYs in a cost-effectiveness analysis permitting comparisons across different conditions. Such information has the potential to identify the comparative value of services for children with ASDs to other conditions covered by private and public health insurance. Cost-effectiveness information also can help identify optimal treatment strategies and reduce unnecessary treatment variations.

In the US, treatment services for children with autism vary substantially according to the child's state of residence. Much of the variation in services is due to differences in funding at the state level for special education and Medicaid services. States also have been active in pursuing policies to increase access to services for children with autism through mandates on private insurers. Both Pennsylvania and Arkansas have passed comprehensive bills to support autism services requiring health insurers to cover yearly behavioural and clinical treatments at a cost of up to $US36 000 and $US50 000, respectively. Despite considerable variation in spending on services by states, there is scant evidence on the value of increased spending as information necessary for economic evaluations is lacking. Indeed, reports from the insurance industry criticize treatment emphasis on applied behavioural analysis – an expensive therapy – because they argue the value of alternative treatment services has not been demonstrated.[56]

This study had two objectives. We sought to test the sensitivity of two generic instruments for calculating preference-based HR-QOL outcomes for children with ASDs and to identify the magnitude of potential QALY gains from treatment. This initial investigation finds evidence of construct validity for both the HUI3 and QWB-SA, but the HUI3 score appears to be more sensitive to ASD symptoms and severity for children with ASDs. Correlations between the clinical variables, especially the Vineland-II and cognitive functioning, were generally higher for the HUI3 compared with the QWB-SA (tables IV, V and VII). Changes in the scores from the two instruments were generally in the correct direction when compared across varying levels of ASD-related symptoms. The magnitude of score changes was higher at the mean for the HUI3 consistent with the larger range in scores for the HUI3 relative to the QWB-SA and is likely a better choice for describing QALY gains from treatment or prevention (tables IV and VI). The scales differ across a number of dimensions beyond score range, including time of administration, domains of health, and valuation strategies for assigning weights. The HUI3 is easier to administer and appears to capture health states associated with language better than the QWB-SA. Still, it is clear that more research is necessary to be able to determine which generic HR-QOL instrument would be most suitable in this context, as other instruments suitable for children were not considered and evidence from other study designs, especially randomized trials, is needed.

Only two prior studies have measured preference-based HR-QOL for children with ASDs. One study[21] reported on a sample of children (N = 105) eligible for support programmes using the HUI3 with family caregivers as proxy respondents. Mean HUI3 scores from that study (0.433) were generally inconsistent with mean scores from this study (0.66) likely due to selection bias associated with support eligibility. The second study[22] reported mean HUI3 scores (0.61) for autistic disorder (N = 11) that were more consistent

with mean scores (0.64) for autistic disorder from the current study. While the prior studies provide HR-QOL scores that can be used to measure the disutility for the health state 'autism', information regarding HR-QOL scores associated with different behavioural states and symptoms associated with autism were not available. The current study provides initial evidence on how variation in behavioural states and symptoms for children with autism may be related to preference-based HR-QOL. A full mapping of ASD conditions into preference-based HR-QOL using larger samples and additional HR-QOL instruments remains an area for future research. Findings from this study suggest that the HUI3 is a useful instrument to measure the effectiveness of services for children with ASDs and should be included in clinical trials.

The large change in HR-QOL across the range of ASD-related conditions and symptoms may also signal that preventing such conditions could have significant spillover effects for family members of children with ASDs. Theoretical and empirical work on developing estimates of family and caregiver effects, in terms of health and well-being, for use in cost-effectiveness evaluations are in the early stages of development.[57-60] It will be interesting to assess whether the general associations between ASD-related conditions and symptoms in children translate into similar associations between the health and well-being of family members and caregivers. Incorporating family effects in economic evaluations of effective interventions for children with ASDs would provide a fuller account of (health) gains in economic evaluations. If treatment of children results in an increase in health in family members and caregivers as well, the total number of QALYs gained due to the intervention may increase, resulting in a more favourable cost-effectiveness ratio.[57]

In this study, we found the largest correlations between the HR-QOL scores and the clinical measures describing behavioural conditions and symptoms. None of the correlations between the clinical measures and the HR-QOL scores were strong as the two types of measures provide information on different constructs.[14] It needs noting that correlations between the HR-QOL scores and the ADOS severity score were weak at best. Correlations between the HR-QOL scores and cognitive functioning were better, but still not as strong as the behavioural measures. Future research will need to better elucidate the interactions between cognitive functioning and behavioural conditions associated with ASDs.

The study has a number of limitations. First, we used caregivers as proxy respondents to obtain information on HR-QOL for the child. Use of other methods to obtain HR-QOL scores in this population, such as direct elicitation techniques or discrete-choice experiments, may generate findings that differ from the present study. In addition, this study uses two generic instruments with weights based on adult respondents. Instruments designed for use in children with weights developed from a child's perspective[19] may also alter study findings. For example, this study did not test the sensitivity of the HUI2 instrument that was designed to better reflect preferences of children,[61] because the domains of the HUI3 appear most appropriate for neurodevelopmental conditions. Responses to the HUI3 indicate that most caregivers could respond to the questions about their child, although a higher percentage of caregivers did not complete answers in the most subjective domains – emotion, pain and cognition. Whether other methods or instruments for obtaining preference-based HR-QOL scores, such as the Assessment of Quality of Life 8D (AQoL-8D),[62] could significantly influence QALY estimates and associated cost-effectiveness ratios remains to be answered. At a minimum, the estimates in this study provide an important benchmark for comparing alternative methods and future studies.

The findings also could be influenced by the timing of the clinical and survey assessments. Children who enrolled in the ATN at the beginning of the registry will have had a longer time period between clinical assessment and responses to the HR-QOL instruments. If the child's ASD-related conditions and symptoms changed over time, this could reduce the correlation between the clinical measures and the HR-QOL scores. While many children with ASDs do improve over time, improvement does not occur rapidly,

if at all. We have information on dates for the clinical assessment and survey response and tested whether time significantly influenced reported estimates. We found a positive but insignificant relationship between time differences in clinical measures and preference scores. Controlling for the timing of instrument administration did not significantly change the findings because of correlation with the child's age.

Finally, the study is limited by the relatively small sample size and the population studied. Our sample is not representative of population-based surveys as we enrolled from treatment clinics with presumably higher severity subjects. Also, we did not include non-English speaking respondents in the sample. Because of the small sample size, it is not possible to account for other factors that may be associated with HR-QOL score changes across different levels or severity of clinical conditions and symptoms. For example, our descriptive analysis indicates a large change in scores associated with language development, but we are unable to assess the extent to which other clinical conditions are correlated with language development. If other unmeasured factors are correlated, it can reduce the impact of language development on HR-QOL outcomes. Because of this limitation, it is not currently possible to use the reported scores as 'off-the-shelf' weights for cost-effectiveness evaluations. Future research with larger sample sizes will be needed to map or cross-walk clinical conditions and symptoms into HR-QOL scores. Ideally, data on HR-QOL scores should be obtained over time from randomized controlled trials.[43] The primary contribution of this study is to suggest that such data collection schemes are feasible using the HUI3.

A larger sample size also will be necessary to assess whether the 'correct' health domains are included in the instruments used in this study.[30] Future research may consider psychometric approaches based on item response theory to assess this issue. The framework used in this study, where clinical information is combined with responses from preference-based HR-QOL instruments, is a promising approach for psychometric testing of the instruments. Indeed, a major strength of the study is the use of a clinically identified sample of children diagnosed with an ASD following standardized protocols.

Conclusions

Despite the need to identify optimal treatment strategies for children with ASDs and describe the value of services to public and private payers, research describing health outcomes in relation to clinical conditions is lacking. This study provides evidence of associations between ASD-related conditions and symptoms and preference-based HR-QOL outcomes. We find support for the use of generic preference-based instruments to describe HR-QOL in children with ASDs, especially for the HUI3 instrument. Researchers should consider incorporating generic instruments to describe preference-based HR-QOL in clinical trials and other longitudinal research studies involving children with ASDs to build the evidence base describing the cost effectiveness of services provided in the care of this important population.

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