

# Evaluating Health-related Quality of Life Among Tuberos Sclerosis Complex Individuals Using Health Utilities Index: a Local Study and Comparison With Existing Data

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## Research Article

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# Abstract

## Background:

Tuberous sclerosis complex (TSC) is a rare autosomal dominant disorder characterized by benign tumor growth in multiple organs, which may cause significant negative impact on patients' health-related quality of life (HRQoL). Since HRQoL studies in Asian TSC population are scarce, we aim to evaluate the HRQoL of our local TSC patients, who are mainly ethnic Chinese, so as to provide a holistic view and information for better understanding of TSC patients in this part of the world.

## Methods:

HUI-Ch is a validated Chinese multiple-choice questionnaire for scoring Health Utilities Index Mark 2 (HUI2) and Health Utilities Index Mark 3 (HUI3). It was used to assess HRQoL of TSC individuals in Hong Kong. Proxy-data on socio-demographics and common chronic health conditions for TSC patients were collected. Data analyses involved multiple imputation with two-sample t-test, Pearson correlation and multiple regression to predict variations in HRQoL in relation to different factors. Data was compared with existing data on HUI of other disease entities.

## Results:

Of 27 patients in the study sample, mean HUI2 and HUI3 scores were 0.64 and 0.50 respectively (1 = perfect health, 0 = death). 81.5% and 77.8% of TSC patients belonged to the "severe" disability category on HUI2 and HUI3, which were higher than the proportion of Down syndrome patients (60.0% and 72.0%). Behavioral problems on HUI2 and attention deficit hyperactivity disorder (ADHD) on HUI3 were statistically significant predictors (both  $p < 0.01$ ) of poorer HRQoL. Patients with behavioral problems, compared to those without, had significantly lower scores in cognition (0.88 vs 0.98,  $p < 0.01$ ) and self-care (0.96 vs 1.00,  $p < 0.01$ ) on HUI2. Patients with ADHD, compared to those without, had significantly lower scores in cognition (0.71 vs 0.95,  $p < 0.001$ ) and speech (0.87 vs 0.95,  $p < 0.05$ ) on HUI3. Patients with multiple chronic health conditions (6 or above) had lower HUI2 and HUI3 scores.

## Conclusions:

Local TSC patients have poorer HRQoL than Down syndrome and other chronic conditions. Findings from our study can serve as a baseline for evaluating management outcome in TSC patients with similar cultural backgrounds. Further HRQoL studies can be conducted in other regions to improve the assessment accuracy of these data collected.

# Background

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder characterized by the growth of benign tumors in multiple organ systems such as the brain, skin, kidneys and lungs. It affects 1

in 5,000 newborns worldwide and with a prevalence of 3.87 in 100,000 (i.e. 1 in 25,833) in Hong Kong (1, 2).

Amongst the array of clinical manifestation, epileptic seizure is considered as one of the most debilitating symptoms (3). Patients with epileptic seizure are susceptible to developmental delay, which may severely affect one's activities of daily living and cognitive function (4).

Skin lesions, such as ash-leaf spots, shagreen patches, angiofibroma and subungual fibroma cause facial disfigurement (5, 6). This will potentially cause negative psychosocial effects in TSC patients (7, 8).

Individuals with numerous or large angiomyolipoma are at risk of spontaneous hemorrhage, kidney failure and urinary tract infection (9-11). Continuous long-term follow-up care will be necessary for these patients, so as to monitor the progressively growing neoplasm. Moreover, bleeding from the neoplasm is the first cause of mortality in patients over the age of 30 and ranks second in all ages combined (12-16).

These multiple physical manifestations of TSC bring about significant negative physical, psychosocial and mental impact on TSC sufferers and potentially incur a burden on the healthcare system. Therefore, it is essential to evaluate the burden of illness (BOI) to improve care for these patients. It can also serve as a reference for healthcare service and resource allocation.

BOI can be defined on both societal and individual levels. The former includes mortality and morbidity, economic cost and health burden. This has been evaluated in our local Hong Kong population, and the results can be found in our previous study (1). TSC has a comparatively higher BOI than the general population on societal level; however, individual BOI can be highly variable (17). Hence, in this study, we would like to assess the individual BOI of our local population by means of standardized quality of life (QoL) questionnaire.

WHO defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (18). Whereas in the context of measuring the QoL of patients with chronic disabling illnesses, health-related quality of life (HRQoL) is often used. HRQoL is an important measurement to assess treatment outcome, predict mortality and service utilization (19, 20). Questionnaires used in assessing the QoL of TSC patients in the recent 10 years can be found in Table 1.

Several factors have to be balanced in order to choose the most appropriate instrument for measuring the HRQoL of TSC patients. First of all, it is the relevance of the HRQoL instrument. HRQoL can be largely divided into generic questionnaires with or without specific domains, and disease-specific questionnaires (Table 1). Disease-specific questionnaires are theoretically more sensitive to change and may be useful in measuring subtle effects of treatment outcome. In 2018, TSC disease-specific questionnaires evaluating the psychometric properties of the TSC individuals with refractory epilepsy were introduced (21). However, they may not be suitable for our local patient group due to language barrier and limited coverage on manifestations. Proper translation and validation should be performed before its application on Chinese patients.

Second consideration lies on the validity, reliability and suitability of the questionnaire. A number of HRQoL generic questionnaires have been translated into traditional Chinese (Hong Kong) and have been validated. These include, but not limited to, Health Utilities Index (HUI), 36-item Short Form Health Survey (SF-36), 12-item Short Form Health Survey\_Version 2 (SF-12v2), Chinese Quality of Life instrument (ChQoL), Child Health Questionnaire and Pediatric Quality of Life Inventory (PedsQL) (22-25). Amongst these questionnaires, ChQoL is a self-reported questionnaire, whereas HUI, SF-36, SF-12v2, Child Health Questionnaire and PedsQL can be administered in both proxy- and self-reported formats (26). With regards to our patient group, some may be unable to fill in the questionnaire themselves. Hence, a proxy-reported questionnaire is deemed necessary.

Thirdly, the use of these questionnaires requires a suitable reference for comparison. HUI has been used to examine the HRQoL of Chinese Down syndrome (DS) patients in our locality (23). Both TSC and DS are genetic diseases affecting multiple organs and hence would be useful for comparison. Moreover, HUI score is found to be sensitive to clinical measures and is a better suited generic questionnaire for children with autism spectrum disorder (ASD), which is a frequent manifestation in TSC (27). In addition, HUI has been widely used in children context as it was designed for all people aged 5 years or older in both clinical and general populations (28). Therefore, HUI is considered a suitable choice in establishing the baseline BOI measures of the local TSC population, which allows comparison with the known HRQoL data of related disease entities and provides policy makers a clear reference for resource allocation.

Data regarding HRQoL in Asian TSC population is limited. Two cross-sectional studies evaluated the QoL of TSC patients using PedsQL in China and Malaysia respectively, but their study populations were limited to the pediatric age group (29, 30). Another retrospective analysis study documented the QoL of post-epileptic surgery TSC patients in China (31). Even so, this post-epileptic surgery study only considered the QoL profile of a selected group of patients - patients with intractable epilepsy, therefore may not fully reflect the HRQoL of the general TSC population. The objective of our study is to evaluate the HRQoL of the general Chinese TSC population so as to provide HRQoL data for diversification of TSC databases, improving resource allocation and providing baseline data for assessing effectiveness of management of TSC patients in this part of the world.

## Methods

### *Survey components*

Data was collected through a study-specific survey which included questions to assess local TSC HRQoL and disease manifestations.

In documenting the HRQoL, two health-state classification systems, namely Health Utilities Index Mark 2 (HUI2) and Health Utilities Index Mark 3 (HUI3) were utilized. These instruments are non-disease specific index applicable to individuals who are 5 years of age or greater and have been shown to be responsive to various chronic diseases such as rheumatoid arthritis, type 2 diabetes mellitus and stroke (32-34). HUI2

and HUI3 are two independent yet complementary systems assessing HRQoL. It considers assessment of vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain and discomfort.

A validated HUI questionnaire in traditional Chinese (HUI-Ch) was obtained from Health Utilities Inc. (HUInc) and adapted into our study. Due to the varying intellectual ability of TSC subjects, respondents were the families or caregivers who provided answers in lieu of the individual with TSC.

Disease manifestations were categorized in accordance with the chronic health conditions in the Chinese version of the Child Health Questionnaire (35). The Child Health Questionnaire is a survey instrument developed by the Department of Paediatrics and Adolescent Medicine and the School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, in consultation with the Department of Health and a group of experts in 2005. It was used in the first local population-based health survey targeted to Hong Kong children and is a HRQoL questionnaire adapted for children concerning two main categories: mental and physical health conditions. We have selected 7 and 10 items from the mental and physical health categories respectively to represent the more common chronic health issues in TSC patients. Mental health traits include aspects such as “autism”, “anxiety problems”, “attention deficit hyperactivity disorder” (ADHD), “depression”, “behavioral problems”, “developmental delay or mental retardation” and “learning problems”. Physical health conditions include “chronic respiratory, lung or breathing trouble”, “epilepsy”, “hearing impairment or deafness”, “vision problems”, “speech problems”, “cancer”, “skin problems”, “gastrointestinal and liver problems”, “chronic renal disease” as well as “sleep disturbance (including obstructive sleep apnea)”.

#### *Source of data*

Patients were recruited in collaboration with Tuberos Sclerosis Complex Association of Hong Kong (TSCAHK) which is a Hong Kong-based patient advocacy organization with more than forty local TSC patients as members. The fieldwork was carried out from July 2019 to September 2020, with the use of proxy-administered questionnaires. To ensure accurate understanding of the questionnaire, a trained assistant was nearby, either face-to-face or over the phone, while the proxy was filling in the survey.

All respondents were provided with information sheets. Consent was obtained prior to completing the survey. The study group was defined as a TSC patient who was  $\geq 5$  years old, of Hong Kong Chinese ethnicity (i.e. Ethnically Chinese with Hong Kong identity documentation), and had a proxy that could provide accurate information representing the study subject in Chinese.

To protect participants' privacy, a unique study number was assigned to each respondent and the data was all kept in a computer with a protected password locked in our University office.

#### *Statistical analysis*

Demographics, including HRQoL and chronic conditions (as defined by the aforementioned local population-based health survey (36)) of the subjects were analyzed. Demographic information included male: female ratio, distribution by age, ethnicity and family history of TSC.

HUI data was analyzed according to the manual provided by HUInc. These attributes have been in use and updated over the past 25 year. They have been deemed by members of the general population as the important dimensions in determining health status (37).

HUI2 considers assessment of 7 attributes: sensation, emotion, pain, cognition, self-care, mobility and fertility; while HUI3 considers assessment of 8 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, pain and discomfort. In each attribute, function level is graded based on the responses to the corresponding multiple-choice questions. Function levels are converted to single-attribute and multi-attribute utility scores based on published utility functions. Single-attribute utility scores for HUI2 and HUI3 are defined on a scale of 0 to 1, with 0 reflecting the lowest level of function (most disabled) and 1 reflecting full function for the attribute. Multi-attribute utility scores (“HUI2 scores” and “HUI3 scores”) reflect the overall health state and are calculated based on the combination of single-attribute scores. HUI2 score is expressed on an interval scale ranging from -0.03 to 1 while HUI3 score is expressed on an interval scale ranging from -0.36 to 1, with 0 depicting dead, 1 for perfect health and negative scores are deemed worse than being dead. The details for the development of single-attribute and multi-attribute utility scoring algorithms were described elsewhere (38, 39). Although the HUI3 health status classification system was developed to address some of the limitations of the HUI2 system, each system has its advantages. Therefore, HUI2 and HUI3 systems are complementary to each other and were both applied in our study (28).

HRQoL scores were tabulated and categorized into 4 disability levels (none, mild, moderate, severe) as proposed by the HUI developers. HUI2 and HUI3 scores of TSC subjects were compared with that of the local DS patients (23).

Analyses using two-sample t-test were performed for both HUI2 and HUI3 in comparing sex, family history and chronic health conditions. Pearson correlation was used to analyze whether there was a correlation between age and HUI2 or HUI3 scores. Significant factors correlating to HRQoL scores were then put into forward-selection multiple linear regression models. For the significant factors that account for a lowered HUI2 or HUI3 score in the multiple regression model, we further analyzed the single attribute scores between the subgroups with and without these factors. Statistically significant difference in single attribute scores between these subgroups was confirmed with two-sample t-test.

TSC subjects were distributed into three groups with roughly similar intervals in terms of their number of chronic health conditions, and the mean HUI2 and HUI3 scores of each group were calculated. One-way analysis of variance (ANOVA) with a post-hoc test was used to determine any significant difference in HUI2 and HUI3 scores between the groups.

HUI3 scores of TSC subjects were tabulated and compared with HUI3 scores of other disease entities in the literature.

Statistical analyses were done with SPSS version 26.0.0.0 (IBM SPSS Statistics).

# Results

## *Demographic characteristics of study population*

With the help of TSCAHK, 37 TSC patients and/or their proxies were approached in this study. 4 patients were excluded due to <5 years old; 3 patients were excluded as they were non-Chinese; 2 patients who met the inclusion criteria refused to join the study; 1 patient who met the inclusion criteria failed to join the study due to the lack of a proxy available to fill in the questionnaire. A total of 27 patients and their proxies were qualified and agreed to participate in our study (Figure 1).

There were 16 (59.3%) male TSC subjects and 11 (40.7%) female TSC subjects. 7 (25.9%) of them were aged 5-12, 2 (7.4%) of them were aged 13-18, 12 (44.4%) of them were aged 19-29, 3 (11.1%) of them were aged 30-39, 2 (7.4%) of them were aged 40-49 and 1 (3.7%) of them was aged above 60. All were Chinese. Among the patients, 5 (18.5%) of them were reported to have family history of TSC (Table 2).

## *Overall HRQoL analysis*

The mean HUI2 and HUI3 scores of our TSC cohort were 0.64 and 0.50 respectively. The descriptive statistics of the overall HUI2 and HUI3 scores were shown in Table 3. Majority of our TSC patients belonged to the “severe” disability group after categorizing them into disability level according to their HUI2 and HUI3 HRQoL score (Figure 2). By comparing both the HUI2 and HUI3 HRQoL scores of our TSC cohort with the Chinese DS patients, the proportion of TSC patients in the “severe” category was greater than that of DS patients (Figure 3).

## *Proxy-reported chronic health conditions*

Among the proxy-reported chronic health conditions (Table 4), mental health conditions included 15 (55.6%) ADHD, 12 (44.4%) anxiety problems, 15 (55.6%) autism, 18 (66.7%) behavioral problems, 7 (25.9%) depression, 20 (74.1%) developmental delay or mental retardation and 22 (81.5%) learning problems. For physical health conditions, 3 (11.1%) chronic respiratory, lung or breathing troubles, 21 (77.8%) epilepsy, 1 (3.7%) hearing impairment or deafness, 9 (33.3%) visual problems, 15 (55.6%) speech problems, 0 (0%) cancer, 11 (40.7%) skin problems, 9 (33.3%) gastrointestinal and liver problems, 9 (33.3%) chronic renal disease, and 7 (25.9%) sleep disturbance were reported.

Analyses using two-sample t-test and multiple regression were conducted for both HUI2 and HUI3 in comparing demographic factors and chronic health conditions. Results revealed that demographic factors such as age, sex and family history did not affect their HUI2 and HUI3 HRQoL scores (HUI2  $p=0.73, 0.63, 0.06$ ; HUI3  $p=0.85, 0.45, 0.55$ ). In evaluation of the effect of different chronic health conditions, a significantly lower HUI2 score was found in those with ADHD ( $p<0.01$ ), anxiety ( $p<0.01$ ), autism ( $p=0.04$ ), behavioral problems ( $p<0.01$ ), epilepsy ( $p<0.01$ ), speech problems ( $p=0.04$ ), learning problems ( $p=0.01$ ) and skin problems ( $p<0.01$ ). With respect to HUI3 scores, individuals with ADHD ( $p<0.01$ ), anxiety problems ( $p=0.04$ ), behavioral problems ( $p<0.01$ ), speech problems ( $p=0.03$ ) and skin problems ( $p<0.01$ ) were found to have significantly lower scores. It is worth noting that among these, the group with skin problems had

the lowest HRQoL scores in both HUI2 (mean=0.54) and HUI3 system (mean=0.31). The chronic health conditions associated with a significantly lower overall HUI2 scores and HUI3 scores have been summarized in Table 5. Among the conditions associated with a lower HUI2 or HUI3 HRQoL score, the forward-selection multiple linear regression model revealed “behavioral problems” being the only significant indicator for a lower HUI2 score ( $p<0.01$ ), whereas “ADHD” was the only significant indicator for a lower HUI3 score ( $p<0.01$ ).

### *Single-attribute HRQoL analysis*

To scrutinize the health attributes affected by behavioral problems and ADHD, single-attribute HUI2 and HUI3 score analyses were performed on the subgroups with behavioral problems and ADHD respectively, with the results presented in Figure 4. Significantly lower mean HUI2 scores in cognition attribute ( $p<0.01$ ) and self-care attribute ( $p<0.01$ ) were found in the subgroup with behavioral problems compared with the subgroup without behavioral problems. Significantly lower mean HUI3 scores in cognition attribute ( $p<0.001$ ) and speech attribute ( $p=0.01$ ) were found in the subgroup with ADHD compared with the subgroup without ADHD.

### *Effect of multiple chronic health conditions on overall HUI2 & HUI3 scores*

The number of chronic health conditions reported in each patient ranged from 1 to 13 (out of 17). We divided our patients into three groups with roughly similar intervals in terms of their number of chronic health conditions (1 to 5, 6 to 9, and 10 to 13). Figure 5 showed the mean HUI2 and HUI3 scores of these groups. One-way ANOVA with Games-Howell post-hoc test was performed (equal variances not assumed) and statistically significant difference was found between groups. For HUI2 scores, those with 1 to 5 chronic health conditions had significantly higher mean HUI2 scores than those with 6 to 9 chronic health conditions ( $p<0.01$ ) and those with 10 to 13 chronic health conditions ( $p=0.02$ ). Analysis on HUI3 scores showed similar findings, in which those with 1 to 5 chronic health conditions had significantly higher mean HUI3 scores than those with 6 to 9 chronic health conditions ( $p<0.01$ ) and 10 to 13 chronic health conditions ( $p<0.001$ ).

### *Comparison of HUI3 scores in TSC patients with existing literatures*

Table 6 showed mean HUI3 scores in our whole cohort and in subgroups of TSC patients with epilepsy, autism, anxiety problems and chronic kidney disease (CKD). These scores were compared with our local DS patients as well as the general population, and such comparison revealed that the HUI3 scores of subjects with TSC were generally lower.

## **Discussion**

Individual BOI of TSC is variable given the wide spectrum of disease manifestation in TSC (17). To evaluate the disease burden, in parallel to direct cost analysis, QoL assessment is an important outcome measure, and has increasing attention in recent years (40-42).

### *Novel findings on HRQoL of TSC patients*

This is the first study to establish HRQoL measurements in the general Chinese TSC population, which includes both pediatric and adult subjects. Besides serving as a quantitative reference for future research and resource allocation to improve the QoL of our TSC population, it also provides an array of new perspectives regarding QoL of TSC patients.

Firstly, this is a unique study in making a direct comparison of HRQoL of TSC with DS, the latter being the most common chromosomal disease with well-known impact on HRQoL. Our findings suggested that subjects with TSC had a poorer HRQoL than those with DS. Such comparison is justified because, on a robust sample recruited through TSC patient support group, we applied the same validated health-state classification system (i.e. HUI-Ch) used in the local DS cohort recruited through its patient support group. Previous studies compared QoL of TSC patients with other illnesses such as asthma, cancer, inflammatory bowel disease and diabetes, but this study is the first study comparing QoL of TSC with another multi-organ-involved genetic disease with well-known impact on HRQoL (41).

Secondly, it is worth highlighting that the mental and physical health conditions in TSC correlated with a significantly lower HRQoL. Putting it into clinical context, we recommend physicians to identify these health conditions and take notice of their association with poorer HRQoL, so as to provide better care for these TSC patients. Our study found that physical problems, such as epilepsy and skin problems, were associated with a significantly poorer HRQoL. On the other hand, the mental problems were arguably a bigger issue to attend to. The prevalence of mental problems including ADHD, anxiety, autism, behavioral problems, learning difficulties was high, and the presence of these problems were associated with significantly lower HUI2 and/or HUI3 scores. With reference to the TOSCA (TuberOus SClerosis registry to increase disease Awareness) study, inadequately assessed neuropsychiatric problems of TSC patients were common (43). Development of TAND checklist aimed to address the previous lack of evaluation of these problems (44). However, TAND checklist has not been applied in local clinical settings, and the prevalence of TANDs in local TSC patients was previously unknown. The findings in our study reveals the service gap in evaluating TANDs in our TSC patients and addressing the implication on their HRQoL. On top of that, our study attempts to address a research gap since the potential relationship of TAND with impaired HRQoL has been inadequately investigated in the literature. A number of studies have suggested the association between seizure, intellectual disabilities, ASD, ADHD and other neurobehavioral manifestations (45-48). However, the coexistence of seizure and various mental problems makes it difficult to determine the key factor that can independently predict an impaired HRQoL in TSC patients. The multiple regression model in this study suggested that behavioral problems and ADHD are the significant independent predictors for a deficit in HUI2 and HUI3 scores respectively. We further looked into the score decrements in individual health attributes in patients with these problems. It was found that besides their significant association with impaired cognitive functioning, ADHD was also associated with impaired speech, and having behavioral problems was associated with impaired self-care. In the background of a dearth of research on neuropsychological therapy for TSC patients, our study provides insights for future therapeutic research that might target ADHD and behavioral problems, and the associated functional impairment these problems cause, in order to improve the QoL of TSC patients (17). Local healthcare

providers should take particular notes of ADHD and behavioral problems in TSC patients. When therapies are developed for these problems, our study provides essential baseline HRQoL measurement in local TSC patients for outcome evaluation.

Thirdly, we demonstrated that the TSC patients with multiple (in particular, 6 or more) physical and mental health conditions were associated with a lower HRQoL. Similar patterns were observed in the local DS population, in which a gradient relationship was found, with an increasing number of developmental behavioral problems resulting in a lower HRQoL. However, it has not been reported in previous TSC literature. Physicians should pay particular attention to patients' HRQoL when seeing TSC patients with multiple physical and mental problems. To our knowledge, these patients might visit multiple specialty outpatient clinics locally. Now we know that multiple outpatient clinic visits in these patients raised two issues: first, it contributes to a substantial direct cost in our healthcare system; second, their QoL impairment is related to multiple physical and mental problems, and could not be addressed adequately unless by a multidisciplinary team (1). Overseas research provides guidance on setting up a TSC multidisciplinary team, and we believe such a team would benefit our TSC patients by giving a holistic care plan addressing various physical problems and individual QoL issues (49).

#### *Strength of this study*

Our study provides a robust account of HRQoL of Chinese TSC patients. HUI-Ch has been chosen because it is a validated system and allows reliable comparison between HRQoL of normal population and populations with various diseases. Informant report is shown to give more complete information than merely self-reported for TSC, as there is a wide variation in intellectual disability in TSC patients which affects their ability to self-report (21, 50, 51). Validation process was completed with direct oversight by HUI developers, and the HUI-Ch received final approval from the developers of HUI(23). Therefore, the use of HUI-Ch allows healthcare professionals to make reliable interpretations on the HRQoL of the local TSC population and comparison across various disease entities with their HUI3 scores previously reported. As exemplified in Table 6, when subgroups of our TSC cohort with certain conditions (epilepsy, autism, anxiety problems, CKD) were compared with the general population with these conditions, the HUI3 scores of individuals with TSC were generally lower. This quantitative comparison has broad implications in terms of policy making, as well as communicating and counselling with parents about the outcome of TSC. As part of our TSC patient registry, this study reflects patients' QoL, which complements our previous TSC study that focused on the direct cost incurred by TSC patients on the healthcare system (1). Together they provide direction for better local healthcare planning towards a tailored management for local TSC patients.

#### *Comparison with other studies on QoL of TSC population*

While previous TSC QoL studies mainly focused on its correlation with drug trials, epileptic status or surgery outcome, there is a paucity of study on the QoL of TSC patients as a whole (3, 52-54). We are aware of one study in the published literature that reported on HRQoL of TSC patients using HUI scores (42). Of the 214 patients in their study, the mean HUI3 score was 0.43, which was quite similar to our

findings (0.49). While their study involved TSC patients from the Netherlands only, independent findings from our results on a group of Chinese TSC patients support the generalizability of the finding that TSC patients have poorer HRQoL. Our study provides additional analysis of the overall and single-attribute HUI2 scores, besides the HUI3 scores used in their study. Since HUI2 and HUI3 systems have their own advantages, findings on HUI2 scores can provide complementary information regarding the HRQoL of TSC patients (28). Considering the health conditions correlating with a lower HUI score, our study concurs with them that the presence of CKD did not associate with a significantly lower HRQoL. In their study, TSC-associated epilepsy and the refractory status were found to correlate with HRQoL score. Our finding is in line with theirs, as the presence of epilepsy was associated with significantly lower HUI3 scores from two-sample t-test. On the other hand, their study did not take into account the mental problems in TSC patients. Our study takes another step by considering a number of mental problems TSC patients have and finding the significant indicators for HUI score decrements by multiple regression. Epilepsy and TAND are closely interrelated in pathogenesis and treatment perspective as reported in various recently developed models (45, 46, 55). While epilepsy and TAND coexist in many TSC patients, our study gives insights that ADHD and behavioral problems are the independent predictors for impairment in HRQoL. Further research is needed to look into the cause-and-effect between seizure and different neurobehavioral problems in TSC patients.

There are two recent studies conducted in Asia assessing the QoL of TSC patients in Malaysia and mainland China respectively (29, 30). We compared these two studies with our study and identified 3 distinctive differences.

First of all, both of these studies assessed TSC children aged 2 to 18 years using PedsQL. Their results may provide useful reference for managing TSC children. Whereas in our study, we included both pediatric and adult populations and this patient group is representative of all surviving TSC patients in our public healthcare system as shown in our previous study (1). Since TSC has a changing clinical course throughout lifetime, patients may experience extra HRQoL impairment as they grow into adulthood (17). Adult TSC patients had inadequate surveillance rates as reported in Chopra M. et al. This might be accounted by the difficulties they faced during transition from multidisciplinary pediatric care to the fragmented adult healthcare sectors (17, 56). They also experienced impaired work productivity, and significantly higher out-of-pocket direct cost than that of TSC incurred in pediatric patients (57). Therefore, our study would provide a more holistic view of the general TSC population and may be useful in healthcare policy making.

Secondly, different QoL assessment tools were used. PedsQL 4.0 and HUI have different psychometric properties. Existing evidence showed various strengths and limitations in these QoL tools respectively (58). The HUI2 and HUI3 measurements provided in our study can serve as an additional reference in evaluating the QoL in the TSC population.

Thirdly, the healthcare system and policy are different in all 3 studies' settings. Notably, in our locality, mTOR inhibitors were only prescribed to a restricted proportion of patients (16.5%) (1), whilst in mainland China, mTOR inhibitors (Sirolimus) are widely available to children with TSC. mTOR inhibitors alter the

disease progression in TSC by inhibiting the mTOR pathway (59), hence may bring about changes to the QoL in TSC patients. The variation in prescription patterns of mTOR inhibitors may reflect a different QoL profile. Our study provides HRQoL data in a distinct healthcare system and contributes to the diversification of QoL database of the TSC population.

Of note, epilepsy was found to be an independent predictor for poorer HRQoL in Ding Y et al's study, which targeted children with TSC (30), but not in our study which targeted adult and pediatric TSC patients. This may be related to the proxy-reported nature of questionnaires used in evaluating QoL of children. As caregivers are easily burdened by taking care of patients with severe forms of epilepsy and the correlating neurological and psychiatric manifestations (60, 61), the perceived HRQoL of a child with epilepsy in various attributes may be lower in a parent-reported questionnaire. Previous psychometric studies in PedsQL showed disparity between child- and parent-reported QoL scores in children with neurodisability (58). Whilst caregivers for pediatric TSC patients reported seizure as one of the most bothersome concerns in Rentz AM et. al's study (62), it is worthwhile for future studies to evaluate whether psychosocial support and referral to patient advocacy groups would be an effective solution (17). Moreover, the effect of caregiver perception on proxy-reported QoL evaluation of pediatric TSC patients remains to be further explored.

The recent publication by TOSCA Consortium Investigators reported BOI on 143 individuals from 7 European countries, ranging from 3 to 58 patients from each country, using both self- and caregiver-reported questionnaires (40). Their study evaluated BOI in a comprehensive approach, in terms of impact on education, employment status, satisfaction of medical care, QoL etc. Considering QoL measures alone, both our study and the TOSCA study demonstrated a large impact of TSC on the QoL of TSC individuals and their families. However, direct comparison cannot be made as different QoL tools were used. One of the limitations mentioned in the TOSCA study is the potential overestimation of the overall QoL of the TSC population, because their patient sample consisted of a smaller proportion of epileptic TSC patients as compared to the overall TSC cohort. Although epilepsy was not shown to be an independent predictor of poorer QoL in our study, patients with epilepsy are known to have poorer QoL from our two-sample t-test results and from the literature (42). On the contrary, the proportion of patients with seizure reported in our study was 77.8%.

The study by Sam Amin et al. also reported impaired overall QoL in TSC adult and pediatric patients (41). They suggested that QoL of TSC patients remains poor after adjusting for epilepsy and learning disability, which may be related to other comorbidities impacting their QoL and requires further study. This concurs with our suggestion that epilepsy is not an independent predictor of poorer QoL in TSC patients. Rather, ADHD and behavioral problems, which coexist in many but not all TSC patients with a history of epilepsy, are the independent predictors of poorer QoL found in our study. Another point to note is that their study compared the QoL of TSC patients evaluated on the PedsQL scale with children who suffered from asthma, diabetes, cancer and inflammatory bowel disease. However, the impact of TSC does not confine to childhood and may even worsen with age, as elaborated above. Our study does not limit to pediatric age groups, and provides additional insight by comparing the QoL of TSC patients with DS patients. This comparison is of high clinical relevance, as DS is similar to TSC – both are multisystem-involved genetic

diseases requiring long-term multidisciplinary surveillance and with well-recognized long-term impact on HRQoL (23, 63).

### *Limitations*

While interpreting the results of this study, certain caveats need to be taken into account. HUI questionnaires were distributed with the help of TSCAHK, so selection bias may exist. The selected population may be of higher activity of daily living, resulting in overestimation of HRQoL of the whole cohort. To ensure the reliability of the data collected, we compared this cohort with the cohort of all surviving TSC patients in Hong Kong as retrieved from our previous study (1). There was no statistically significant difference in terms of age, sex and epileptic status. With the use of proxy-assessed questionnaires, there was intrinsic limitation in the accuracy of HRQoL assessed, especially on the subjective domains. Nevertheless, it was shown that reliability and agreement of proxy responses to the index patients tended to be the best for close relatives (64). In our study, all proxy respondents were the close relatives of the respective index patients. Lastly, this study was observational in nature. There were limitations regarding establishing the causal relationship between the presence of Child Health Questionnaire and HRQoL.

## **Conclusions**

Local Chinese TSC population was found to have poorer HRQoL as compared to patients with DS or other chronic diseases. A more comprehensive interdisciplinary care for our local TSC population is necessary to improve their HRQoL. Since this is the first locoregional HRQoL study for general TSC patients, results from this study can serve as a baseline of the quality of care and effectiveness of intervention of TSC patients with similar cultural backgrounds. Similar studies can be reproduced in other regions, so as to enrich the database and verify our data.

## **Declarations**

### DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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### Contributions

DC, LC and WC contributed equally to this work. DC, LC, WC, WW and GC contributed to the conception and design of the work. DC coordinated with HUInc, acquired and interpreted data, drafted and revised the manuscript. LC and WC acquired, analyzed and interpreted data, drafted and revised the manuscript. CC and NH analyzed and interpreted the data and drafted the manuscript. WW oversaw the statistical analysis and revised the manuscript. GC revised the manuscript and is a clinician managing a large cohort of TSC patients. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Ethics approval was obtained from the Institutional Review Board, The University of Hong Kong and West Cluster of Hospital Authority, Hong Kong. Written informed consent to participate in this study was provided by the patient's proxy.

### Consent for publication

Not applicable

### Competing interests

The authors declare that they have no competing interests.

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## Tables

**Table 1** | Questionnaires that have been used to assess QOL in TSC individuals in the past 10 years

		Questionnaire list
Generic QOL questionnaire		<p>Short Form 12 (SF-12) (62, 65, 66)</p> <p>Short Form 36 (SF-36) (41)</p> <p>Pediatric Quality of Life Inventory (PedsQL) (29, 30, 41, 67)</p> <p>Work Productivity and Activity Impairment plus Classroom Impairment Questions (WPAI+CIQ) (65, 66)</p> <p>Brief-Illness Perception Questionnaire (Brief-IPQ) (68)</p> <p>Quality of Life Scale (QOLS) (69)</p> <p>EuroQOL-5D (EQ-5D) (3, 40)</p> <p>EuroQOL-5D-Youth (EQ-5D-Y) (67)</p> <p>Health Utilities Index version 3 (HUI-3) (42)</p>
Specific domain:	Epilepsy	<p>Quality of life in epilepsy inventory-31-Problems (QOLIE-31-P) (21, 31, 40, 53)</p> <p>Quality of Life in Children with Epilepsy (QOLCE) (21, 31, 40, 54)</p> <p>Nisonger Child Behavioral Rating Form (NCBRF) (54)</p> <p>Quality of Life in Epilepsy Inventory for Adolescents-48 (QOLIE-AD-48) (21, 31, 40)</p>
	Skin	<p>Children's Dermatology Life Quality Index (CDLQI) (70)</p> <p>Skindex-Teen (70)</p>
	Depression	<p>Hamilton Depression Rating Scale-Short Form (HDI-SF) (62, 65, 66)</p> <p>Beck Depression Inventory-II (BDI-II) (68)</p>
	Anxiety	<p>Beck Anxiety Inventory (BAI) (68)</p>
	Sleep	<p>Epworth Sleepiness Scale (ESS) (71)</p> <p>Sleep and Epilepsy Questionnaire (SEQ) (71)</p> <p>Sleep Diagnosis List (SDL) (71)</p> <p>Adult Self-Report Scale (ASRS) (71)</p>
	Fatigue	<p>Multidimensional Fatigue Inventory-20 (MFI-20) (69)</p>

**Table 2** | Demographic characteristics of the study sample (Total = 27)

Demographic	Number (%)	
Sex		
Male	16	(59.3)
Female	11	(40.7)
Age		
5-12	7	(25.9)
13-18	2	(7.4)
19-29	12	(44.4)
30-39	3	(11.1)
40-49	2	(7.4)
50-59	0	(0)
60+	1	(3.7)
Ethnicity		
Chinese	27	(100)
Others	0	(0)
Family history of TSC		
Yes	5	(18.5)
No	22	(81.5)

**Table 3** | Overall HUI2 and HUI3 scores of the TSC subjects (For both HUI2 and HUI3 scores, 0 depicts death, 1 depicts perfect health and negative scores are deemed worse than being dead.)

	HUI2 (scale: -0.03 to 1)			HUI3 (scale: -0.36 to 1)		
	Mean (SD)	Max	Min	Mean (SD)	Max	Min
All patients (n=27)	0.64 (0.17)	0.85	0.29	0.50 (0.31)	0.92	-0.02
Male (n=16)	0.63 (0.18)	0.85	0.29	0.46 (0.34)	0.92	-0.02
Female (n=11)	0.67 (0.15)	0.85	0.42	0.56 (0.25)	0.92	0.14

**Table 4** | Proxy-reported chronic health conditions of the TSC subjects

Chronic health condition	Number (%)	
<b>Mental</b>	24	(88.9)
Learning problems	22	(81.5)
Developmental delay or mental retardation	20	(74.1)
Behavioral problems	18	(66.7)
Autism	15	(55.6)
ADHD	15	(55.6)
Anxiety problems	12	(44.4)
Depression	7	(25.9)
<b>Physical</b>	24	(88.9)
Epilepsy	21	(77.8)
Speech problems	15	(55.6)
Skin problems	11	(40.7)
Chronic renal disease	9	(33.3)
Gastrointestinal and liver problems	9	(33.3)
Vision	9	(33.3)
Sleep disturbance (including OSA)	7	(25.9)
Chronic respiratory, lung or breathing trouble	3	(11.1)
Hearing impairment or deafness	1	(3.7)
Cancer	0	(0)

**Table 5** | The chronic health conditions associated with lower HUI2 and HUI3 scores

	HUI2		HUI3			
	Two-sample t-test		Multiple regression	Two-sample t-test		Multiple regression
	Mean (SD)	p-value	p-value	Mean (SD)	p-value	p-value
<b>ADHD</b>		<0.01*	0.10		<0.01*	<0.01*
Yes	0.55 (0.17)			0.33 (0.28)		
No	0.76 (0.09)			0.71 (0.18)		
<b>Anxiety problems</b>		<0.01*	0.15		0.04*	0.51
Yes	0.55 (0.15)			0.36 (0.23)		
No	0.72 (0.15)			0.61 (0.32)		
<b>Autism</b>		0.04*	0.97		0.06	0.84
Yes	0.58 (0.18)			0.40 (0.32)		
No	0.72 (0.13)			0.63 (0.24)		
<b>Behavioral problems</b>		<0.01*	<0.01*		<0.01*	0.07
Yes	0.57 (0.16)			0.37 (0.28)		
No	0.80 (0.05)			0.76 (0.13)		
<b>Epilepsy</b>		<0.01*	0.38		0.07	0.55
Yes	0.61 (0.18)			0.44 (0.31)		
No	0.76 (0.06)			0.70 (0.23)		
<b>Speech problems</b>		0.04*	0.49	0.39 (0.30)	0.03*	0.91
Yes	0.58 (0.18)			0.64 (0.25)		
No	0.72 (0.13)					
<b>Learning problems</b>		0.01*	0.81		0.13	0.58
Yes	0.62 (0.18)			0.46 (0.31)		

No	0.76 (0.08)			0.69 (0.25)		
<b>Skin problems</b>		<0.01*	0.22		<0.01*	0.09
Yes	0.54 (0.16)			0.31 (0.21)		
No	0.72 (0.14)			0.63 (0.30)		

\*p-value < 0.05

**Table 6** | Comparison of HUI3 scores in other studies

	Current study (n=27)	Menno Vergeer et al. 2019 (42) (n=214)	WKY Mok et al. 2014 (23) (n=109)	JT Langfitt et al. 2006 (72) (n=165)	Payakachat et al. 2014 (57) (n=224)	Guertin et al. 2018 (73) (n=128,310)	A Tong et al. 2013 (35) (n=27)
<b>Region</b>	Hong Kong	The Netherlands	Hong Kong	USA	USA	Canada	Australia
<b>Sex</b>	F: 40.7%	Not reported	F: 44%	F: 53%	F: 13.4%	F: 50.6%	F: 59%
<b>Age mean <math>\pm</math> SD (range)</b>	23.7 y $\pm$ 13.2 (5.6-64.1)	Not reported	23.6 y $\pm$ 8.5 (5-53)	37.4 y $\pm$ 11.4	8.8 y $\pm$ 3.5 (4.0-17.9)	44.8 y	17.1 y (12-25)
<b>Condition studied</b>	TSC	TSC	DS	Chronic epilepsy	ASD	Anxiety Disorder	CKD
<b>Self- / Proxy-reported</b>	Proxy-reported	Proxy-reported	Proxy-reported	Self-reported	Proxy-reported	Self-reported	Self-reported
<b>Mean HUI3 scores</b>							
<b>Overall</b>	0.49 $\pm$ 0.31	0.43	0.55 $\pm$ 0.27				
<b>Epilepsy</b>	0.44 $\pm$ 0.31 (n=21)	0.47 (n=171)		0.610 $\pm$ 0.298 (n=140)			
<b>Autism</b>	0.40 $\pm$ 0.33 (n=15)				0.66 $\pm$ 0.23 (n=218)		
<b>Anxiety</b>	0.36 $\pm$ 0.23 (n=12)					0.677 (n=8,802)	
<b>CKD</b>	0.45 $\pm$ 0.22 (n=9)						0.74 $\pm$ 0.26

## Figures

37 TSC patients ± their proxies were contacted

- 4 patients were excluded as they were <5 years old
- 3 patients were excluded as they were non-Chinese ethnic origin
- 2 patients refused to participate in the study
- 1 patient was excluded as there was no proxy available to fill in the questionnaire

27 subjects met the inclusion criteria and agreed to participate in our study

Figure 1

Details about patient selection

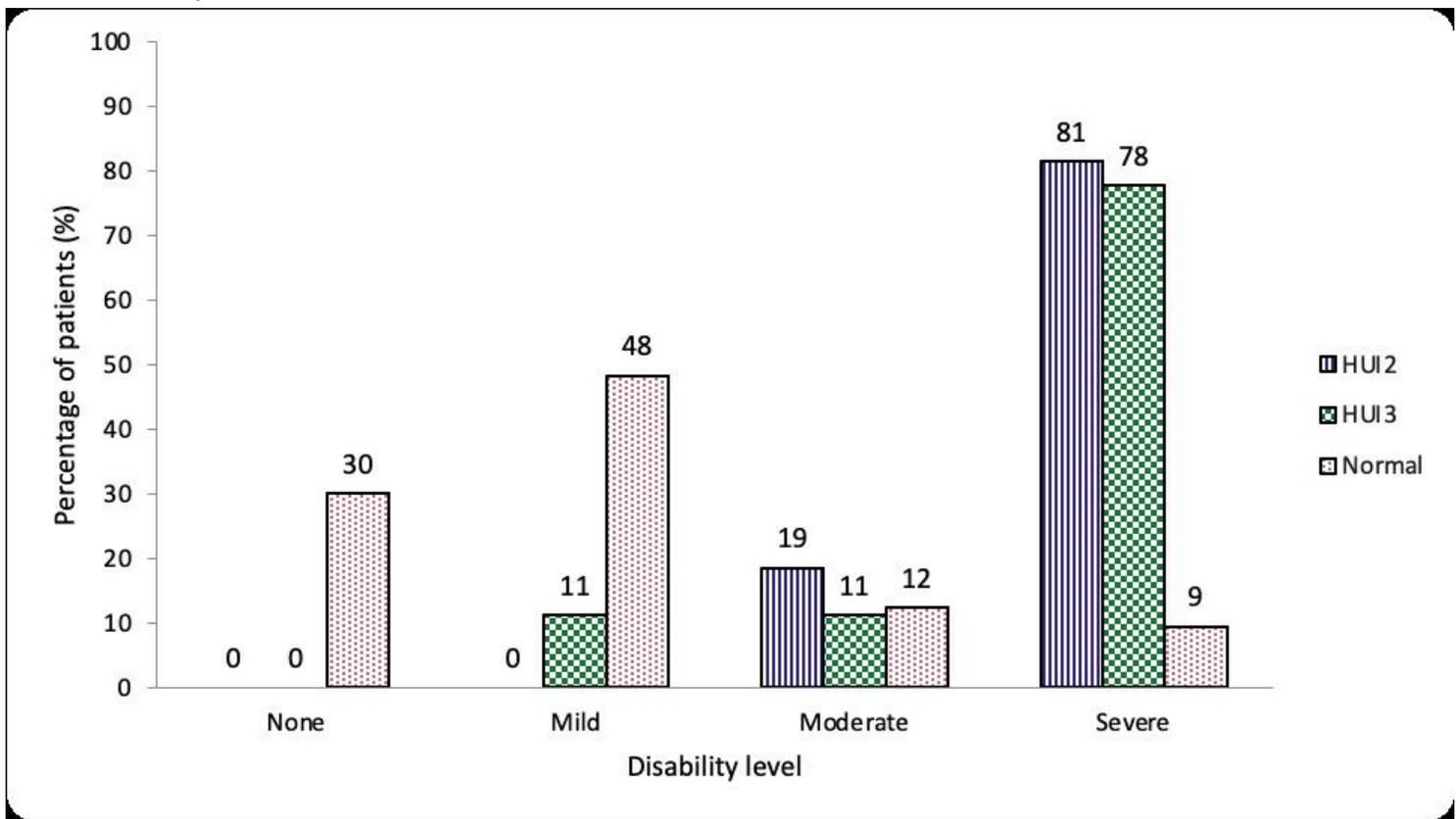
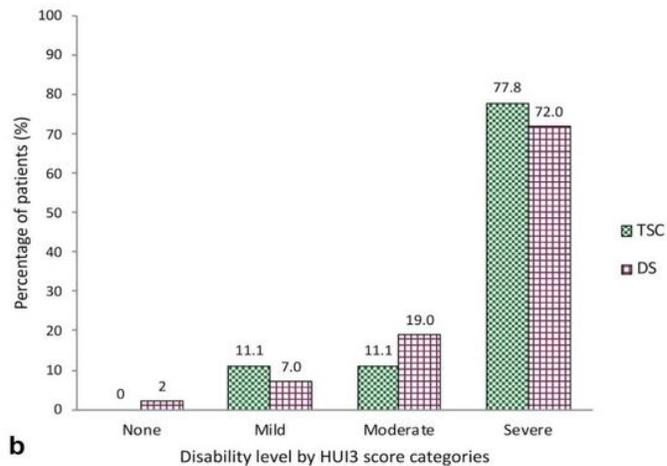
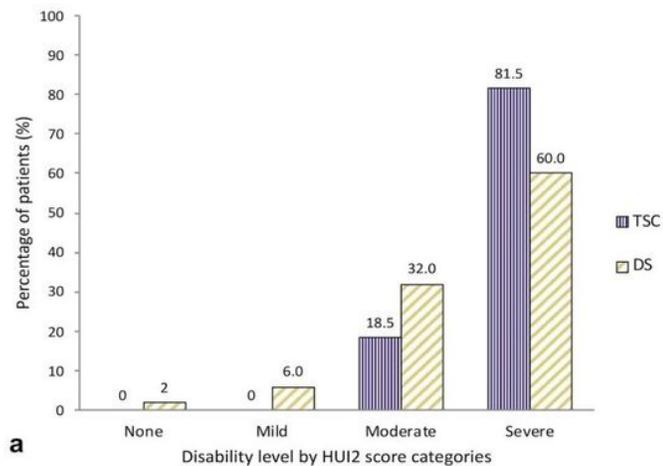


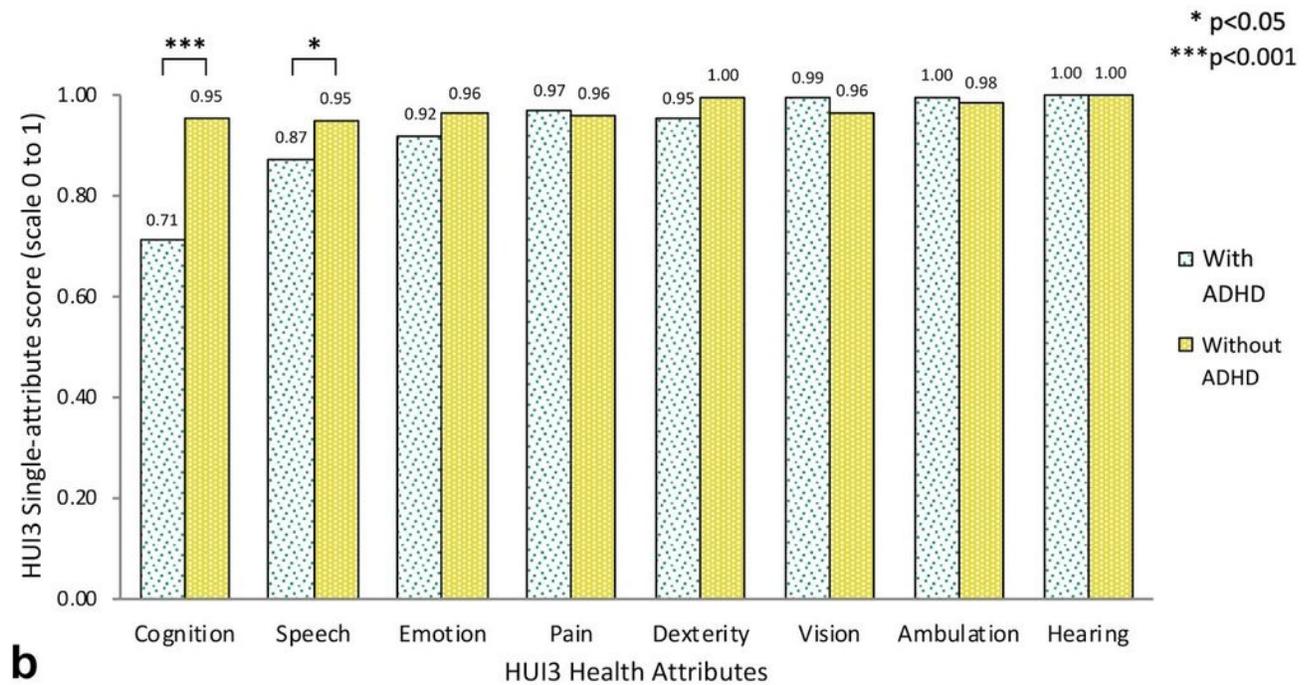
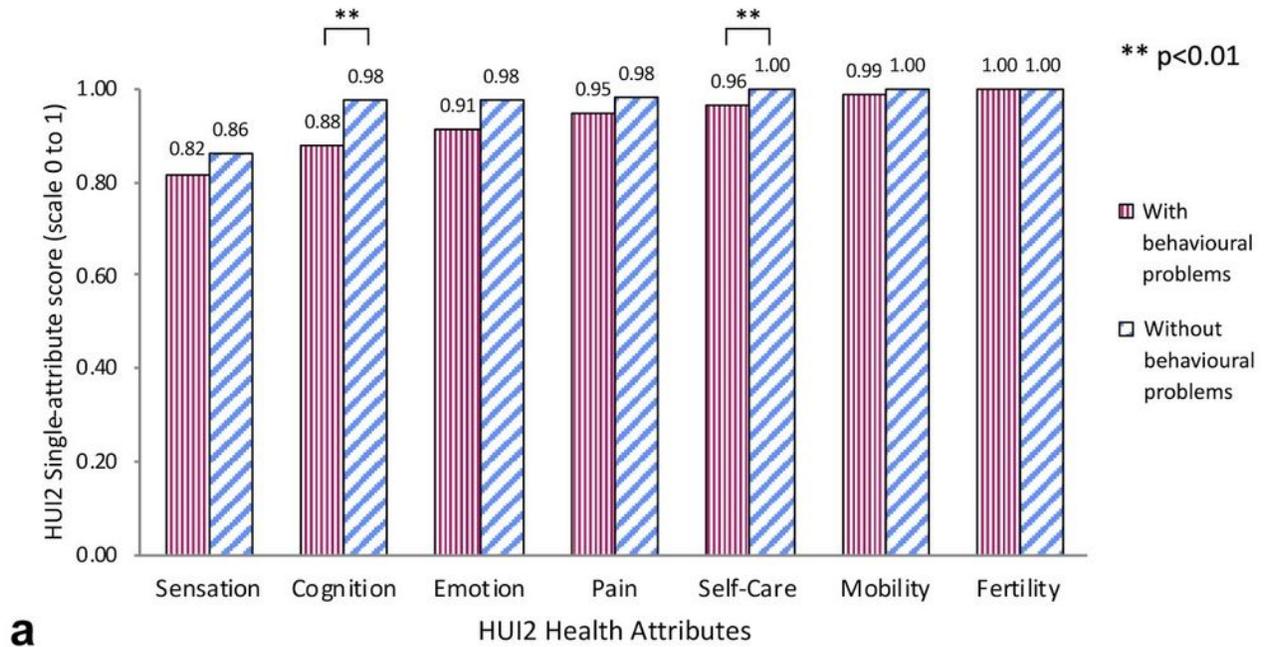
Figure 2

Disability level of TSC patients categorized by their overall HUI2 and HUI3 scores



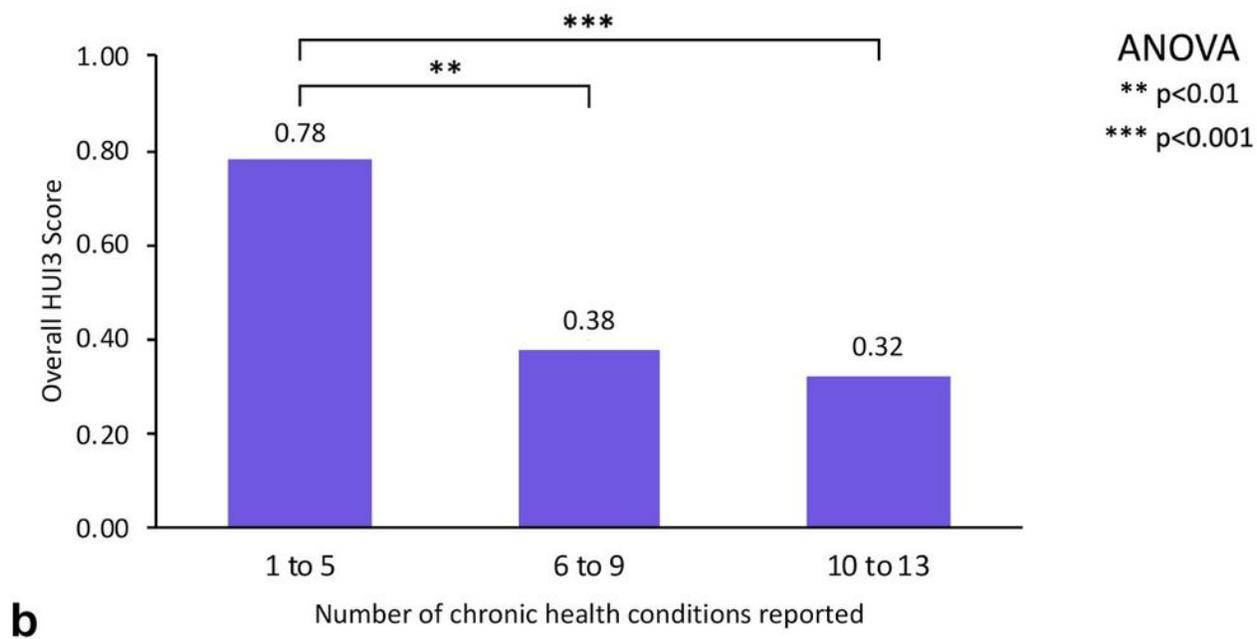
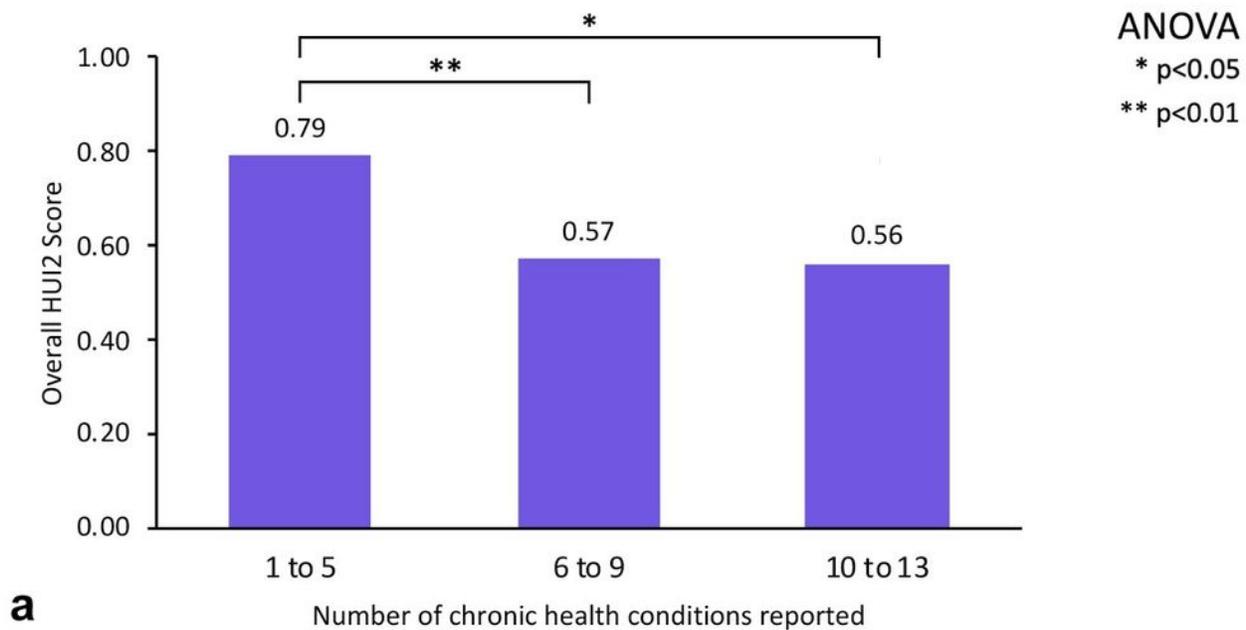
**Figure 3**

Disability level of TSC patients compared with DS patients by (a) HUI2 score categories and (b) HUI3 score categories



**Figure 4**

Subgroup single-attribute HUI2 and HUI3 scores analysis on significant indicators of lower HRQoL (a) Comparing HUI2 single-attribute scores between the subgroups with and without behavioral problems. (b) Comparing HUI3 single-attribute scores between the subgroups with and without ADHD.



**Figure 5**

HRQoL of TSC patients with different numbers of chronic health conditions, in terms of (a) overall HUI2 scores and (b) overall HUI3 scores