BMJ Open

Yale Global Tic Severity Scale is a Valid Tool for Self-reported Assessment in the Pediatric Population: A Prospective Observational Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034634
Article Type:	Original research
Date Submitted by the Author:	15-Oct-2019
Complete List of Authors:	Ho, Che-Sheng ; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Huang, Jia-Yun; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Yang, Chien-Hui; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Lin, Yi-Jie; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Huang, Ming-Yuan; Mackay Memorial Hospital, Taipei, Taiwan , Department of Emergency Medicine, Su, Yung-Cheng; Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, Emergency Department
Keywords:	Paediatric neurology < NEUROLOGY, Paediatric neurology < PAEDIATRICS, PUBLIC HEALTH, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Yale Global Tic Severity Scale is a Valid Tool for Self-reported Assessment in the Pediatric Population: A Prospective Observational Study

Che-Sheng Ho, MD[1,2]; Jia-Yun Huang, MD[2]; Chien-Hui Yang, MD[2]; Yi-Jie Lin, MD[1,2]; Ming-Yuan Huang*, MD, MS[1,3] and Yung-Cheng Su*, MD, MPH.[4,5]

[1]Department of Medicine, MacKay Medical College, New Taipei City, Taiwan

[2]Division of Pediatric Neurology, Department of Pediatrics, MacKay Children's Hospital, Taipei, Taiwan

[3]Department of Emergency Medicine, Mackay Memorial Hospital, Taipei, Taiwan

[4]Emergency Department, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan

[5]School of Medicine, Tzu Chi University, Hualien, Taiwan

*these authors contributed equally

Corresponding Author

Yung-Cheng Su, MD, MPH

Emergency Department,

Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation

No. 2, Minsheng Rd., Dalin Township,

Chiayi County 622, Taiwan (R.O.C.)

Tel: 886-5-2648000 ext 5838

Fax: 886-5-2648499

E-mail: drsu119@gmail.com

Declarations

Ethics approval and consent to participate

This study was initiated after approval from the Institutional Review Board of Taipei Mackay Memorial Hospital, Taiwan.

Consent for publication

Not applicable

Data sharing statement

The datasets used and analyzed for the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None declared

Contributorship statement

MYH analyzed and interpreted the data. JYH, CHY and YJL interpreted the data and contribute to manuscript development. CSH supervised the study and interpreted the data. YCS analyzed the data, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Yale Global Tic Severity Scale is a Valid Tool for Self-reported Assessment in the Pediatric Population: A Prospective Observational Study

Abstract

Objective: The Yale Global Tic Severity Scale (YGTSS) is the most commonly used evaluation tool for Tourette Syndrome (TS), with established reliability and validity. Administration of the YGTSS is relatively time consuming and requires a highly trained, experienced interviewer to ensure accurate and reliable use of the assessment, making its use in a busy clinical setting unfeasible. This study aims to determine whether the YGTSS is a valid tool for self-reporting in the TS population.

Methods: YGTSS was made available to participants via Google docs. Participants were encouraged to complete the YGTSS the day before each outpatient clinic visit. At each visit, a pediatric neurology fellow also administered the YGTSS assessment. The results of these physician assessments were taken as the expert standard for evaluating the sensitivity and specificity of the participant assessments conducted at the same visit. We also investigated whether differences in scores between physicians and participants changed as the number of self-evaluations increased.

Results: The differences in the YGTSS scores between participants and physicians were small. The mean difference in the total assessment score was 4.15 points. As the number of times the self-evaluation was performed increased, the difference between the participant and physician scores decreased. Discrimination of mild attacks was good using the self-assessed YGTSS (AUROC, 0.858; 95% CI, 0.839–0.876). The sensitivity for detecting a mild attack by

YGTSS self-assessment was 91.8% (95% CI, 89.9–93.7), and the specificity was 79.7 % (95% CI, 76.6–82.8).

Conclusions: The self-reported YGTSS is a promising tool for TS assessment, demonstrating good discriminative ability for disease severity, with user precision increasing with experience.

Strengths and limitations of this study

- The YGTSS is a promising tool for self-reporting assessment in the TS population.
- The precision of self-reported YGTSS increases with experience.
- As more than 500 patients are included in the database, the internal reliability may be difficult to be evaluated between the participants.

Introduction

Tourette Syndrome (TS) is characterized by persistent motor and vocal tics that begin before the age of 18 years. The prevalence in children is estimated at 6 per 1000.[1] The clinical presentation is complex, as the symptoms may wax and wane in frequency, intensity, and type.[2 3] The severity is influenced by multiple factors, including stress and social interactions,[4-6] making clinical assessment challenging. The most widely used measure to assess the severity of TS is the Yale Global Tic Severity Scale (YGTSS),[7 8] a clinician-administered, semi-structured interview that assesses tic and tic-related impairment severity over the previous week.

The YGTSS includes a symptom checklist for motor and vocal tics. As a group, all motor and vocal tics are rated for number, frequency, intensity, complexity, and interference on a 0–5 Likert scale. Scores are then added up to reflect the severity of motor tics (0–25), vocal tics (0–25), and combined tics (0–50). A separate tic-related impairment scale, ranging from 0–50, is also included. Although several other assessments have been developed, the YGTSS is still the most commonly used, with established reliability and validity.[7 9 10 11]

Administration of the YGTSS is relatively time consuming and requires a highly trained, experienced interviewer to ensure accurate and reliable use of the measure,[5] making use in the busy clinical setting unfeasible. In addition, even clinicians rely in part on patient awareness; that is, not all tics present during the interview.[12] The use of patient reported outcome measures (PROMs) has the potential to narrow the gap in clinical manifestations observed between clinicians and patients and to help adjust treatment plans.[13 14] This study evaluates the hypothesis that YGTSS is a valid tool for self-reporting in the TS population. Such a tool would allow for better communication and decision making between doctors and patients, and patient satisfaction with their care may also improve.

Methods

This study was initiated after approval from the Institutional Review Board of Taipei Mackay Memorial Hospital, Taiwan. We set up a database to collect patient information. Pediatric patients with TS who are regular followed up in the Taipei Mackay Memorial Hospital were enrolled after informed consent by their guardians, and the guardians were regarded as participants. Starting from June 2018, a revised traditional Chinese version of the YGTSS was made available to patients via Google docs (Figure 1). Upon introduction of the assessment to patients, a pediatric neurologist explained the use of the assessment scales to make sure participants clearly understood how to rate their symptoms. Participants were encouraged to fill in the YGTSS the day before each outpatient clinic visit. On the date of the visit, a pediatric neurology fellow was assigned to the patient by convenience sampling in the waiting room and also administered the YGTSS. The participants and the pediatric fellows were blind to the YGTSS results of the other. Some patients were administered the YGTSS evaluation by both the guardian and the pediatric fellow during the same visit. The attending physicians used the YGTSS results as a reference for making medical decisions during the visit.

Patient age and sex, date of visit, and self-assessed or pediatric-fellow–administered YGTSS scores were recorded. We further defined a YGTSS score <20 as a mild tic attack and >20 as a moderate to severe tic attack.[15] The results of the pediatric fellow assessments were taken as the expert standard for evaluating the sensitivity and specificity of the participant assessments conducted at the same visit. We also investigated whether differences in scores between these physicians and the participants changed as the number of self-evaluations

increased. Feedback from the participants was collected by convenience sampling at outpatient clinics.

All analyses were performed using Statistical Analysis Software for Windows, version V.9.4 (SAS Institute Inc., Cary, NC, USA). To adjust the correlated data from multiple evaluations by the same participants, the generalized estimate equation method was adapted to account for clustering of participants in the evaluation of score differences. The discriminatory power of a mild attack was determined using area under the receiver operating characteristic curve (AUROC) analysis of self-assessed YGTSS scores. A two-tailed $p < 0.05$ was considered statistically significant.

Patient and Public involvement

No patients involved.

Results

Study Population

A total of 594 patients was enrolled in this study during June 2018—April 2019, and 3356 evaluations were contributed by their guardians. On average, each participant contributed 5.65 self-reported YGTSS evaluations during the study period. Among these self-reports, 1455 were paired with simultaneous evaluations by pediatric fellows and were used for analyses. The final analysis included 527 patients. The mean patient age was 8.8 years (SD, 2.97), and 82.5% (n = 435) of the patients was male. A flow chart of the patient selection process is illustrated in Figure 2.

Comparison of assessment scores between participants and physicians

The differences in the YGTSS scores between participants and physicians were small. The mean difference in the total assessment score was 4.15 points, with greater contributions coming from the 'tic-related impairments' section. The results are summarized in Table 1. As the number of times the self-evaluation was performed increased, the difference between the participant and physician scores decreased. After taking participant clustering into account, the absolute difference in total scores between participants and physicians decreased by 0.24 points (95% C.I., 0.14—0.34; $p < 0.001$) for each repetition of the assessment. Subgroup analysis of the combined tic severity was perform revealed an absolute average difference of 2.40 points. The absolute difference in combined tic severity decreased by 0.17 (95% CI, 0.11–0.22; $p < 0.001$) for each repetition of the assessment. After participants completed the assessment 4 times, the difference between participant and physician scores was no longer significant (Figure 3).

Diagnostic accuracy of the YGTSS self-evaluation

The power of discriminating mild attacks with YGTSS self-assessment was good (AUROC, 0.858; 95% CI, 0.839–0.876). The sensitivity with which a mild attack was detected by using YGTSS self-assessment was significantly high. Of 819 self-assessments of mild attacks, 752 were in accordance with that of the physician, yielding a sensitivity of 91.8% (95% CI, 89.9–93.7). In 636 self-assessments of moderate to severe attacks, 507 were in accordance with that of the physician, yielding a specificity of 79.7% (95% CI, 76.6–82.8).

Evaluation of Feedback

Most comments from participants were positive, as the following examples indicate:

1) After self-assessment of my child, I know better what the doctor needs to know, and this process also helps me better understand how to take care of my child.

2) With these long-term, objective trends in my self-report results, I think discussing the goals of treatment with doctors is clearer.

Feedback taken by convenience sampling from physicians at hospital outpatient clinics was also encouraging:

1) Being able to understand the patient's condition outside of the hospital allows me to communicate more effectively with caregivers.

Discussions

The aim of the present study was to evaluate the potential use of the YGTSS as a self-reported measure of tic severity in children with TS. The results show overall good ability to discriminate a mild TS attack via self-reporting (AUROC, 0.858). The sensitivity and specificity for detecting a mild TS attack of were reasonably high. With repeated practice responding to the assessment, the self-report scores became similar to those of physicians, with no difference after the 4th assessment. Our sample size in this study is large enough that insufficient power was not an issue. Our results show that the YGTSS, the most widely used TS assessment tool, may be as accurate when used by patients as a self-report tool as it is when administered by clinicians.

Although administration of the YGTSS is relatively time-consuming, we used a step-by-step online google doc interface to help the participants fill out the forms with little difficulty. The

online self-report YGTSS database also allows participants to complete the evaluation without time and space limits, and more than three thousand self-evaluations during the study period is one factor contributing to the efficiency of the system. The feedback from both participants and clinicians was positive, and the database is still growing as the number of self-report submissions increases. Pediatric neurologists now rely more often on self-report assessments for adjusting treatment plans.[3 4] Because self-assessments allow guardians and clinicians to share the same information regarding a patient's condition, the communication is more fluent and efficient.[16 17]

Another reason for our positive results is that the participants were aware of their disease and highly motivated to be involved in their TS management. Patients generally welcome systems that routinely use PROMs.[13] The self-report YGTSS correlates highly with factors that have value to clinicians. Even for the clinician-administered YGTSS, the interviewer relies heavily on participants' insights, as patients may not present with the full range of tics during the interview. As a result, self-reports from participants may more closely reflect the actual patient condition.

Limitations

Our study has several limitations. First, the participants were guardians of TS children, and most of them have already participated in regular follow-up at our outpatient clinics. Thus, these participants may be more aware of their children's symptoms, allowing for an easier understanding of the YGTSS parameters, leading to a good correlation between the responses of participants and physicians. We were unable to perform subgroup analyses for patients with newly diagnosed TS. Second, as more than 500 patients are included in the database, the internal reliability may be difficult to be evaluated between the participants. However,

these results are representative of the real clinical situation. Finally, the evaluations from the physicians were not performed simultaneously with the participants. Since the physicians retrieved information by directly observing patients, the symptoms may have differed from those at the time of the self-report.

Conclusion

The self-reported YGTSS is a promising tool for TS assessment, demonstrating good discriminative ability for disease severity, with user precision increasing with experience.

References

1. Jeon S, Walkup JT, Woods DW, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods. *Contemp Clin Trials* 2013;36(2):414-20. doi: 10.1016/j.cct.2013.08.012 [published Online First: 2013/09/05]
2. Abramovitch A, Reese H, Woods DW, et al. Psychometric Properties of a Self-Report Instrument for the Assessment of Tic Severity in Adults With Tic Disorders. *Behav Ther* 2015;46(6):786-96. doi: 10.1016/j.beth.2015.06.002 [published Online First: 2015/11/02]
3. Lin H, Yeh CB, Peterson BS, et al. Assessment of symptom exacerbations in a longitudinal study of children with Tourette's syndrome or obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002;41(9):1070-7. doi: 10.1097/00004583-200209000-00007 [published Online First: 2002/09/10]
4. Eapen V, Fox-Hiley P, Banerjee S, et al. Clinical features and associated psychopathology in a Tourette syndrome cohort. *Acta neurologica Scandinavica* 2004;109(4):255-60. [published Online First: 2004/03/16]
5. Chang S, Himle MB, Tucker BTP, et al. Initial Psychometric Properties of a Brief Parent-Report Instrument for Assessing Tic Severity in Children with Chronic Tic Disorders. *Child & Family Behavior Therapy* 2009;31(3):181-91. doi: 10.1080/07317100903099100
6. Silva RR, Munoz DM, Barickman J, et al. Environmental Factors and Related Fluctuation of Symptoms in Children and Adolescents with Tourette's Disorder. *Journal of Child*

Psychology and Psychiatry 1995;36(2):305-12. doi: 10.1111/j.1469-7610.1995.tb01826.x

7. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity. *Journal of the American Academy of Child & Adolescent Psychiatry* 1989;28(4):566-73. doi: https://doi.org/10.1097/00004583-198907000-00015
8. Ho CS, Chiu NC, Tseng CF, et al. Clinical effectiveness of aripiprazole in short-term treatment of tic disorder in children and adolescents: a naturalistic study. *Pediatr Neonatol* 2014;55(1):48-52. doi: 10.1016/j.pedneo.2013.05.009 [published Online First: 2013/08/08]
9. Storch EA, Murphy TK, Geffken GR, et al. Reliability and validity of the Yale Global Tic Severity Scale. *Psychol Assess* 2005;17(4):486-91. doi: 10.1037/1040-3590.17.4.486 [published Online First: 2006/01/06]
10. Storch EA, De Nadai AS, Lewin AB, et al. Defining treatment response in pediatric tic disorders: a signal detection analysis of the Yale Global Tic Severity Scale. *J Child Adolesc Psychopharmacol* 2011;21(6):621-7. doi: 10.1089/cap.2010.0149 [published Online First: 2011/11/11]
11. Ho CS, Chen HJ, Chiu NC, et al. Short-term sulpiride treatment of children and adolescents with Tourette syndrome or chronic tic disorder. *Journal of the Formosan Medical Association = Taiwan yi zhi* 2009;108(10):788-93. doi: 10.1016/s0929-6646(09)60406-x [published Online First: 2009/10/30]
12. Conelea CA, Woods DW. The influence of contextual factors on tic expression in Tourette's syndrome: A review. *Journal of Psychosomatic Research* 2008;65(5):487-96. doi: https://doi.org/10.1016/j.jpsychores.2008.04.010
13. Nelson EC, Eftimovska E, Lind C, et al. Patient reported outcome measures in practice. *BMJ* 2015;350:g7818. doi: 10.1136/bmj.g7818 [published Online First: 2015/02/12]
14. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. *The New England journal of medicine* 2012;366(9):780-1. doi: 10.1056/NEJMp1109283 [published Online First: 2012/03/02]
15. Sallee F, Kohegyi E, Zhao J, et al. Randomized, Double-Blind, Placebo-Controlled Trial Demonstrates the Efficacy and Safety of Oral Aripiprazole for the Treatment of Tourette's Disorder in Children and Adolescents. *Journal of Child and Adolescent Psychopharmacology* 2017;27(9):771-81. doi: 10.1089/cap.2016.0026
16. Crandall W, Kappelman MD, Colletti RB, et al. ImproveCareNow: The development of a pediatric inflammatory bowel disease improvement network. *Inflammatory bowel diseases* 2011;17(1):450-7. doi: 10.1002/ibd.21394 [published Online First: 2010/07/06]
17. Lannon CM, Peterson LE. Pediatric collaborative networks for quality improvement and research. *Academic pediatrics* 2013;13(6 Suppl):S69-74. doi: 10.1016/j.acap.2013.07.004 [published Online First: 2013/12/07]

Table and Figure Legends

Table 1. Comparison of participant- and physician-assessed YGTSS scores according to assessment category

Figure 1. Revised traditional Chinese version of YGTSS made available via Google docs

Figure 2. Flow chart of patient selection

Figure 3. Distribution of average score differences

Table 1. Comparison of participant- and physician-assessed YGTSS scores according to assessment category*

Assessment Category	Mean difference† (points)	95% CI
Entire assessment (all categories)	4.15	3.82—4.48
motor tic severity	1.17	1.07—1.28
vocal tic severity	1.23	1.11—1.35
combined tic severity	2.40	2.22—2.58
tic-related impairment	2.41	2.14—2.68

*n = 1455

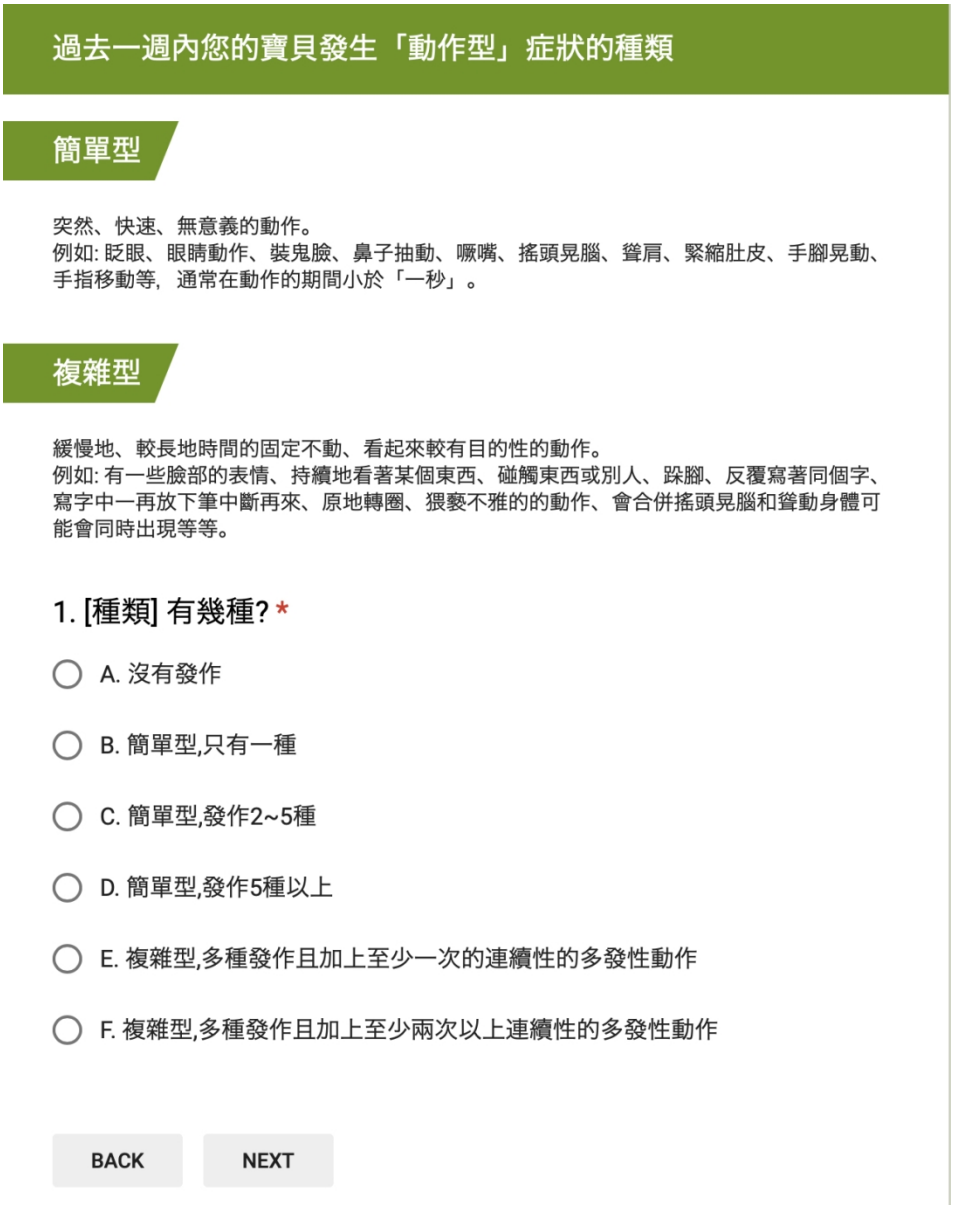


Figure 1

452x571mm (72 x 72 DPI)

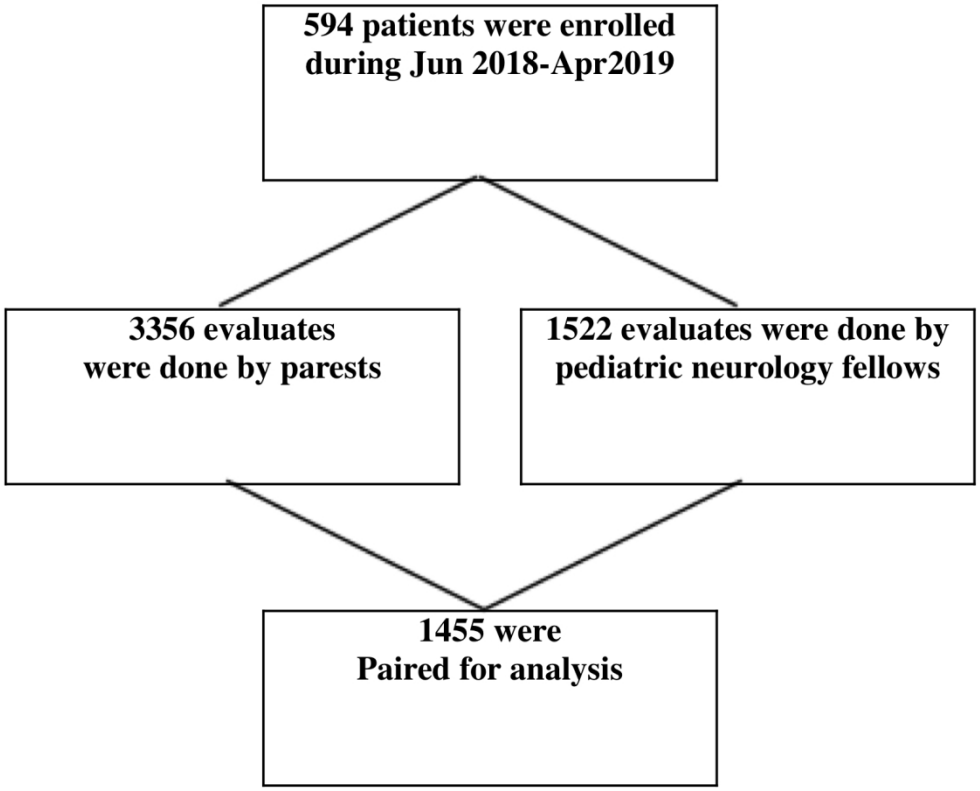


Figure 2

590x525mm (72 x 72 DPI)

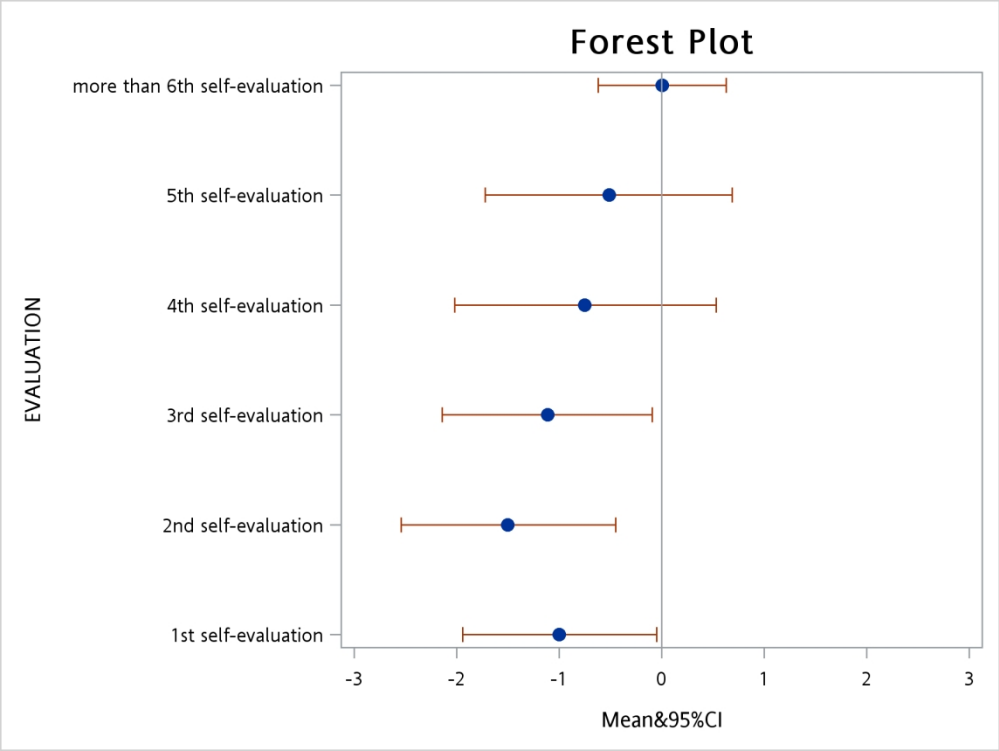


Figure 3

169x127mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Is Yale Global Tic Severity Scale a Valid Tool for Parent-reported Assessment in the Pediatric Population? A Prospective Observational Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034634.R1
Article Type:	Original research
Date Submitted by the Author:	03-Mar-2020
Complete List of Authors:	Ho, Che-Sheng ; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Huang, Jia-Yun; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Yang, Chien-Hui; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Lin, Yi-Jie; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Huang, Ming-Yuan; Mackay Memorial Hospital, Taipei, Taiwan , Department of Emergency Medicine, Su, Yung-Cheng; Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, Emergency Department
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology
Keywords:	Paediatric neurology < NEUROLOGY, Paediatric neurology < PAEDIATRICS, PUBLIC HEALTH, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Is Yale Global Tic Severity Scale a Valid Tool for Parent-reported Assessment in the Pediatric Population? A Prospective Observational Study

Che-Sheng Ho, MD[1,2]; Jia-Yun Huang, MD[2]; Chien-Hui Yang, MD[2]; Yi-Jie Lin, MD[1,2]; Ming-Yuan Huang*, MD, MS[1,3] and Yung-Cheng Su*, MD, MPH.[4,5]

[1]Department of Medicine, MacKay Medical College, New Taipei City, Taiwan

[2]Division of Pediatric Neurology, Department of Pediatrics, MacKay Children's Hospital, Taipei, Taiwan

[3]Department of Emergency Medicine, Mackay Memorial Hospital, Taipei, Taiwan

[4]Emergency Department, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan

[5]School of Medicine, Tzu Chi University, Hualien, Taiwan

*these authors contributed equally

Corresponding Author

Yung-Cheng Su, MD, MPH

Emergency Department,

Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation

No. 2, Minsheng Rd., Dalin Township,

Chiayi County 622, Taiwan (R.O.C.)

Tel: 886-5-2648000 ext 5838

Fax: 886-5-2648499

E-mail: drsu119@gmail.com

Declarations

Ethics approval and consent to participate

This study was initiated after approval from the Institutional Review Board of Taipei Mackay Memorial Hospital, Taiwan.

Consent for publication

Not applicable

Data sharing statement

The datasets used and analyzed for the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None declared

Contributorship statement

MYH analyzed and interpreted the data. JYH, CHY and YJL interpreted the data and contribute to manuscript development. CSH supervised the study and interpreted the data. YCS analyzed the data, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Is Yale Global Tic Severity Scale a Valid Tool for Parent-reported Assessment in the Pediatric Population? A Prospective Cohort Study

Abstract

Objective: The Yale Global Tic Severity Scale (YGTSS) is the most commonly used evaluation tool for Tourette Syndrome (TS), with established reliability and validity. Administration of the YGTSS is relatively time consuming and requires a highly trained, experienced interviewer to ensure accurate and reliable use of the assessment. This study aims to determine whether the YGTSS is a valid tool for parent -reporting in the TS population.

Design: prospective cohort study

Setting: A major medical center in Taiwan.

Methods: A total of 594 patients was enrolled. YGTSS was made available to participants via Google docs. Participants were encouraged to complete the YGTSS the day before each outpatient clinic visit. At each visit, a pediatric neurology fellow also administered the YGTSS assessment. The results of these physician assessments were taken as the expert standard for evaluating the sensitivity and specificity of the participant assessments conducted at the same visit. We also investigated whether differences in scores between physicians and participants changed as the number of parent-evaluations increased.

Results: The differences in the YGTSS scores between participants and physicians were small. The mean difference in the total assessment score was 4.15 points. As the number of times the parent-evaluation was performed increased, the difference between the participant and physician scores decreased. Discrimination of mild attacks was good using the parent-

assessed YGTSS (AUROC, 0.858; 95% CI, 0.839–0.876). The sensitivity for detecting a mild attack by YGTSS parent-assessment was 91.8% (95% CI, 89.9–93.7), and the specificity was 79.7 % (95% CI, 76.6–82.8).

Conclusions: The parent-reported YGTSS is a promising tool for TS assessment, demonstrating good discriminative ability for disease severity, with user precision increasing with experience.

Strengths and limitations of this study

- This study evaluates the hypothesis that YGTSS is a valid tool for parent-reporting, allowing for better communication and decision making between doctors and patients.
- The YGTSS is a promising tool for parent-reporting assessment in the TS population, and the precision of parent-reported YGTSS increases with experience.
- It is difficult to train many parents repeatedly to ensure them to achieve an acceptable level before they posted their scores, and the internal reliability may be difficult to be evaluated.

Introduction

Tourette Syndrome (TS) is characterized by persistent motor and vocal tics that begin before the age of 18 years. The prevalence in children is estimated at 6 per 1000.[1] The clinical presentation is complex, as the symptoms may wax and wane in frequency, intensity, and type.[2 3] The severity is influenced by multiple factors, including stress and social interactions,[4-6] making clinical assessment challenging. The most widely used measure to assess the severity of TS is the Yale Global Tic Severity Scale (YGTSS),[7 8] a clinician-administered, semi-structured interview that assesses tic and tic-related impairment severity over the previous week.

The YGTSS includes a symptom checklist for motor and vocal tics. As a group, all motor and vocal tics are rated for number, frequency, intensity, complexity, and interference on a 0–5 Likert scale. Scores are then added up to reflect the severity of motor tics (0–25), vocal tics (0–25), and combined tics (0–50). A separate tic-related impairment scale, ranging from 0–50, is also included. Although several other assessments have been developed, the YGTSS is still the most commonly used, with established reliability and validity.[7 9 10-12]

Administration of the YGTSS is relatively time consuming and requires a highly trained, experienced interviewer to ensure accurate and reliable use of the measure.[5 12] In addition, even clinicians rely in part on patient awareness; that is, not all tics present during the interview.[13] The use of patient reported outcome measures (PROMs) has the potential to narrow the gap in clinical manifestations observed between clinicians and patients and to help adjust treatment plans.[14 15] Several self-report instruments for TS have been developed for this purpose. The Proxy Report Questionnaire for Parents and Teachers and the Apter 4-questions are limited by insufficient validation and relatively low specificity.[12 16 17] The Premonitory Urges for Tics Scale has shown good psychometric properties. However, its use

is not acceptable for patients younger than 10 years.[12 18] This study evaluates the hypothesis that YGTSS is a valid tool for parent-reporting in the TS population. Such a tool would allow for better communication and decision making between doctors and patients, and patient satisfaction with their care may also improve.

Methods

This study was initiated after approval from the Institutional Review Board of Taipei Mackay Memorial Hospital, Taiwan. We set up a database to collect patient information. Pediatric patients with TS who are regular followed up in the Taipei Mackay Memorial Hospital were enrolled after informed consent by their guardians, and the guardians were regarded as participants. Starting from June 2018, a revised traditional Chinese version of the YGTSS was made available to patients via Google docs (Figure 1). Upon introduction of the assessment to patients, a pediatric neurologist explained the use of the assessment scales to make sure participants clearly understood how to rate their symptoms. Participants were encouraged to fill in the YGTSS the day before each outpatient clinic visit. On the date of the visit, a pediatric neurology fellow was assigned to the patient by convenience sampling in the waiting room and also administered the YGTSS. The participants and the pediatric fellows were blind to the YGTSS results of the other. Some patients were administered the YGTSS evaluation by both the guardian and the pediatric fellow during the same visit. The attending physicians used the YGTSS results as a reference for making medical decisions during the visit.

Patient age and sex, date of visit, and parent-assessed or pediatric-fellow–administered YGTSS scores were recorded. We further defined a YGTSS score <20 as a mild tic attack and

>20 as a moderate to severe tic attack.[19] The results of the pediatric fellow assessments were taken as the expert standard for evaluating the sensitivity and specificity of the participant assessments conducted at the same visit. We also investigated whether differences in scores between these physicians and the participants changed as the number of parent-evaluations increased. Feedback from the participants was collected by convenience sampling at outpatient clinics.

All analyses were performed using Statistical Analysis Software for Windows, version V.9.4 (SAS Institute Inc., Cary, NC, USA). Linear regression was used to evaluate differences of scores among participants and pediatric fellows. To adjust the correlated data from multiple evaluations by the same participants, the generalized estimate equation method was adapted to account for clustering of participants in the evaluation of score differences. The discriminatory power of a mild attack was determined using area under the receiver operating characteristic curve (AUROC) analysis of parent-assessed YGTSS scores. A two-tailed $p < 0.05$ was considered statistically significant.

Patient and Public involvement

Patients and the public were not involved in the design or planning of the study.

Results

Study Population

A total of 594 patients was enrolled in this study during June 2018—April 2019, and 3356 evaluations were contributed by their guardians. On average, each participant contributed

5.65 parent-reported YGTSS evaluations during the study period. Among these parent-reports, 1455 were paired with simultaneous evaluations by pediatric fellows and were used for analyses. The final analysis included 527 patients. The mean patient age was 8.8 years (SD, 2.97), and 82.5% (n = 435) of the patients was male. A flow chart of the patient selection process is illustrated in Figure 2.

Comparison of assessment scores between participants and physicians

The differences in the YGTSS scores between participants and physicians were small. The mean difference in the total assessment score was 4.15 points, with greater contributions coming from the 'tic-related impairments' section. The results are summarized in Table 1. As the number of times the parent-evaluation was performed increased, the difference between the participant and physician scores decreased. After taking participant clustering into account, the absolute difference in total scores between participants and physicians decreased by 0.24 points (95% C.I., 0.14—0.34; $p < 0.001$) for each repetition of the assessment. Subgroup analysis of the combined tic severity was perform revealed an absolute average difference of 2.40 points. The absolute difference in combined tic severity decreased by 0.17 (95% CI, 0.11–0.22; $p < 0.001$) for each repetition of the assessment. After participants completed the assessment 4 times, the difference between participant and physician scores was no longer significant (Figure 3).

Diagnostic accuracy of the YGTSS parent-evaluation

The power of discriminating mild attacks with YGTSS parent-assessment was good (AUROC, 0.858; 95% CI, 0.839–0.876). The sensitivity with which a mild attack was detected by using YGTSS parent-assessment was significantly high. Of 819 parent-assessments of mild attacks,

752 were in accordance with that of the physician, yielding a sensitivity of 91.8% (95% CI, 89.9–93.7). In 636 parent-assessments of moderate to severe attacks, 507 were in accordance with that of the physician, yielding a specificity of 79.7% (95% CI, 76.6–82.8).

Evaluation of Feedback

Most comments from participants were positive, as the following examples indicate:

1) After assessment of my child, I know better what the doctor needs to know, and this process also helps me better understand how to take care of my child.

2) With these long-term, objective trends in my results, I think discussing the goals of treatment with doctors is clearer.

Feedback taken by convenience sampling from physicians at hospital outpatient clinics was also encouraging:

1) Being able to understand the patient's condition outside of the hospital allows me to communicate more effectively with caregivers.

Discussions

The aim of the present study was to evaluate the potential use of the YGTSS as a parent-reported measure of tic severity in children with TS. The results show overall good ability to discriminate a mild TS attack via parent-reporting (AUROC, 0.858). The sensitivity and specificity for detecting a mild TS attack of were reasonably high. With repeated practice responding to the assessment, the parent-report scores became similar to those of physicians,

with no difference after the 4th assessment. Our results show that the YGTSS, the most widely used TS assessment tool, may be as accurate when used by patients as a self-report tool as it is when administered by clinicians.

Although administration of the YGTSS is relatively time-consuming, we used a step-by-step online google doc interface to help the participants fill out the forms with little difficulty. The online parent-report YGTSS database also allows participants to complete the evaluation without time and space limits, and more than three thousand parent-evaluations during the study period is one factor contributing to the efficiency of the system. The feedback from both participants and clinicians was positive, and the database is still growing as the number of parent-report submissions increases. Pediatric neurologists now rely more often on parent-report assessments for adjusting treatment plans.[3] [4] Because self-assessments allow guardians and clinicians to share the same information regarding a patient's condition, the communication is more fluent and efficient.[20] [21]

Another reason for our positive results is that the participants were aware of the disease and highly motivated to be involved in the TS management. They may be more likely to present precise evaluations if possible. During the multiple interactions about the conditions with their clinicians, participants may become more practiced over time. Patients generally welcome systems that routinely use PROMs.[14] The parent-report YGTSS correlates highly with factors that have value to clinicians. Even for the clinician-administered YGTSS, the interviewer relies heavily on participants' insights, as patients may not present with the full range of tics during the interview. As a result, self-reports from participants may more closely reflect the actual patient condition.

Limitations

Our study has several limitations. First, the participants were guardians of TS children, and most of them have already participated in regular follow-up at our outpatient clinics. Thus, these participants may be more aware of their children's symptoms, allowing for an easier understanding of the YGTSS parameters, leading to a good correlation between the responses of participants and physicians. Second, as more than 500 patients are included in the database, it is difficult to train many parents repeatedly to ensure them to achieve an acceptable level before they posted their scores, and the internal reliability may be difficult to be evaluated. There may also be variability in the evaluation of the YGTSS among pediatric fellows. However, these results are representative of the real clinical situation. Third, the pediatric fellows visit and evaluate the patients in the waiting room by convivence sampling, which may lead to sampling bias. Forth, in our cohort there are only a few patients with newly diagnosed TS. As a result, we were unable to perform subgroup analyses for these patients. We also did not adjust for important patient characteristics such as severity of tics and duration since initial diagnosis because of lack of information. Finally, the evaluations from the physicians were not performed simultaneously with the participants. Since the physicians retrieved information by directly observing patients, the symptoms may have differed from those at the time of the parent-report.

Conclusion

The parent-reported YGTSS is a promising tool for TS assessment, demonstrating good discriminative ability for disease severity, with user precision increasing with experience.

References

1. Jeon S, Walkup JT, Woods DW, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods. *Contemp Clin Trials* 2013;36(2):414-20. doi: 10.1016/j.cct.2013.08.012 [published Online First: 2013/09/05]
2. Abramovitch A, Reese H, Woods DW, et al. Psychometric Properties of a Self-Report Instrument for the Assessment of Tic Severity in Adults With Tic Disorders. *Behav Ther* 2015;46(6):786-96. doi: 10.1016/j.beth.2015.06.002 [published Online First: 2015/11/02]
3. Lin H, Yeh CB, Peterson BS, et al. Assessment of symptom exacerbations in a longitudinal study of children with Tourette's syndrome or obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002;41(9):1070-7. doi: 10.1097/00004583-200209000-00007 [published Online First: 2002/09/10]
4. Eapen V, Fox-Hiley P, Banerjee S, et al. Clinical features and associated psychopathology in a Tourette syndrome cohort. *Acta neurologica Scandinavica* 2004;109(4):255-60. [published Online First: 2004/03/16]
5. Chang S, Himle MB, Tucker BTP, et al. Initial Psychometric Properties of a Brief Parent-Report Instrument for Assessing Tic Severity in Children with Chronic Tic Disorders. *Child & Family Behavior Therapy* 2009;31(3):181-91. doi: 10.1080/07317100903099100
6. Silva RR, Munoz DM, Barickman J, et al. Environmental Factors and Related Fluctuation of Symptoms in Children and Adolescents with Tourette's Disorder. *Journal of Child Psychology and Psychiatry* 1995;36(2):305-12. doi: 10.1111/j.1469-7610.1995.tb01826.x
7. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity. *Journal of the American Academy of Child & Adolescent Psychiatry* 1989;28(4):566-73. doi: https://doi.org/10.1097/00004583-198907000-00015
8. Ho CS, Chiu NC, Tseng CF, et al. Clinical effectiveness of aripiprazole in short-term treatment of tic disorder in children and adolescents: a naturalistic study. *Pediatr Neonatol* 2014;55(1):48-52. doi: 10.1016/j.pedneo.2013.05.009 [published Online First: 2013/08/08]
9. Storch EA, Murphy TK, Geffken GR, et al. Reliability and validity of the Yale Global Tic Severity Scale. *Psychol Assess* 2005;17(4):486-91. doi: 10.1037/1040-3590.17.4.486 [published Online First: 2006/01/06]
10. Storch EA, De Nadai AS, Lewin AB, et al. Defining treatment response in pediatric tic disorders: a signal detection analysis of the Yale Global Tic Severity Scale. *J Child Adolesc Psychopharmacol* 2011;21(6):621-7. doi: 10.1089/cap.2010.0149 [published Online First: 2011/11/11]
11. Ho CS, Chen HJ, Chiu NC, et al. Short-term sulpiride treatment of children and adolescents with Tourette syndrome or chronic tic disorder. *Journal of the Formosan Medical Association = Taiwan yi zhi* 2009;108(10):788-93. doi: 10.1016/s0929-6646(09)60406-x [published Online First: 2009/10/30]

12. Martino D, Pringsheim TM, Cavanna AE, et al. Systematic review of severity scales and screening instruments for tics: Critique and recommendations. *Mov Disord* 2017;32(3):467-73. doi: 10.1002/mds.26891 [published Online First: 2017/01/11]
13. Conelea CA, Woods DW. The influence of contextual factors on tic expression in Tourette's syndrome: A review. *Journal of Psychosomatic Research* 2008;65(5):487-96. doi: https://doi.org/10.1016/j.jpsychores.2008.04.010
14. Nelson EC, Eftimovska E, Lind C, et al. Patient reported outcome measures in practice. *BMJ* 2015;350:g7818. doi: 10.1136/bmj.g7818 [published Online First: 2015/02/12]
15. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. *The New England journal of medicine* 2012;366(9):780-1. doi: 10.1056/NEJMp1109283 [published Online First: 2012/03/02]
16. Cubo E, Saez Velasco S, Delgado Benito V, et al. Validation of screening instruments for neuroepidemiological surveys of tic disorders. *Mov Disord* 2011;26(3):520-6. doi: 10.1002/mds.23460 [published Online First: 2011/01/25]
17. Linazasoro G, Van Blercom N, de Zarate CO. Prevalence of tic disorder in two schools in the Basque country: Results and methodological caveats. *Mov Disord* 2006;21(12):2106-9. doi: 10.1002/mds.21117 [published Online First: 2006/10/03]
18. Woods DW, Piacentini J, Himle MB, et al. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. *J Dev Behav Pediatr* 2005;26(6):397-403. doi: 10.1097/00004703-200512000-00001 [published Online First: 2005/12/14]
19. Sallee F, Kohegyi E, Zhao J, et al. Randomized, Double-Blind, Placebo-Controlled Trial Demonstrates the Efficacy and Safety of Oral Aripiprazole for the Treatment of Tourette's Disorder in Children and Adolescents. *Journal of Child and Adolescent Psychopharmacology* 2017;27(9):771-81. doi: 10.1089/cap.2016.0026
20. Crandall W, Kappelman MD, Colletti RB, et al. ImproveCareNow: The development of a pediatric inflammatory bowel disease improvement network. *Inflammatory bowel diseases* 2011;17(1):450-7. doi: 10.1002/ibd.21394 [published Online First: 2010/07/06]
21. Lannon CM, Peterson LE. Pediatric collaborative networks for quality improvement and research. *Academic pediatrics* 2013;13(6 Suppl):S69-74. doi: 10.1016/j.acap.2013.07.004 [published Online First: 2013/12/07]

Table and Figure Legends

Table 1. Comparison of participant- and physician-assessed YGTSS scores according to assessment category

Figure 1. Revised traditional Chinese version of YGTSS made available via Google docs

Figure 2. Flow chart of patient selection

Figure 3. Distribution of average score differences

Table 1. Comparison of participant- and physician-assessed YGTSS scores according to assessment category*

Assessment Category	Mean difference† (points)	95% CI
Entire assessment (all categories)	4.15	3.82—4.48
motor tic severity	1.17	1.07—1.28
vocal tic severity	1.23	1.11—1.35
combined tic severity	2.40	2.22—2.58
tic-related impairment	2.41	2.14—2.68

*n = 1455

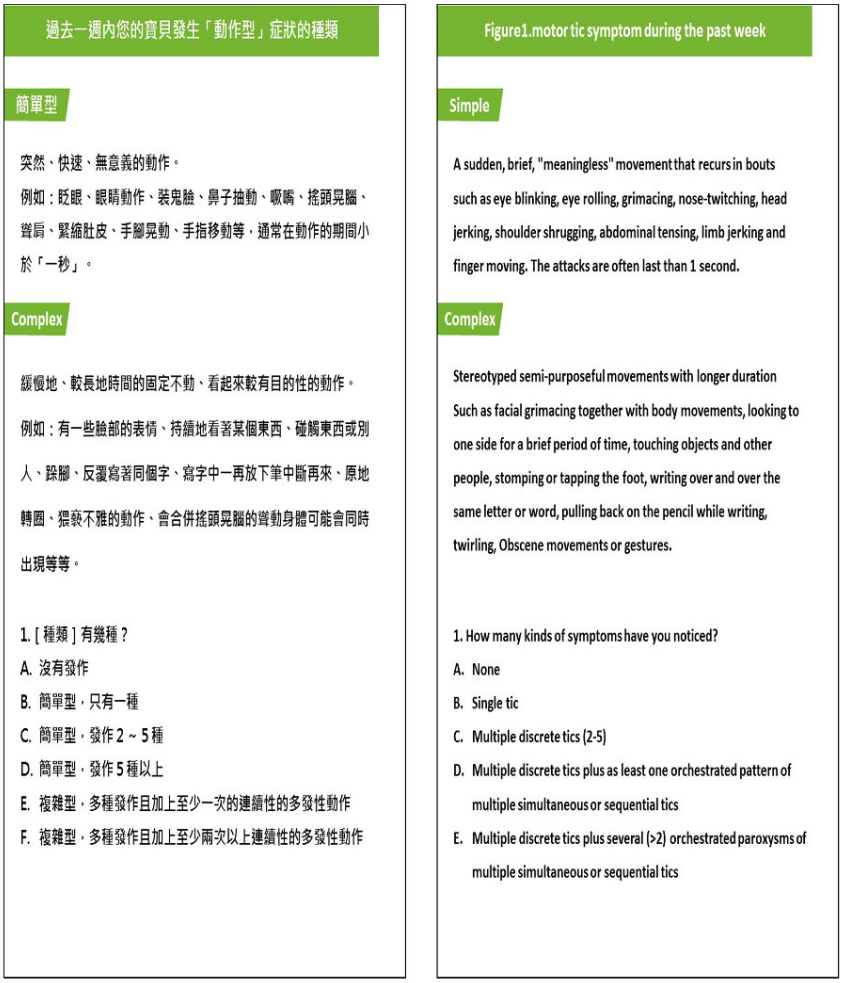
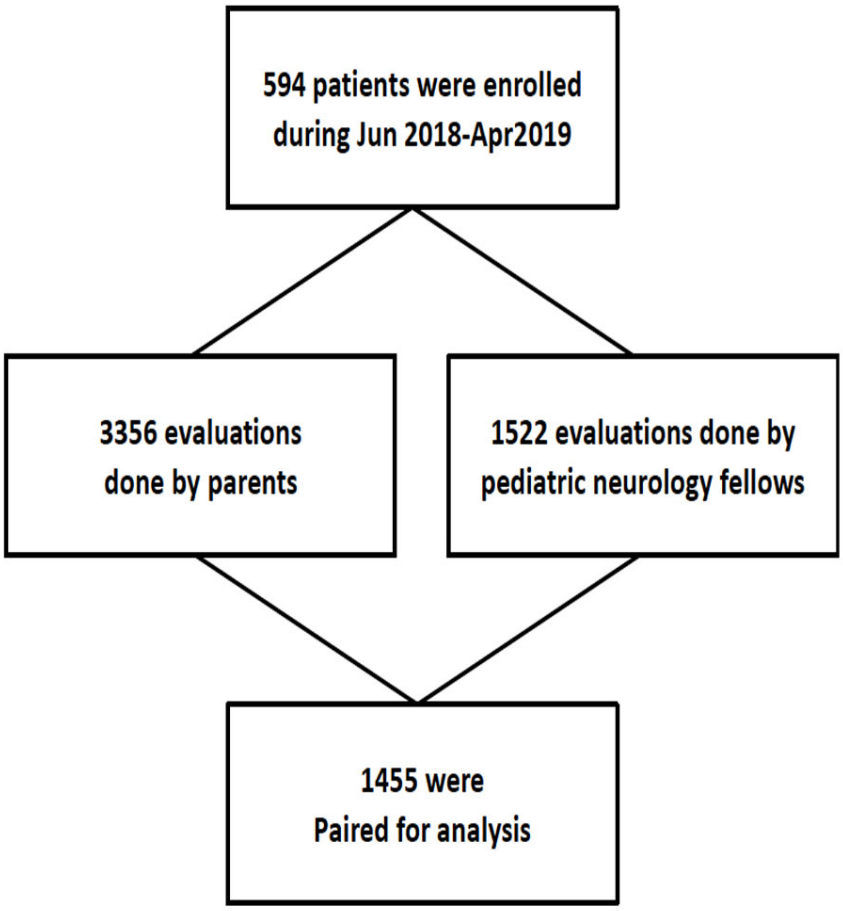


Figure 1

90x90mm (300 x 300 DPI)



90x90mm (300 x 300 DPI)

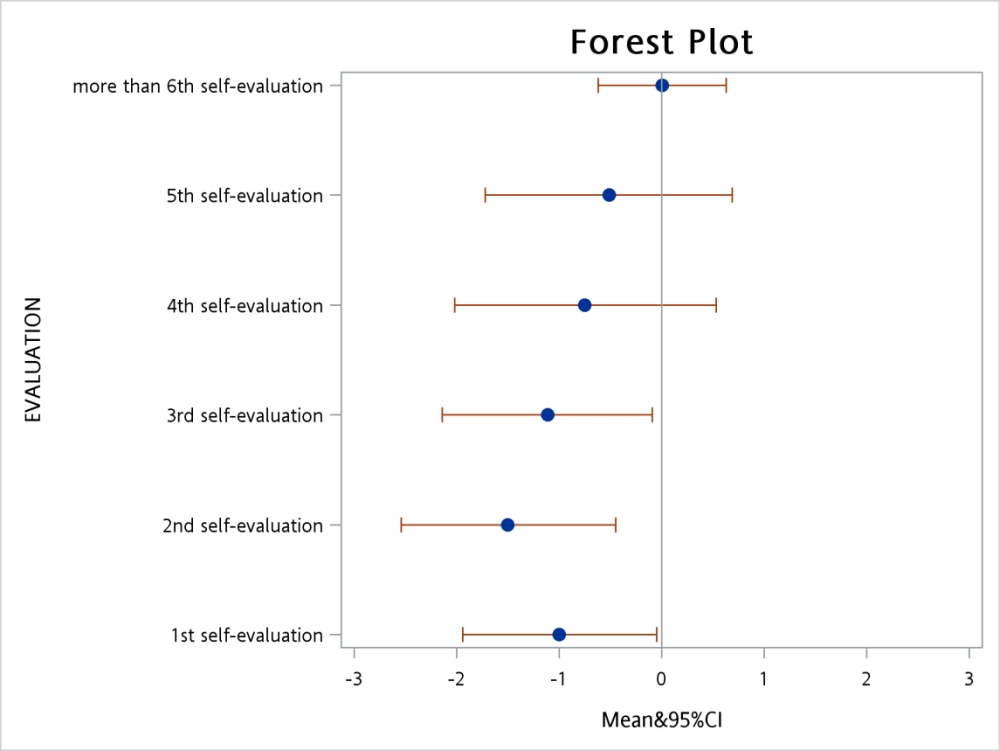


Figure 3

169x127mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Is the Yale Global Tic Severity Scale a valid tool for parent-reported assessment in the pediatric population? A prospective observational study in Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034634.R2
Article Type:	Original research
Date Submitted by the Author:	04-May-2020
Complete List of Authors:	Ho, Che-Sheng ; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Huang, Jia-Yun; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Yang, Chien-Hui; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Lin, Yi-Jie; Mackay Memorial Hospital, Taipei, Taiwan , Division of Pediatric Neurology, Department of Pediatrics Huang, Ming-Yuan; Mackay Memorial Hospital, Taipei, Taiwan , Department of Emergency Medicine, Su, Yung-Cheng; Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, Emergency Department
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology
Keywords:	Paediatric neurology < NEUROLOGY, Paediatric neurology < PAEDIATRICS, PUBLIC HEALTH, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Is the Yale Global Tic Severity Scale a valid tool for parent-reported assessment in the pediatric population? A prospective observational study in Taiwan

Che-Sheng Ho, MD[1,2]; Jia-Yun Huang, MD[2]; Chien-Hui Yang, MD[2]; Yi-Jie Lin, MD[1,2]; Ming-Yuan Huang*, MD, MS[1,3] and Yung-Cheng Su*, MD, MPH.[4,5]

[1]Department of Medicine, MacKay Medical College, New Taipei City, Taiwan

[2]Division of Pediatric Neurology, Department of Pediatrics, MacKay Children's Hospital, Taipei, Taiwan

[3]Department of Emergency Medicine, Mackay Memorial Hospital, Taipei, Taiwan

[4]Emergency Department, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan

[5]School of Medicine, Tzu Chi University, Hualien, Taiwan

*these authors contributed equally

Corresponding author

Yung-Cheng Su, MD, MPH

Emergency Department,

Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation

No. 2, Minsheng Rd., Dalin Township,

Chiayi County 622, Taiwan (R.O.C.)

Tel: 886-5-2648000 ext 5838

Fax: 886-5-2648499

E-mail: drsu119@gmail.com

Declarations

Ethics approval and consent to participate

This study was initiated after approval from the Institutional Review Board of Taipei Mackay Memorial Hospital, Taiwan.

Consent for publication

Not applicable

Data sharing statement

No additional data available

Competing interests

The authors declare that they have no competing interests.

Funding

None declared

Contributorship statement

MYH analyzed and interpreted the data. JYH, CHY and YJL interpreted the data and contribute to manuscript development. CSH supervised the study and interpreted the data. YCS analyzed the data, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Is the Yale Global Tic Severity Scale a valid tool for parent-reported assessment in the pediatric population? A prospective observational study in Taiwan

Abstract

Objective: The Yale Global Tic Severity Scale (YGTSS) is the most commonly used clinician-rated evaluation tool for Tourette Syndrome (TS), with established reliability and validity. This study aims to determine whether the YGTSS is a valid parent-report assessment in the TS population.

Design: prospective cohort study

Setting: A major medical center in Taiwan.

Methods: A total of 594 patients were enrolled. A revised traditional Chinese version of the YGTSS was made available to parents via Google docs. Parents were encouraged to complete the YGTSS the day before each outpatient clinic visit. At each visit, a pediatric neurology fellow also administered the YGTSS assessment. We investigated whether differences in scores between physicians and parents changed as the number of parent-evaluations increased. The results of the physician assessments were also taken as the expert standard for evaluating the sensitivity and specificity of the parent-report assessments conducted for the same visit.

Results: The differences in the YGTSS scores between participants and physicians were small. The mean difference in the total assessment score was 4.15 points. As the number of times the parent-evaluation was performed increased, the difference between the parent and physician scores decreased. Discrimination of moderate to severe attacks was good using

the parent-assessed YGTSS (area under the receiver operating characteristic curve, 0.858; 95% confidence interval [CI], 0.839–0.876). The sensitivity for detecting a moderate to severe attack by YGTSS parent-assessment was 79.7 % (95% CI 76.6–82.8), and the specificity was 91.8% (95% CI 89.9–93.7).

Conclusions: The parent-reported YGTSS is a promising tool for TS assessment, demonstrating good discriminative ability for disease severity, with user precision increasing with experience.

Strengths and limitations of this study

- This study evaluated the hypothesis that the YGTSS is a valid tool for parent-reporting, allowing for better communication and decision making between doctors and patients.
- It is difficult to train many parents repeatedly to ensure them to achieve an acceptable level before they posted their scores, and the internal reliability may be difficult to be evaluated.
- There may also have been variability in the YGTSS evaluations from pedestrians.

Introduction

Tourette Syndrome (TS) is characterized by persistent motor and vocal tics that begin before 18 years of age, and is estimated to affect 6 per 1000 children.[1] The clinical presentation of TS is complex, as the symptoms may wax and wane in frequency, intensity, and type.[2 3] The severity is influenced by multiple factors, including stress and social interactions,[4-6] making clinical assessment challenging. The most widely used measure to assess the severity of TS is the Yale Global Tic Severity Scale (YGTSS),[7 8] a clinician-administered, semi-structured interview that assesses tic and tic-related impairment severity over the previous week.

The YGTSS includes a symptom checklist for motor and vocal tics. Both motor and vocal tics are assessed for symptom number, frequency, intensity, complexity, and interference on a 0–5 Likert scale. Scores from each dimension are totaled to reflect the severity of motor tics (range 0–25), vocal tics (range 0–25), and combined tics (range 0–50). A separate tic-related impairment scale, scored from 0–50, is also included. Although several other assessments have been developed, the YGTSS is still the most commonly used, with established reliability and validity.[7 9 10-12]

In practice, clinicians do rely in part on patient report to make their assessment; that is, not all tics present during the interview.[13] The use of patient reported outcome measures (PROMs) has the potential to narrow the gap in clinical manifestations observed between clinicians and patients and to help adjust treatment plans.[14 15] Several self-report instruments for TS have been developed for this purpose. The Proxy Report Questionnaire for Parents and Teachers and the Apter 4-questions are limited by insufficient validation and relatively low specificity.[12 16 17] The Premonitory Urges for Tics Scale has shown good psychometric properties; however, it is not acceptable for patients younger than 10 years of

age.[12 18] This study evaluates the hypothesis that YGTSS is a valid tool for parent-reporting in the TS population. Such a tool would allow for better communication and decision making between doctors and patients, and patient satisfaction regarding their care may also improve.

Methods

participants

Data collection

This study was approved by the Institutional Review Board of Taipei Mackay Memorial Hospital, Taiwan. A database was created to collect patient information. Pediatric patients with TS who are regular followed up in the Taipei Mackay Memorial Hospital were enrolled after informed consent was provided by their parents. The authors carried out a Chinese translation of the YGTSS. Physicians in the Division of Pediatric Neurology, Department of Pediatrics, MacKay Children's Hospital, Taipei, Taiwan reviewed the contents to reach a consensus, and differing perspectives were resolved by group discussions. Beginning in June 2018, a revised traditional Chinese version of the YGTSS was made available to parents via Google docs (Figure 1). Upon introduction of the assessment to parents, a pediatric neurologist explained the use of the assessment scales to make sure parents clearly understood how to rate their symptoms. Parents were encouraged to complete the YGTSS the day before each outpatient clinic visit. On the date of the visit, a pediatric neurology fellow was assigned to the patients by convenience sampling in the waiting room and also administered the YGTSS. The parents and the pediatric fellows were blind to the YGTSS

results of the other. Some patients were administered the YGTSS evaluation by both the parents and the pediatric fellow during the same visit. The attending physicians used the YGTSS results as a reference for making medical decisions during the visit. Patient age and sex, date of visit, and parent-assessed or pediatric-fellow–administered YGTSS scores were recorded.

Statistical analyses

We first evaluated the absolute differences in the YGTSS scores by subtracting the scores of parents from that of physicians. We also assessed the difference between the two measurements across multiple visits using linear regression. To adjust for correlations in the data due to being collected at multiple times by the same participants, the generalized estimating equation (GEE) method[19] was adapted to account for clustering of participants in the evaluation of score differences.

We also dichotomized tic attack as mild or moderate/severe by defining a mild attack as a YGTSS score <20 and a moderate to severe tic attack as >20.[20] The discriminatory power of the parent-reported YGTSS for a moderate to severe attack was assessed by using the area under the receiver operating characteristic curve (AUROC) based on a logistic regression model with GEE. Feedback from the parents was collected by convenience sampling at outpatient clinics. All p values were two-tailed, and $p < 0.05$ was considered statistically significant. All analyses were performed using Statistical Analysis Software for Windows, version V.9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and Public involvement

Patients and the public were not involved in the design or planning of this study.

Results

Study Population

A total of 594 patients were enrolled in this study between June 2018 and April 2019, with 3356 evaluations contributed by their parents. On average, each participant contributed 5.65 parent-reported YGTSS evaluations during the study period. Among these parent-reports, 1455 were paired with simultaneous evaluations by pediatric fellows and were used for analyses. The final analysis included 527 patients. The mean patient age was 8.8 years (SD, 2.97), and 82.5% (n = 435) of the patients were male. A flow chart of the patient selection process is illustrated in Figure 2.

Comparison of assessment scores between participants and physicians

The differences in the YGTSS scores between participants and physicians were small (Table 1). The mean difference in the total assessment score was 4.15 points, with the greatest difference being for 'tic-related impairments'. As the number of times the parent-evaluation was completed increased, the difference between the parent and physician scores decreased. After taking parent clustering into account, the absolute difference in total scores between participants and physicians decreased by 0.24 points (95% C.I., 0.14—0.34; $p < 0.001$) for each repetition of the assessment. A subgroup analysis of the combined tic severity category revealed an absolute average difference of 2.40 points. The absolute difference in combined tic severity decreased by 0.17 (95% CI, 0.11–0.22; $p < 0.001$) for each repetition of the assessment. After participants completed the assessment 4 times, the difference between participant and physician scores was no longer significant (Figure 3).

Diagnostic accuracy of the YGTSS parent-evaluation

The power of discriminating moderate to severe attacks with the YGTSS parent-assessment was good (AUROC, 0.858; 95% CI, 0.839–0.876). The specificity for detecting a moderate to severe attack using the YGTSS parent-assessment was significantly high. Of 819 physician-assessments of mild attacks, 752 were in accordance with that of the parents, yielding a specificity of 91.8% (95% CI, 89.9–93.7). In 636 physician-assessments of moderate to severe attacks, 507 were in accordance with that of the parents, yielding a sensitivity of 79.7% (95% CI, 76.6–82.8).

Evaluation of Feedback

Most comments from participants were positive, as the following examples indicate:

1) After assessment of my child, I know better what the doctor needs to know, and this process also helps me better understand how to take care of my child.

2) With these long-term, objective trends in my results, I think discussing the goals of treatment with doctors is clearer.

Feedback taken by convenience sampling from physicians at hospital outpatient clinics was also encouraging:

1) Being able to understand the patient's condition outside of the hospital allows me to communicate more effectively with caregivers.

Discussions

The aim of the present study was to evaluate the potential use of the YGTSS as a parent-report measure of tic severity in children with TS. The results showed an overall good ability to discriminate a moderate to severe TS attack via parent-reporting (AUROC, 0.858). The sensitivity and specificity for detecting a moderate to severe TS attack of were reasonably high. With repeated practice responding to the assessment, the parent-report scores became similar to those of physicians, with no difference after the 4th assessment. Our results indicate that the YGTSS, the most widely used TS assessment tool, may be as accurate when used by a child's parent as it is when administered by the child's clinician.

In the study, we used a step-by-step online Google doc interface to help the participants fill out the forms with little difficulty. The online parent-report YGTSS database also allowed participants to complete the evaluation without time and space limits, and more than 3000 parent-evaluations submitted during the study period is one factor contributing to the efficiency of the system. The feedback from both parents and clinicians was positive, and the database continues to grow as the number of parent-report submissions increases. Pediatric neurologists now often rely on parent-report assessments to adjusting treatment plans.[3 4] As self-assessments allow parents and clinicians to share the same information regarding a patient's condition, the communication is more fluent and efficient.[21 22]

Another reason for our positive results is that the parents were aware of the disease and highly motivated to be involved in the management of their child's TS. They may be more likely to present precise evaluations if possible. During the multiple interactions about the conditions with their clinicians, parents became more practiced and accurate with their evaluations. Patients generally welcome systems that routinely use PROMs.[14] The parent-report YGTSS correlates highly with factors that have value to clinicians. Even for the

clinician-administered YGTSS, the interviewer relies heavily on patients' and their family members' insights, as patients may not present with the full range of tics during the interview. As a result, parent-report may more closely reflect the actual patient condition.

Limitations

Our study has several limitations. First, the participants were parents of children with TS, and most of them had already participated in regular follow-up at our outpatient clinics. Thus, these parents may have been more aware of their child's symptoms, allowing for an easier understanding of the YGTSS parameters, resulting in a high correlation between the responses of the parents and physicians. Second, as more than 500 patients were included in the database, it was difficult to provide parents intensive training to ensure that they had achieved an acceptable level of performance before they began submitting their scores; thus, the internal reliability may be difficult to be evaluated. There may also have been variability in the YGTSS evaluations from pediatric fellows. However, these results are representative of real clinical situations. Third, the pediatric fellows visit and evaluate the patients in the waiting room by convivence sampling, which may have led to sampling bias. Fourth, in our cohort there were only a few patients newly diagnosed with TS. As a result, we were unable to perform subgroup analyses for these patients, comparing between those whose child was recently diagnosed, and thus were less familiar with the symptoms, versus those whose child had the diagnosis for quite a while and were therefore very familiar with the symptoms. We also did not adjust for important patient characteristics such as severity of tics and duration since initial diagnosis as that information was lacking. Lastly, the evaluations from the physicians were not performed simultaneously with the participants.

Since the physicians evaluated information by directly observing patients, the symptoms may have differed from those at the time of the parent-report.

Conclusion

The parent-reported YGTSS is a promising tool for TS assessment, demonstrating good discriminative ability for disease severity, with user precision increasing with experience.

Acknowledgments

The authors thank Dr. Chen-Yang Hsu (Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan) for the in-depth discussion on statistical methods. The authors thank Dr. James F. Leckman (Yale Child Study Center, New Haven, CT, USA) and Dr. Jung-Chieh Du (Department of Pediatrics, Taipei City Hospital, Zhongxiao Branch, Taipei, Taiwan) for the development of Chinese version of YGTSS.

References

1. Jeon S, Walkup JT, Woods DW, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods. *Contemp Clin Trials* 2013;36(2):414-20. doi: 10.1016/j.cct.2013.08.012 [published Online First: 2013/09/05]
2. Abramovitch A, Reese H, Woods DW, et al. Psychometric Properties of a Self-Report Instrument for the Assessment of Tic Severity in Adults With Tic Disorders. *Behav Ther* 2015;46(6):786-96. doi: 10.1016/j.beth.2015.06.002 [published Online First: 2015/11/02]
3. Lin H, Yeh CB, Peterson BS, et al. Assessment of symptom exacerbations in a longitudinal study of children with Tourette's syndrome or obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002;41(9):1070-7. doi: 10.1097/00004583-200209000-00007 [published Online First: 2002/09/10]

4. Eapen V, Fox-Hiley P, Banerjee S, et al. Clinical features and associated psychopathology in a Tourette syndrome cohort. *Acta neurologica Scandinavica* 2004;109(4):255-60. [published Online First: 2004/03/16]
5. Chang S, Himle MB, Tucker BTP, et al. Initial Psychometric Properties of a Brief Parent-Report Instrument for Assessing Tic Severity in Children with Chronic Tic Disorders. *Child & Family Behavior Therapy* 2009;31(3):181-91. doi: 10.1080/07317100903099100
6. Silva RR, Munoz DM, Barickman J, et al. Environmental Factors and Related Fluctuation of Symptoms in Children and Adolescents with Tourette's Disorder. *Journal of Child Psychology and Psychiatry* 1995;36(2):305-12. doi: 10.1111/j.1469-7610.1995.tb01826.x
7. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity. *Journal of the American Academy of Child & Adolescent Psychiatry* 1989;28(4):566-73. doi: https://doi.org/10.1097/00004583-198907000-00015
8. Ho CS, Chiu NC, Tseng CF, et al. Clinical effectiveness of aripiprazole in short-term treatment of tic disorder in children and adolescents: a naturalistic study. *Pediatr Neonatol* 2014;55(1):48-52. doi: 10.1016/j.pedneo.2013.05.009 [published Online First: 2013/08/08]
9. Storch EA, Murphy TK, Geffken GR, et al. Reliability and validity of the Yale Global Tic Severity Scale. *Psychol Assess* 2005;17(4):486-91. doi: 10.1037/1040-3590.17.4.486 [published Online First: 2006/01/06]
10. Storch EA, De Nadai AS, Lewin AB, et al. Defining treatment response in pediatric tic disorders: a signal detection analysis of the Yale Global Tic Severity Scale. *J Child Adolesc Psychopharmacol* 2011;21(6):621-7. doi: 10.1089/cap.2010.0149 [published Online First: 2011/11/11]
11. Ho CS, Chen HJ, Chiu NC, et al. Short-term sulpiride treatment of children and adolescents with Tourette syndrome or chronic tic disorder. *Journal of the Formosan Medical Association = Taiwan yi zhi* 2009;108(10):788-93. doi: 10.1016/s0929-6646(09)60406-x [published Online First: 2009/10/30]
12. Martino D, Pringsheim TM, Cavanna AE, et al. Systematic review of severity scales and screening instruments for tics: Critique and recommendations. *Mov Disord* 2017;32(3):467-73. doi: 10.1002/mds.26891 [published Online First: 2017/01/11]
13. Conelea CA, Woods DW. The influence of contextual factors on tic expression in Tourette's syndrome: A review. *Journal of Psychosomatic Research* 2008;65(5):487-96. doi: https://doi.org/10.1016/j.jpsychores.2008.04.010
14. Nelson EC, Eftimovska E, Lind C, et al. Patient reported outcome measures in practice. *BMJ* 2015;350:g7818. doi: 10.1136/bmj.g7818 [published Online First: 2015/02/12]
15. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. *The New England journal of medicine* 2012;366(9):780-1. doi: 10.1056/NEJMp1109283 [published Online First: 2012/03/02]
16. Cubo E, Saez Velasco S, Delgado Benito V, et al. Validation of screening instruments for neuroepidemiological surveys of tic disorders. *Mov Disord* 2011;26(3):520-6. doi: 10.1002/mds.23460 [published Online First: 2011/01/25]
17. Linazasoro G, Van Blercom N, de Zarate CO. Prevalence of tic disorder in two schools in the Basque country: Results and methodological caveats. *Mov Disord* 2006;21(12):2106-9. doi: 10.1002/mds.21117 [published Online First: 2006/10/03]

18. Woods DW, Piacentini J, Himle MB, et al. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. *J Dev Behav Pediatr* 2005;26(6):397-403. doi: 10.1097/00004703-200512000-00001 [published Online First: 2005/12/14]
19. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42(1):121-30. [published Online First: 1986/03/01]
20. Sallee F, Kohegyi E, Zhao J, et al. Randomized, Double-Blind, Placebo-Controlled Trial Demonstrates the Efficacy and Safety of Oral Aripiprazole for the Treatment of Tourette's Disorder in Children and Adolescents. *Journal of Child and Adolescent Psychopharmacology* 2017;27(9):771-81. doi: 10.1089/cap.2016.0026
21. Crandall W, Kappelman MD, Colletti RB, et al. ImproveCareNow: The development of a pediatric inflammatory bowel disease improvement network. *Inflammatory bowel diseases* 2011;17(1):450-7. doi: 10.1002/ibd.21394 [published Online First: 2010/07/06]
22. Lannon CM, Peterson LE. Pediatric collaborative networks for quality improvement and research. *Academic pediatrics* 2013;13(6 Suppl):S69-74. doi: 10.1016/j.acap.2013.07.004 [published Online First: 2013/12/07]

Table and Figure Legends

Table 1. Comparison of parent- and physician-reported YGTSS scores according to assessment category

Figure 1. Revised traditional Chinese version of the Yale Global Tic Severity Scale made available via Google docs

Figure 2. Flow chart of patient selection

Figure 3. Distribution of average score differences

Table 1. Comparison of parent- and physician-assessed YGTSS scores according to assessment category*

Assessment Category	Mean difference† (points)	95% CI
Entire assessment (all categories)	4.15	3.82—4.48
motor tic severity	1.17	1.07—1.28
vocal tic severity	1.23	1.11—1.35
combined tic severity	2.40	2.22—2.58
tic-related impairment	2.41	2.14—2.68

*n = 1455

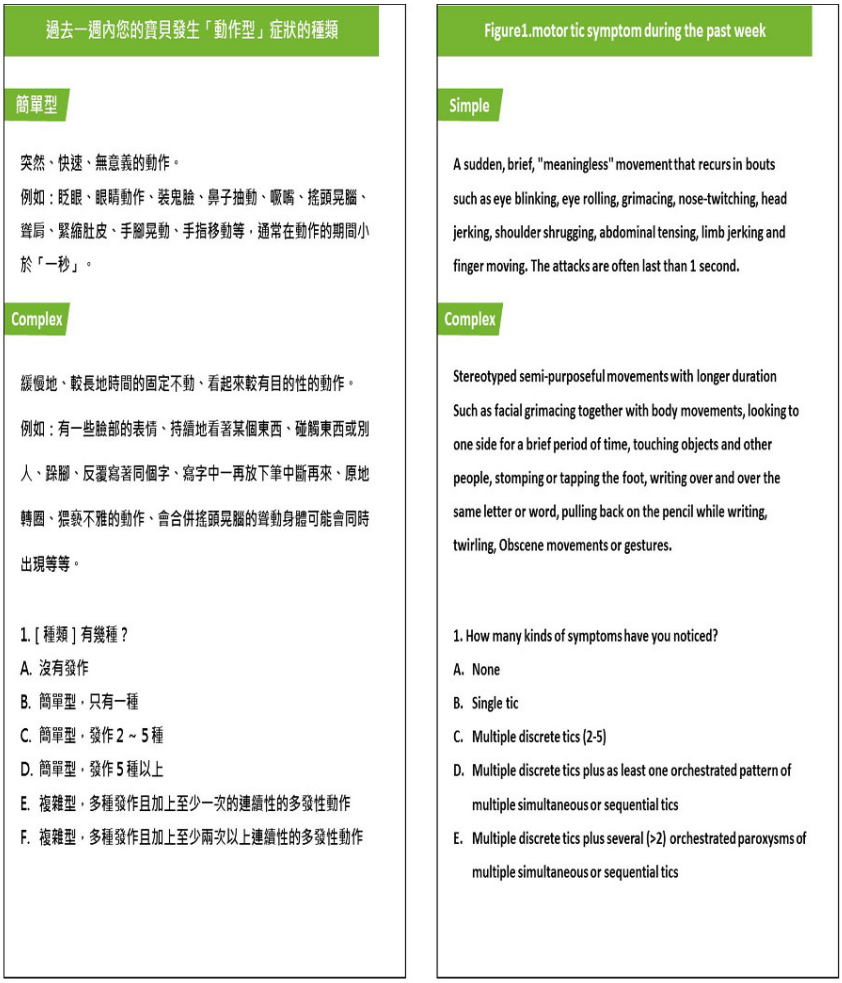
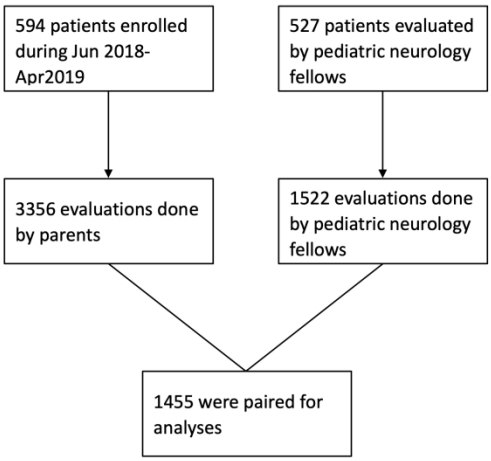


Figure 1

90x90mm (300 x 300 DPI)



209x297mm (300 x 300 DPI)

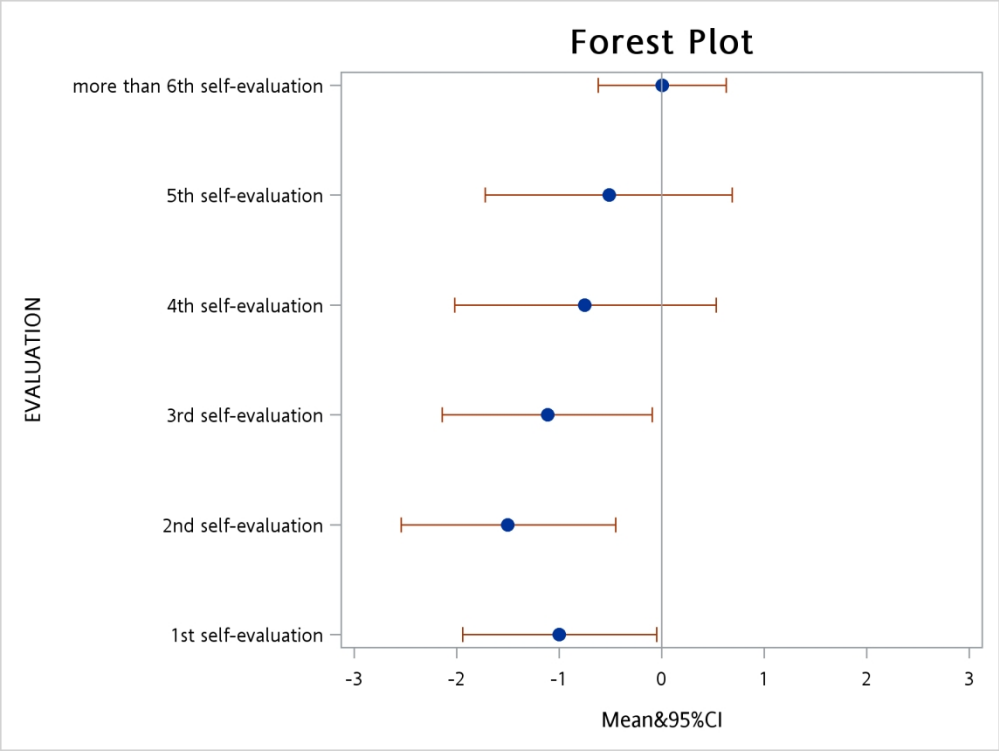


Figure 3

169x127mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.