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Quality of life in children and adolescents with Tourette's disorder: The Role of Psychiatric Comorbidities and Sex

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Abstract

Background

Psychiatric comorbidities are common in children and adolescents with Tourette's disorder (TD) and may have a greater impact on quality of life (QoL) than tics. However, the relative contribution of different comorbidities and the potential moderating effect of sex remain insufficiently understood. This study examined the associations between psychiatric comorbidities and QoL in a large European pediatric sample with TD.

Methods

Data were obtained from 667 children and adolescents with TD (aged 3–16 years) participating in the European Multicenter Tics in Children Studies (EMTICS). QoL was assessed using the parent-reported KINDL-R. Linear mixed-effects models were used to examine associations between QoL and categorical psychiatric comorbidities (obsessive-compulsive disorder [OCD], attention-deficit/hyperactivity disorder [ADHD], oppositional defiant disorder [ODD], autism spectrum disorder [ASD], and emotional disorders), continuous symptom severity measures, and the number of comorbid disorders. Sex moderation effects were also explored.

Results

All comorbid psychiatric disorders were associated with lower QoL. In multivariable analysis, emotional disorders showed the strongest independent association with reduced QoL. These associations remained significant after adjustment for tic severity. Similar findings were observed in analyses using dimensional symptom measures. QoL decreased progressively with the increasing number of psychiatric comorbidities. Sex moderated the associations between tic severity, OCD symptoms, and ASD symptoms and QoL, with stronger negative associations observed in girls than in boys.

Conclusions

Psychiatric comorbidities, particularly emotional disorders, are strongly associated with impaired QoL in pediatric TD, beyond the effects of tic severity. Assessment and treatment of comorbid psychopathology may be critical for improving QoL, especially among girls and those with multiple comorbid conditions.

INTRODUCTION

Tourette's disorder (TD) is a neurodevelopmental disorder characterized by multiple motor tics and at least one vocal tic that persist for more than one year [1]. In addition to tics, most individuals with TD present with one or more psychiatric comorbidities [2]. Attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are the most common co-occurring conditions, with prevalences reaching up to 50% in clinical pediatric samples [2, 3]. Elevated rates of autism spectrum disorder (ASD), disruptive behavior disorders, anxiety disorders, and mood disorders have also been reported [2].

Children and adolescents with TD experience lower quality of life (QoL) than their peers [4, 5]. QoL refers to an individual's subjective perception of well-being across multiple domains, including physical health, emotional well-being, social relationships, and school or occupational functioning [6]. QoL is increasingly recognized as a clinically meaningful measure, given the demonstrated association between reduced QoL and later adverse mental health outcomes such as depression or suicidality [7, 8].

Reduced QoL in TD appears to be multifactorial. Early studies suggested that this reduction was more strongly related to the presence of co-occurring mental disorders than to tics [9]. This conclusion was largely based on case-control studies showing that children and adolescents with TD without psychiatric comorbidities had QoL levels comparable to healthy controls [4–5, 10]. However, more recent research has demonstrated that greater tic severity is also associated with poorer QoL across studies using both generic and TD-specific QoL measures [11–14]. These results highlight the importance of integrating categorical and dimensional approaches when examining QoL in TD.

Among psychiatric comorbidities, attention-deficit/hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD) have been the most studied in pediatric TD research. Both disorders have been associated with reduced QoL when examined categorically (i.e., presence versus absence of ADHD/OCD) [4, 10] and dimensionally (i.e., symptom severity). In contrast, evidence regarding anxiety and depressive disorders is more limited and derives mainly from dimensional analyses relating higher symptom severity to poorer QoL [11, 16–19]. Consequently, the contribution of emotional disorders, compared with more established comorbidities such as ADHD and OCD, remains insufficiently understood.

Surprisingly, the role of other clinically relevant comorbidities, such as oppositional defiant disorder (ODD) and autism spectrum disorder (ASD), has received little attention. Several factors may contribute to this gap. For ODD, the lack of data may reflect the tendency to conceptualize oppositional symptoms as part of a behavioral dysregulation frequently reported in TD (e.g., “rage attacks” [20]) or grouped under broader categories such as disruptive, impulsive-control and conduct disorders [21]. In contrast, the limited evidence regarding ASD may be related to its relatively lower prevalence in TD populations (5–20%) [22, 23], which makes it challenging to recruit an adequately powered sample. Examining the relationship between ODD and ASD with QoL in TD is timely, given the substantial impact of both disorders on QoL in non-TD populations [24, 25].

Another understudied issue concerns the cumulative impact of multiple psychiatric comorbidities on QoL. Previous studies have suggested that QoL is poorer among individuals with multiple psychiatric comorbidities than among those with a single comorbid condition. However, this evidence has been largely restricted to the co-occurrence of both OCD and ADHD, and differences between individuals with both disorders and those with a single comorbid disorder have not consistently reached statistical significance [4, 10]. Limited statistical power may partly explain these findings, as previous studies included relatively small samples. Further evidence comes from a study of 83 individuals with TD (43 children and 40 adults), in which a higher number of psychiatric comorbidities was significantly

associated with poorer QoL [26]. In that study, reductions in QoL were particularly pronounced among participants presenting with three or more comorbidities.

Finally, further research is also needed to clarify sex differences in the associations between tics, psychiatric comorbidities, and QoL. Most previous TD studies examining sex differences in QoL have been limited to comparisons of mean QoL scores between boys and girls and have generally reported non-significant findings [14, 18, 27]. However, female sex has been associated with greater tic-related impairment in both pediatric and adult samples [28, 29] and with higher severity of OCD symptoms with increasing age than male sex [30]. These findings raise the possibility that sex may act as a moderator in the association between tics and psychiatric comorbidities and QoL, rather than as a direct determinant of QoL.

The present study used data from the *European Multicenter Tics in Children Study* (EMTICS) [31] to examine the relationship between tics, psychiatric comorbidities, and QoL of children and adolescents with TD or other persistent tic disorders (hereafter collectively referred to as TD). Specifically, we aimed to: 1) investigate associations between comorbid psychiatric disorders, including ASD and ODD, and QoL; 2) examine the association between the number of comorbid psychiatric disorders and QoL; 3) investigate the association between tics and psychiatric symptom dimensions and QoL; and 4) determine whether sex moderates the association between tics or comorbid psychiatric symptoms and QoL.

METHODS

Participants

The study sample consisted of 667 children and adolescents aged 3–16 years with TD (n = 587, 88%) or another chronic tic disorder (n = 80, 12%) who participated in the baseline assessment of the *European Multicenter Tics in Children Study* (EMTICS) [31]. We excluded 42 participants from the original sample (n = 709) who did not complete the questionnaire used to assess QoL. Participants were recruited from 16 specialized outpatient clinics across Europe, including child and adolescent psychiatry and pediatric neurology clinics, via clinician referrals or patient organization advertisements. Exclusion criteria included serious medical illness, antibiotic treatment in the previous month, and/or inability to understand and comply with the study protocol.

During the baseline study visit, experienced clinicians established diagnoses of tic disorders, OCD, and ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [32]. Diagnostic uncertainties were resolved through consensus discussions within an expert team at each clinical center. Clinician-administered diagnostic assessments for ODD, ASD, and emotional disorders were not available within the EMTICS protocol.

The severity of tics and OCD symptoms was assessed using standardized clinician-rated interviews (see below). Moreover, based on parent-reported questionnaires completed within two weeks preceding the

study visit, we defined children in the clinical range regarding ODD, ASD, and emotional problems (anxiety and depression) using validated questionnaire cutoffs [33–35]. These groups are hereafter referred to as the ODD, ASD, and emotional-disorders group. Parents also completed questionnaires to assess participants' QoL. Parents reported their education level on a 6-point scale (1 = 7 years of schooling, 2 = junior high school, 3 = high school diploma, 4 = associate degree, 5 = bachelor's degree, and 6 = postgraduate/professional degree), which was used as a proxy for socio-economic status. The use of psychotropic medication during the previous two weeks was also recorded as a dichotomous variable (yes/no).

Clinician-rated interviews

The *Yale Global Tic Severity Scale* (YGTSS) was used to assess tic severity [36] (Cronbach's alpha in our study was α = 0.87). Motor and vocal tics present during the previous week were rated separately across five dimensions (number, frequency, intensity, complexity, and interference) using 0-5-point scales. Motor and vocal tic scores (range 0–25 each) were summed to obtain a total tic severity score (range 0–50).

The *Children's Yale–Brown Obsessive Compulsive Scale* (CY-BOCS) was used to assess the severity of obsessive-compulsive symptoms [37] (Cronbach's alpha in our study was α = 0.93). Obsessions and compulsions during the previous week were rated across five dimensions (time spent, interference, distress, resistance, and control) using 0-4-point scales. Obsession and compulsion scores (range 0–20 each) were summed to obtain a total score (range 0–40).

Parent-rated questionnaires

The *Swanson, Nolan, and Pelham Scale, version IV* (SNAP-IV) was used to assess the severity of ADHD and ODD symptoms [35] (Cronbach's alpha in our study was α = 0.95). Parents rated inattentive, hyperactive-impulsive, and oppositional defiant behaviors during the previous week on a 4-point Likert scale (0–3). Mean scores were calculated for each subscale. An overall ADHD severity score was computed by averaging inattentive and hyperactive-impulsive symptom scores. Scores > 1.88 on the ODD subscale were considered clinically significant [35].

The *Autism Spectrum Screening Questionnaire* (ASSQ) was used to assess the severity of ASD symptoms [33] (Cronbach's alpha in our study was α = 0.91). Parents rated autistic symptoms on a 3-point scale. Items were summed to generate a total score (range 0–54), with scores of ≥ 19 indicating probable high-functioning ASD [33].

The emotional symptom subscale of the *Strengths and Difficulties Questionnaire* (SDQ) was used to evaluate emotional problems [34]. Parents rated emotional symptoms occurring during the previous two weeks on a 0-3-point scale (Cronbach's alpha in our study was α = 0.73). Subscale scores ≥ 5 were considered clinically relevant [34].

Age-appropriate versions of the Revised Children's Quality of Life Questionnaire (KINDL-R) were used to assess QoL. The Kiddy KINDL-R was administered by parents of children aged 4–6 years, whereas the Kid/Kiddo KINDL-R was used for participants aged 7–17 years [38]. Because these versions share an equivalent structure, they were combined into a single scale for analyses (the Kiddy KINDL-R includes an extra subscale with 22 items on "other important questions", which we did not use in this study). Parents rated QoL during the previous week on a 5-point scale across six domains: physical well-being, emotional well-being, self-esteem, family functioning, social life, and school functioning. Scores of these six domains were summed to obtain a total QoL score (Cronbach's α = 0.88). For ease of interpretation, the total score was transformed to 0-100 scale using the following formula: [(sum of all items − minimum possible score) / score range] × 100.

Statistical analyses

Preliminary analyses

Model assumptions, including linearity, normality, and homoscedasticity of residuals, were assessed through visual inspection of diagnostic plots. Missing data across clinical measures were low (< 4.6%) and were primarily attributable to incomplete questionnaires. Mean imputation of scale scores was applied only when at least 20% of the items within a given (sub)scale had been completed; otherwise, the corresponding score was coded as missing. Independent-samples *t*-tests and chi-squared tests were used to examine sex differences in demographic and clinical characteristics.

Main analyses

Linear mixed-effects models were used to examine the association between psychiatric comorbidities and QoL (KINDL-R total score). In a first set of analyses, comorbidities were treated as categorical variables (absent/present), enabling direct comparisons among disorders. First, univariable models were conducted to assess the association between each individual comorbid disorder (i.e., OCD, ADHD, ODD, ASD, and emotional disorders) and QoL. In these models, regression coefficients (β) represent the mean difference in QoL between participants with and without the respective comorbid disorder. Second, a multivariable model simultaneously including all psychiatric comorbid disorders was conducted to estimate the unique association of each disorder with QoL while adjusting for the presence of the other comorbid psychiatric disorders. Reductions in β coefficients relative to univariable models were interpreted as indicative of shared variance among comorbid disorders. Finally, an additional linear mixed-effects model was conducted to examine the association between the number of comorbid disorders (range 0–5) and QoL.

In a second set of analyses, univariable and multivariable linear mixed-effects models were conducted using continuous measures of symptom severity (YGTSS total score, CY-BOCS total score, SNAP-IV ADHD combined score, SNAP-IV ODD score, ASSQ score, and SDQ Emotional Problems score). Multicollinearity among symptom dimensions was assessed using variance inflation factors (VIFs). All

VIF values were below 2 (range = 1.2–1.9), indicating no evidence of problematic multicollinearity. This dimensional approach complemented the categorical analyses by capturing variation in symptom severity across the full spectrum of symptoms. To facilitate comparison of effect sizes across symptom dimensions, standardized regression coefficients were calculated as: standardized β = (unstandardized β × SD of the predictor) / SD of the outcome.

In a third set of analyses, interaction terms between sex and each symptom dimension were added to the univariable models to examine whether sex moderated the association between symptom severity and QoL. For significant interactions, sex-specific regression coefficients were derived from the interaction models. With male sex specified as the reference group, the female slope was calculated as the sum of the symptom coefficient and the corresponding sex-by-symptom interaction coefficient. Moderation analyses were restricted to dimensional measures because this approach allowed the examination of sex differences in the association between tic severity and QoL, one of the primary objectives of the study. In addition, the relatively small number of girls within some diagnostic categories limited the statistical power to examine sex-by-diagnosis interactions. Multivariable moderation models were not conducted because the inclusion of multiple correlated symptom dimensions and interaction terms would have reduced the power to detect sex-specific effects.

In line with prior literature, all models included the covariates sex, age, parental education level, and psychotropic medication use as fixed effects, with recruitment center (16 sites) included as a random effect. Where appropriate, models were estimated both with and without adjustment for tic severity to examine the contribution of psychiatric comorbidities beyond tics.

All analyses were conducted using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY). Statistical significance was set at $p < .05$, except for interaction terms, for which a threshold of $p < .10$ was adopted because interaction effects are typically associated with reduced statistical power.

RESULTS

Sample characteristics

See Table 1 for the sample characteristics. The study included 667 participants with TD, predominantly Caucasian (n = 568, 85.2%) and male (n = 510, 76.5%), with a mean age of 10.7 ± 2.8 years. Parental education level was in the intermediate range (mean score = 4 ± 1.2). Overall, 405 participants (60.7%) presented with at least one psychiatric comorbidity. The most common presentation was a single comorbid disorder (n = 186, 27.9%), followed by two (n = 113, 16.9%) and three comorbid disorders (n = 64, 9.6%). Regardless of the presence of other comorbidities, approximately one third of participants met DSM-IV-TR criteria for OCD (n = 188, 28.2%) or ADHD (n = 187, 28.0%). Scores were above the clinical cutoff for ODD symptoms in 95 participants (14.2%), for ASD symptoms in 117 (17.5%), and for emotional problems in 247 (37.0%). The most common combination of two disorders was OCD and emotional disorder (n = 98, 14.7 %), followed by ADHD and emotional disorder (n = 91, 13.6%). Co-occurring OCD and ADHD were present in 72 participants (10.8%). Approximately one third of the

participants (n = 219, 32.8%) were receiving psychotropic medication. The mean KINDL-R total score in the total sample was significantly lower than normative data (68.9 ± 12.9 vs 76.3 ± 10.1, respectively, p < .001), with a similar pattern observed in boys and girls (Supplementary Table S1).

No statistically significant sex differences were observed for age, ethnicity, parental education level, psychotropic medication use, or QoL measures. However, significant sex differences emerged for several clinical variables, with girls showing higher rates of emotional disorders, whereas boys showed greater severity of tics, ADHD symptoms, and ASD symptoms, as well as higher rates of ASD (Table 1).

--- Insert Table 1---

Association between comorbid psychiatric disorders and quality of life

*Models without adjustment for tic severity:*In the univariable models, all examined psychiatric comorbidities (OCD, ADHD, ODD, ASD, and emotional disorders) were significantly associated with lower QoL (all p < .001). ODD and emotional disorders showed the strongest negative associations (β = -12.46 and β = -11.72, respectively; Table 2).

In the multivariable model, which adjusted for the simultaneous presence of multiple psychiatric comorbidities, all disorders remained significantly associated with reduced QoL (all p < .001). Emotional disorders showed the strongest association (β = -8.80), followed by ODD (β = -7.40), ASD (β = -4.28), ADHD (β = -3.06), and OCD (β = -2.85). The magnitude of the associations was reduced relative to univariable models.

*Models adjusted for tic severity:*Results remained largely unchanged after adjustment for tic severity (Table 2). All psychiatric comorbidities continued to be significantly associated with lower QoL in both the univariable and multivariable models (all p < .001, except OCD in the multivariable model: p = .006). Although the magnitude of the associations was attenuated after adjustment for tic severity, emotional disorders and ODD remained the strongest correlates of reduced QoL (univariable models: β = -11.70 for ODD, β = -10.86 for emotional disorders; multivariable model: β = -8.47 for emotional disorders, β = -7.37 for ODD).

Full models with and without adjustment for tic severity are presented in Supplementary Table S2.

--- Insert Table 2 ---

Association between the number of comorbid disorders and quality of life

A significant association was observed between the number of psychiatric comorbidities and QoL (F(1, 605) = 41.28, p < .001), with QoL decreasing progressively as the number of comorbid disorders increased (Figure 1). Full models with and without adjustment for tic severity are presented in Supplementary Table S3.

Pairwise comparisons showed progressively lower QoL with increasing comorbidity burden; while this decline appears to plateau among participants with three or more comorbid disorders, it should be noted that the group sizes with 4 and 5 comorbidities were low (Supplementary Table S4). Pairwise comparisons between specific combinations of comorbid disorders were not performed because the classification into mutually exclusive comorbidity categories generated a large number of groups, many of which contained insufficient numbers of participants for meaningful statistical comparisons (Supplementary Table S5).

--- Insert Figure 1---

Association between the severity of tics/comorbid psychiatric symptoms and quality of life

Regarding tic severity, significant associations with lower QoL were observed in both the univariable and multivariable models (standardized β = -0.26, $p < .001$ and standardized β = -0.07, $p = .018$, respectively; Table 3).

*Models without adjustment for tic severity:*In the univariable analyses, higher scores of all psychiatric symptom dimensions were significantly associated with lower QoL (all $p < .001$). Based on standardized coefficients, emotional problems showed the strongest association with reduced QoL (standardized β = -0.54), followed by ADHD and ODD symptoms (both standardized β = -0.46), ASD symptoms (standardized β = -0.42), and OCD symptoms (standardized β = -0.27). In the multivariable model, all symptom dimensions remained significantly associated with lower QoL, although the magnitude of the associations was attenuated. Emotional problems remained the strongest correlate of reduced QoL (standardized β = -0.35).

Models adjusted for tic severity: Results were largely unchanged after adjustment for tic severity. All symptom dimensions remained significantly associated with lower QoL in the univariable analyses (all $p < .001$), with emotional problems showing the strongest association (standardized β = -0.51). In the multivariable model, emotional problems remained the strongest independent correlate of lower QoL (standardized β = -0.34), followed by ODD, ADHD, and ASD symptoms. OCD symptoms were no longer significantly associated with QoL ($p = .111$).

Full models with and without adjustment for tic severity are presented in Supplementary Table S6.

--- Insert Table 3---

Association between the severity of tics/comorbid psychiatric symptoms and quality of life: sex interactions

Significant sex interactions

A significant moderating effect was observed for the association between tic severity and QoL (YGTSS total x sex: β = -0.21, $p = .097$, interaction threshold $p < .10$; Figure 2). Higher tic severity was associated

with lower QoL in both sexes; however, this association was significantly stronger in girls (β = -0.75) than in boys (β = -0.54).

--- Insert Figure 2—

Models without adjustment for tic severity: Significant moderating effects of sex were observed for OCD symptoms (CY-BOCS total × sex: β = -0.33, *p* = .018) and ASD symptoms (ASSQ × sex: β = −0.37, *p* = .004; Figure 2). Higher OCD symptom severity was associated with lower QoL in both sexes; however, this association was significantly stronger in girls (β = -1.00) than in boys (β = -0.67). A similar pattern was observed for ASD symptoms, with a stronger negative association in girls (β = −1.31) than in boys (β = −0.94). Sex did not significantly moderate the associations between QoL and ADHD symptoms, ODD symptoms, or emotional problems.

Models adjusted for tic severity: After adjustment for tic severity, the significant sex interactions for OCD and ASD symptoms remained (CY-BOCS total × sex: β = −0.30, *p* = .027; ASSQ × sex: β = −0.34, *p* = .007). For both symptom dimensions, the associations with QoL were stronger in girls than in boys (OCD symptoms: β = −0.87 vs. β = −0.57; ASD symptoms: β = −1.21 vs. β = −0.87, respectively). No significant interactions were observed between sex and ADHD symptoms, ODD symptoms, or emotional problems.

Main effect models of comorbid symptom severity without significant sex interactions
Models without adjustment for tic severity: For symptom domains that did not show significant sex interactions, higher symptom severity was consistently associated with lower QoL (ADHD symptoms: β = −8.96; ODD symptoms: β = −7.95; emotional problems: β = −2.79; all p < .001). As the sex interactions were not significant, these associations appeared comparable in boys and girls.

Models adjusted for tic severity: After controlling for tic severity, the associations remained significant (ADHD symptoms: β = −8.16; ODD symptoms: β = −7.43; emotional problems: β = −2.63; all p < .001). No evidence was found that these associations differed by sex.

Full models with and without adjustment for tic severity are presented in Supplementary Tables S7 and S8.

DISCUSSION

The present study provides novel insights into the relationship between tics, psychiatric comorbidities, and QoL in a large European sample of children and adolescents with TD. Consistent with previous research, tic severity was associated with poorer QoL; however, a broad range of psychiatric comorbidities also showed significant and often stronger associations with QoL. Importantly, this study is the first to demonstrate that ODD and ASD symptoms are significantly associated to reduced QoL in children with TD, with associations comparable to those observed for more widely recognized comorbidities such as ADHD and OCD symptoms. We also found a cumulative association between psychiatric comorbidity burden and QoL, with progressively lower QoL observed as the number of

comorbidities increased. Finally, we found evidence that sex moderates the association between tics and certain psychiatric symptoms and QoL, with stronger associations observed in girls than in boys.

In line with previous literature, our findings indicate that comorbid psychiatric disorders are associated with reduced QoL beyond the contribution of tic severity [9]. Among comorbid disorders, emotional disorders showed the strongest relationships with QoL in both univariable and multivariable analyses. These findings are clinically relevant because ADHD has traditionally been considered the most impairing comorbidity in pediatric TD, whereas emotional disorders have been identified as major determinants of QoL primarily in adult TD populations [9, 39]. Beyond emotional disorders, our results also emphasize the importance of identifying comorbid ODD and ASD. The persistence of these associations in the multivariable analyses suggests that ODD and ASD contribute to QoL impairment beyond the effects of other comorbid conditions. In the case of ODD, this distinction is particularly relevant given the high co-occurrence of ODD and ADHD in TD populations and the tendency to conceptualize oppositional symptoms as secondary to ADHD-related behavioral dysregulation [40]. Similarly, careful differentiation of ASD in individuals with TD is important, as repetitive behaviours may show some phenomenological overlap [41].

Findings from the dimensional analyses largely converged with the categorical ones, indicating that the observed associations extended across the full range of symptom severity. However, some differences emerged. Whereas ASD showed a stronger association with QoL than ADHD in the categorical analyses (univariable and multivariable), ADHD symptoms were more strongly associated with QoL than ASD symptoms in the dimensional models (univariable and multivariable), suggesting that ADHD symptoms may affect QoL across a broader severity spectrum. In addition, OCD remained significantly associated with lower QoL in the categorical multivariable models but not in the dimensional multivariable model adjusted for tic severity, possibly reflecting shared variance between obsessive-compulsive symptoms and tic severity. Finally, in the multivariable model adjusted for tic severity, emotional problems, ODD, ADHD, and ASD symptoms were more strongly associated with QoL than tic severity itself, consistent with previous findings [5].

To our knowledge, this is the first study to examine sex as a moderator of the relationship between symptom severity and QoL in TD. The associations of tic severity, OCD symptoms, and ASD symptoms with reduced QoL were stronger in girls than in boys. These findings are particularly interesting given that tic disorders, OCD and ASD are generally more prevalent in males during childhood, although this sex difference tends to diminish during adolescence and adulthood [42–44]. One possible explanation is that girls may experience greater subjective distress related to these symptoms, resulting in a larger impact on perceived QoL. This interpretation is consistent with evidence showing higher levels of self-awareness and social evaluative concerns in females than in males, with sex differences becoming more pronounced during adolescence [45]. Our findings regarding OCD differ from previous literature suggesting poorer QoL in males with OCD [46]. However, this other study did not examine a TD sample and inferred sex differences indirectly from between-study comparisons rather than within-sample moderation analyses.

Despite the strengths, including its relatively large sample size and comprehensive assessment of comorbidities, this study has several limitations. First, several psychiatric symptom domains and QoL were assessed exclusively through parent reports, which may be subject to reporting bias and shared-method variance. Second, although validated questionnaires and clinical cutoffs were used to identify emotional disorders, ODD, and ASD, these conditions were not confirmed by clinicians, which may have limited the accuracy of the categorical analyses. Third, the cross-sectional design precludes causal inference. Fourth, the sample was predominantly Caucasian, of intermediate socioeconomic status, and characterized by relatively mild-to-moderate tic severity. Consequently, the generalizability of the findings to more diverse populations and to individuals with more severe psychopathology remains uncertain. Finally, although multivariable models help estimate the unique contribution of individual symptom domains, they do not fully capture the substantial overlap among psychiatric conditions in clinical practice, where comorbidity is common and symptom boundaries are often indistinct.

In conclusion, this study highlights the important contribution of psychiatric comorbidities to reduced QoL in pediatric TD. Emotional disorders emerged as the strongest correlate of poorer QoL, and sex moderated the associations of tic, OCD, and ASD symptom severity with QoL. These findings underscore the importance of comprehensive comorbidity screening and individualized interventions. Future longitudinal studies should clarify the directionality of these associations, incorporate multi-informant QoL assessments, examine patterns of impairments across specific QoL domains, and further investigate moderating factors, such as sex × age interaction, and distinct comorbidity profiles.

Declarations

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Conflict of Interest

P.H. is the chief editor of European Child & Adolescent Psychiatry

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The remaining authors declare that they have no competing interests.

Ethics approval

The EMTICS study was approved by the local research ethics committees of each participating center.

Consent

Written informed consent was obtained from all parents or legal guardians. Children and adolescents provided assent in accordance with local ethics committee requirements and age-appropriate procedures at each participating center.

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Tables

Table 1 Demographic and clinical characteristics of the study sample according to sex (n= 667)

	Total (*n*= 667) ***n* (%) /M (SD)**	**Males** (*n*= 510) ***n* (%) /M (SD)**	**Females** (*n*=157) ***n* (%) /M (SD)**	**p-value**
Age (years)	10.7 (2.8)	10.7 (2.8)	10.7 (2.9)	.877
Ethnicity (white Caucasian)	568 (85.2%)	436 (85.5%)	132 (84.1%)	.760
Parental education level	4.0 (1.2)	3.9 (1.1)	4.1 (1.2)	.185
Use of psychotropic medication	219 (32.8%)	176 (34.5%)	43 (27.4%)	.097
Comorbid psychiatric disorders [a] (with or without other comorbidities)				
OCD	188 (28.2%)	149 (29.2%)	39 (24.8%)	.287
ADHD	187 (28.0%)	150 (29.4%)	37 (23.6%)	.166
ODD	95 (14.2%)	76 (14.9%)	19 (12.1%)	.382
ASD	117 (17.5%)	98 (19.2%)	19 (12.1%)	**.046**
Emotional disorders	247 (37.0%)	178 (34.9%)	69 (43.9%)	**.041**
Number of comorbid psychiatric disorders				.889
0	235 (35.2%)	174 (34.1%)	61 (38.8%)	
1	186 (27.9%)	146 (28.6%)	40 (25.5%)	
2	113 (16.9%)	88 (17.3%)	25 (15.9%)	
3	64 (9.6%)	51 (10%)	13 (8.3%)	
4	33 (4.9%)	25 (4.9%)	8 (5.1%)	
5	9 (1.4%)	7 (1.4%)	2 (1.3%)	
Missing [b]	27 (4.1%)	19 (3.7%)	8 (5.1%)	
Symptom severity (questionnaire score)				
Tics (YGTSS total)	19.6 (8.6)	20.1 (8.6)	18.1 (8.8)	**.010**
OCD (CYBOCS total)	6.5 (8.4)	6.7 (8.5)	5.8 (7.8)	.438
ADHD (SNAP-IV ADHD combined)	1.1 (0.7)	1.1 (0.7)	1.0 (0.7)	**.004**
ODD (SNAP-IV ODD)	1.0 (0.7)	1.0 (0.7)	0.9 (0.8)	.098
ASD (ASSQ)	10.9 (8.4)	11.4 (8.5)	9.1 (7.8)	**.004**

Emotional problems (SDQ Emotional)	3.9 (2.6)	3.8 (2.5)	4.2 (2.9)	.091
Quality of life (KINDL-R Total)	68.9 (12.9)	68.9 (12.5)	69.0 (14.4)	.990

[a]Comorbid diagnoses were defined using DSM-IV criteria for OCD and ADHD, and clinical cutoff scores for ODD, ASD and emotional disorders.

[b] Twenty-seven participants could not be classified according to number of comorbid disorders because of missing data on one or more comorbidity measures

M mean, *SD* standard deviation

OCD obsessive-compulsive disorder, *ADHD* attention-deficit/hyperactivity disorder, *ODD* oppositional defiant disorder, *ASD* autism spectrum disorder, *YGTSS* Yale Global Tic Severity Scale, *CY-BOCS* Children's Yale–Brown Obsessive Compulsive Scale, *SNAP-IV* Swanson, Nolan, and Pelham Rating Scale–IV, *ASSQ* Autism Spectrum Screening Questionnaire, *SDQ* Strengths and Difficulties Questionnaire, *KINDL-R* Revised Children's Quality of Life Questionnaire

Sex differences were examined using independent *t*-tests for continuous variables and chi square tests for categorical variables.

Table 2. Association between comorbid psychiatric disorders and quality of life (KINDL-R total score) in children and adolescents with TD

Comorbid disorder [a]	Univariable model				Multivariable model			
	β (SE), unadjusted for tic severity	p-value	β (SE), adjusted for tic severity	p-value	β (SE), unadjusted for tic severity	p-value	β (SE), adjusted for tic severity	p-value
OCD	-6.78 (1.10)	< .001	-5.33 (1.10)	< .001	-2.85 (0.99)	< .001	-2.27 (1.00)	.006
ADHD	-6.79 (1.10)	< .001	-5.87 (1.09)	< .001	-3.06 (0.99)	< .001	-2.76 (1.00)	< .001
ODD	-12.46 (1.32)	< .001	-11.70 (1.28)	< .001	-7.40 (1.26)	< .001	-7.37 (1.25)	< .001
ASD	-10.06 (1.21)	< .001	-9.14 (1.20)	< .001	-4.28 (1.17)	< .001	-4.06 (1.17)	< .001
Emotional disorders	-11.72 (0.91)	< .001	-10.86 (0.90)	< .001	-8.80 (0.89)	< .001	-8.47 (0.89)	< .001

[a] Comorbid diagnoses were defined using DSM-IV criteria for OCD and ADHD, and clinical cutoff scores for ODD, ASD, and emotional disorders.

SE standard error.

KINDL-R Revised Children's Quality of Life Questionnaire, *OCD* obsessive-compulsive disorder, *ADHD* attention-deficit/hyperactivity disorder, *ODD* oppositional defiant disorder, *ASD* autism spectrum disorder.

Associations between comorbid psychiatric disorders (present vs. absent) and quality of life (KINDL-R total score) were examined using linear mixed-effects models. All models were adjusted for sex, age, parental education level, psychotropic medication use and, where indicated, for tic severity. Recruitment center was included as a random effect.

β coefficients represent adjusted mean differences in KINDL-R total score associated with the presence of each comorbid disorder.

Full models with and without adjustment for tic severity are presented in Supplementary Table S2.

Table 3. Association between tics and comorbid psychiatric symptoms and quality of life (KINDL-R total score)

A. **Univariable models**

Symptom dimension (clinical measure)	**β (SE)**	**p-value**	**Std β**			
Tics (YGTSS total)	-0.39 (0.06)	< .001	-0.26	-	-	-
	Unadjusted for tic severity			**Adjusted for tic severity**		
	β (SE)	**p-value**	**Std β**	**β (SE)**	**p-value**	**Std β**
OCD symptoms (CY-BOCS total)	-0.41 (0.06)	< .001	-0.27	-0.34 (0.06)	< .001	-0.22
ADHD symptoms (SNAP-IV ADHD combined)	-8.53 (0.64)	< .001	-0.46	-7.87 (0.64)	< .001	-0.43
ODD symptoms (SNAP-IV ODD)	-8.47 (0.59)	< .001	-0.46	-7.92 (0.59)	< .001	-0.43
ASD symptoms (ASSQ)	-0.64 (0.05)	< .001	-0.42	-0.59 (0.05)	< .001	-0.38
Emotional problems (SDQ Emotional)	-2.68 (0.16)	< .001	-0.54	-2.53 (0.16)	< .001	-0.51

B. **Multivariable model**

	Unadjusted for tic severity			Adjusted for tic severity		
Symptom dimension (clinical measure)	**β (SE)**	**p-value**	**Std β**	**β (SE)**	**p-value**	**Std β**
Tics (YGTSS total)	-	-	-	-0.11 (0.05)	.018	-0.07
OCD symptoms (CY-BOCS total)	-0.10 (0.05)	.046	-0.07	-0.08 (0.05)	.111	-0.05
ADHD symptoms (SNAP-IV ADHD combined)	-2.69 (0.78)	.001	-0.15	-2.57 (0.78)	.001	-0.14
ODD symptoms (SNAP-IV ODD)	-3.21 (0.71)	< .001	-0.17	-3.24 (0.71)	< .001	-0.18
ASD symptoms (ASSQ)	-0.17 (0.06)	.003	-0.11	-0.16 (0.06)	.007	-0.10
Emotional problems (SDQ Emotional)	-1.72 (0.17)	< .001	-0.35	-1.69 (0.17)	< .001	-0.34

SE standard error, Std β Standardized regression coefficient.

OCD obsessive-compulsive disorder, *ADHD* attention-deficit/hyperactivity disorder, *ODD* oppositional defiant disorder, *ASD* autism spectrum disorder, *YGTSS* Yale Global Tic Severity Scale, *CY-BOCS* Children's Yale–Brown Obsessive Compulsive Scale, *SNAP-IV* Swanson, Nolan, and Pelham Rating Scale–IV, *ASSQ* Autism Spectrum Screening Questionnaire, *SDQ* Strengths and Difficulties Questionnaire, *KINDL-R* Revised Children's Quality of Life Questionnaire

Associations between symptom severity dimensions and quality of life (KINDL-R total score) were examined using linear mixed-effects models. All models were adjusted for sex, age, parental education level, psychotropic medication use and, where indicated, for tic severity. Recruitment center was included as a random effect.

Standardized β coefficients were calculated to facilitate comparison of effect sizes across symptom dimensions.

Full models with and without adjustment for tic severity are presented in Supplementary Table S6.

Figures

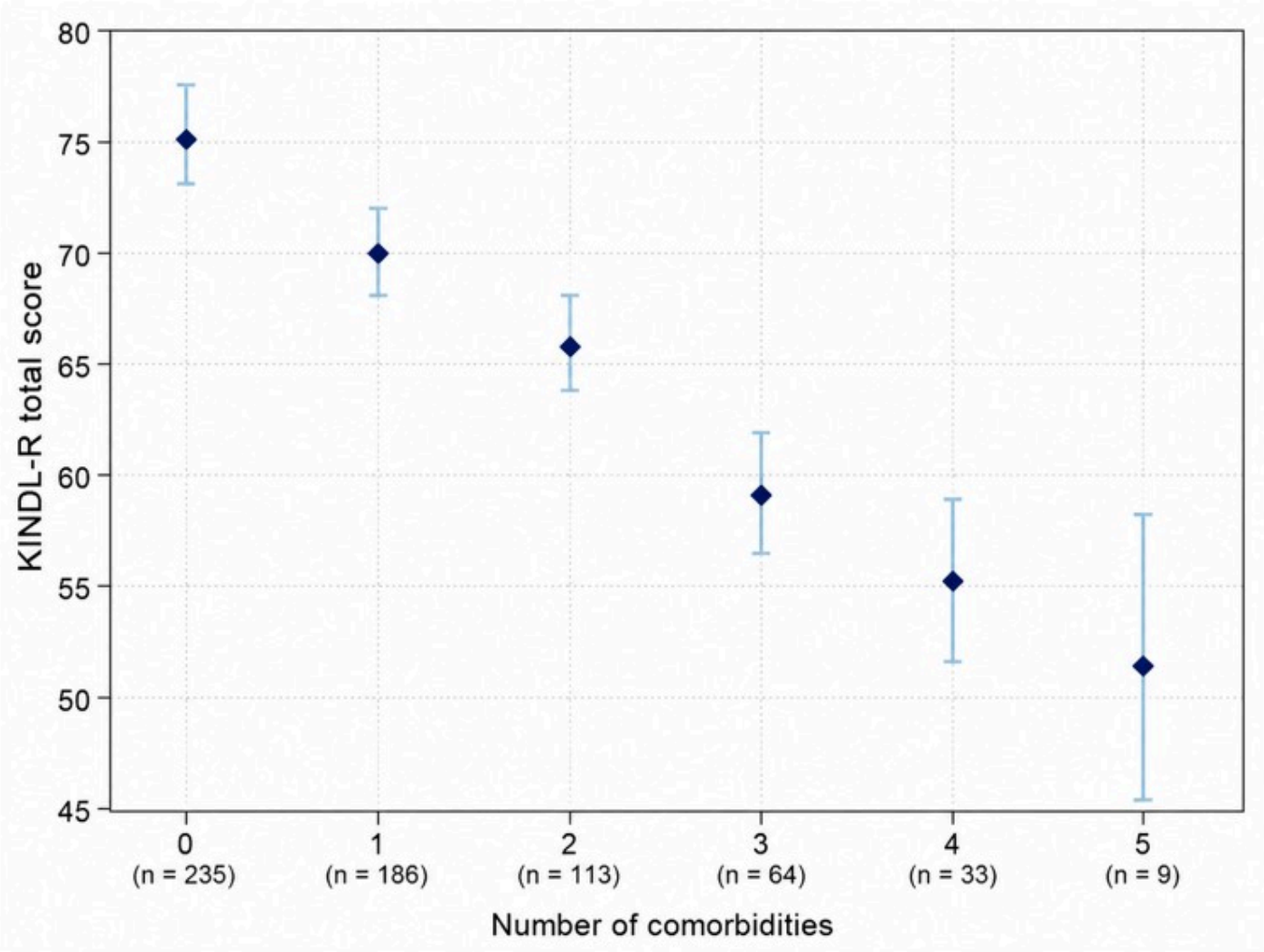


Figure 1

Association between the number of comorbid psychiatric disorders and quality of life (KINDL-R total score)

KINDL-R Revised Children's Quality of Life Questionnaire

Diamonds represent adjusted mean KINDL-R total scores and error bars indicate 95% confidence intervals. Adjusted means were estimated from linear mixed-effects models controlling for age, sex, parental education level, psychotropic medication use, tic severity, and recruitment center. Sample sizes are displayed below each group.

A significant association was observed between the number of psychiatric comorbiddisorders and quality of life, with lower KINDL-R scores associated with a greater number of psychiatric comorbidities. Pairwise comparisons are presented in Supplementary Table S4.

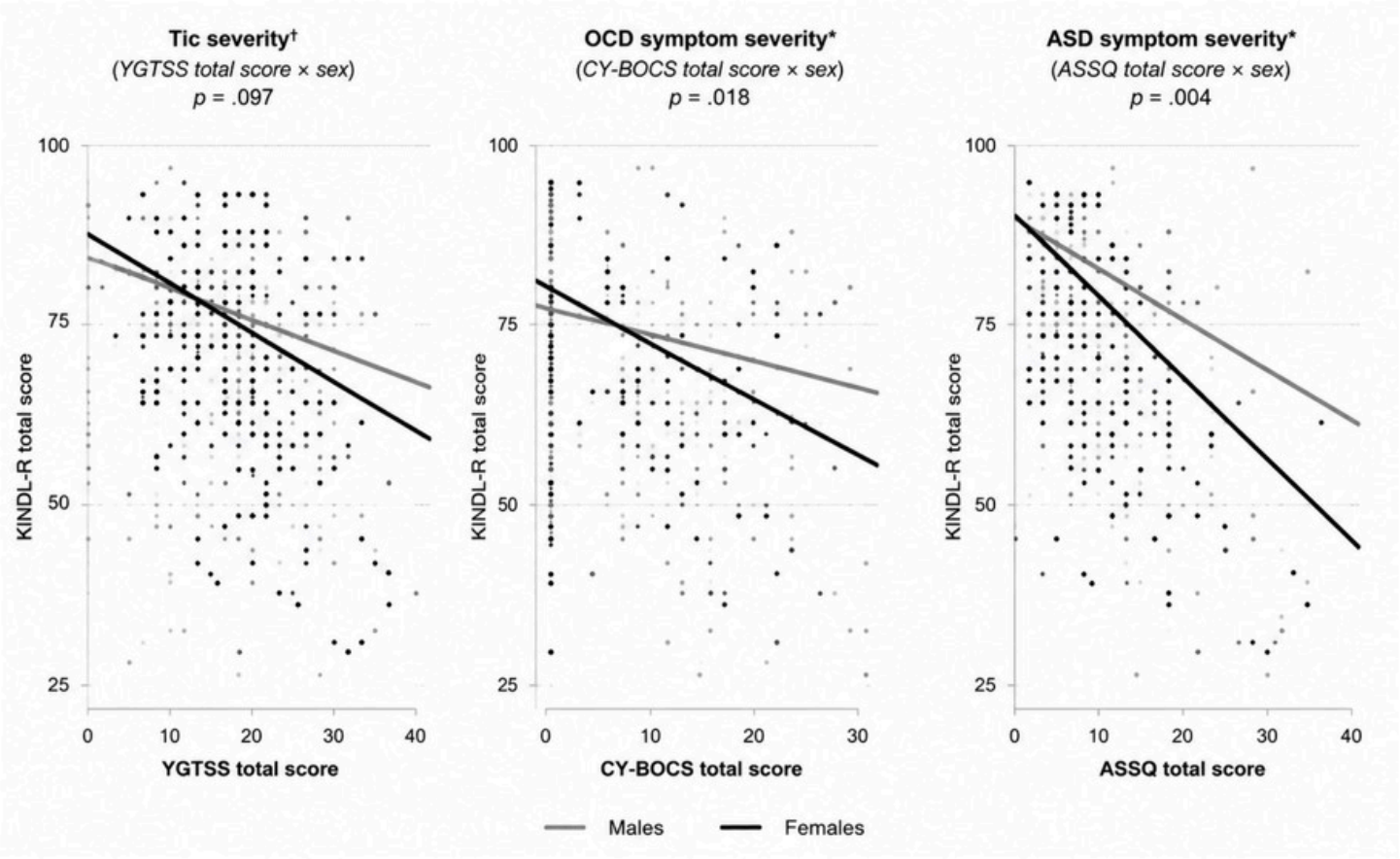


Figure 2

Moderating effect of sex on the association between tic severity, OCD symptoms, ASD symptoms, and quality of life (KINDL-R total score)

The significance level for the interaction effect was set at $p < .10$ due to the lower statistical power typically associated with interaction terms.

† $p < .10$; * $p < .05$

*YGTSS*Yale Global Tics Severity Scale, *OCD* obsessive-compulsive disorder, *CY-BOCS*Children's Yale-Brown Obsessive Compulsive Scale, *ASD* Autism Spectrum Disorder, *ASSQ* Autism Spectrum Screening Questionnaire, *KINDL-R*Revised Children's Quality of Life Questionnaire

Lines represent model-predicted KINDL-R total scores across levels of symptom severity, shown separately for males (grey) and females (black). Models were adjusted for age, parental education level, psychotropic medication use, and recruitment center. Models examining OCD and ASD symptoms were additionally adjusted for tic severity.

Sex-specific beta estimates are presented in Supplementary Table S8.

Supplementary Files

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