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Effects of comorbidity on Tourette's tic severity and quality of life

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Objective: The aim of this study is to gain more insight in the differential contributions of anxiety, depression and obsessive-compulsive (OC) symptom severity to quality of life (QoL) and tic severity in adults with Tourette Disorder (TD).

Methods: Self-reported OC symptom, anxiety and depression severity measures were used to investigate their predictive value on QoL and Tic severity in adult TD patients (N = 187), using correlation, regression, and mediation analyses.

Results: Tic severity has no effect on QoL. Depression severity directly reduces QoL, whereas anxiety and OC symptom severity have an indirect effect on QoL, mediated by depression severity. OC symptom severity directly affects tic severity, whereas depression and anxiety severity do not have a direct effect on tic or OC severity. Finally, anxiety severity *in*directly impacts tic severity, with OC symptom severity functioning as a mediator.

Conclusion: In line with and extending previous studies, these findings indicate that OC symptom severity directly influences tic symptom severity whereas depression severity directly influences QoL in TD. Results imply that to improve QoL in TD patients, treatment should primarily focus on diminishing OC and depressive symptom severity rather than focusing on tic reduction.

KEYWORDS
comorbidity, depression, obsessive-compulsive disorder, quality of life, Tourette syndrome

1 | INTRODUCTION

Tourette's Disorder (TD) is a chronic neuropsychiatric disorder with childhood onset, characterized by multiple motor and one or more vocal (phonic) tics lasting longer than a year, with no tic-free period of more than three consecutive months.[1]

Up to approximately 90% of adult TD patients suffer from comorbid disorders, with obsessive-compulsive disorder (OCD; 20%-60%), attention deficit and hyperactivity disorder (ADHD; 21%-90%), depression (18%-30%) and anxiety disorders (18%) being the most frequent comorbidities occurring in TD.[2-9] In addition,

mood, anxiety, and substance abuse disorders are found to be more prevalent among participants with TD and comorbid OCD compared with TD patients without OCD comorbidity.[5-7,9] The interrelationships between the various comorbidities in TD seem unclear, as well as the differential contributions of these comorbidities to tic severity and Quality of Life (QoL). This study focusses on the relationships between obsessive-compulsive (OC), anxiety and depressive symptom severity on the one hand, and tic symptom severity and QoL on the other.

Although the neurobiological relationship between tics and OC symptoms is widely established,[10] the extent at which OC symptom

severity contributes to tic severity within TD patients is not fully clarified. Some studies indicate no association between tic and OC symptom severity,[11] whereas other studies suggest that OC symptoms in TD are associated with increased tic severity.[9,12,13]

With respect to the relationship between depressive and anxiety symptom severity on the one hand and tic severity on the other, Rizzo et al[7] compared a group of TD patients with comorbid depression diagnoses with TD patients without comorbid depression and found that tic severity was higher in the TD + Depression group. Further, Marwitz and Pringsheim[14] found a positive correlation between depression (r = .37) as well as anxiety severity (r = .22) and tic severity in children. However, the direction of these relationships is unclear: Is there an effect of anxiety or depression *on* tic severity or vice versa, and if so, are those effects additive or multiplicative?

Regarding the relationship between tic symptom severity, OC symptom severity, and/ or depressive and anxiety symptom severity on the one hand, and QoL on the other: Generally, tic and OC symptoms are highly correlated,[15] and have been found to be associated with decreased QoL, lower psychosocial functioning, and lower academic achievement.[16-20] Tic severity in children has been found to be a predictor of poor outcome on physical, psychological and cognitive domains of QoL later in life.[21] Especially, comorbidity with OC symptoms has shown to be an aggravating factor and leads to decreased global functioning,[22] lower self-esteem and difficulties in relationships[23] as well as a negative influence on vitality, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.[12]

Presence and severity of anxiety disorders are positively associated with OCD diagnosis and OC symptom severity in TD, although the nature of the association with QoL is subject to debate.[4,7,9,24,25] Research in TD including both anxiety and OC symptom comorbidity has indicated that depression was the main predictor of QoL in TD patients.[26] Some researchers argue that increased frequencies of comorbid anxiety and depression symptoms in TD are secondary to disease burden[27] and thus negatively impact QoL.[11] Others argue that anxiety and depression negatively influence QoL through an increase in other comorbidities like OCD. Finally, a recent literature review by Evans et al[28] suggests that QoL profiles in TD *children* often reflect the negative effect of comorbid OCD and ADHD while in *adults* QoL is mostly negatively influenced by comorbid depression and anxiety.

1.1 | Aims of the study

To summarize, in adults with TD, there is a complex relationship between OC, anxiety and depression symptom severity on the one hand and tic severity and QoL on the other. In this study, we aimed to extend previous findings by investigating the structure of the interrelationships, using mediation and moderation analyses. Mediation analyses, although cross-sectional in nature, hypothesize causal relations and their directions between various contributors and tic severity and QoL, and thus shed light on how these comorbidities interact and reinforce each other in their effect on QoL and tic

severity. Based on previous findings, we aimed at exploring whether (a) OC, depression and anxiety severity predict an increase in tic severity; (b) OC symptom severity either interact with or mediate the effect of anxiety and depression severity in an aggravating effect on tic severity; (c) Tic severity, OCD, depression, and anxiety severity have a negative effect on QoL; (d) depression severity and OC symptom severity either interact with or mediate the effect of tic severity and anxiety severity in a negative effect on QoL.

2 | MATERIAL AND METHODS

2.1 | Participants

Clinical data were obtained from 187 participants with a DSM-IV-TR diagnosis of TD (72 females and 115 males, with an average age of 36.61; range: 18-65). For a thorough description of the study group, see de Haan et al.[29]

Of these 187 participants, 129 were assessed on psychiatric comorbidity using semi-structured interviews. A table with the frequencies of (comorbid) mental disorders is provided in the Appendix 1.

2.2 | Procedure

Participant recruitment was carried out between 2001 and 2008 in the scope of a genetic study on TD that was approved by the Medical/Ethical Review Board of the VU University Medical Center. All study subjects gave written informed consent. Participants were recruited via two Dutch outpatient clinics (GGZ Ingeest and Altrecht Academic Anxiety center) specialized in diagnosing and treatment of TD, and through the Dutch Tourette's syndrome patients' association. Participants with TD were invited for assessment and were sent self-report questionnaires to fill in. During the assessment a diagnostic interview entailing either the SCID-I or MINI was carried out by research nurses and psychologists trained in diagnosing TD and other DSM-IV axis 1 diagnoses (see the measurements section for a description). Participants were reimbursed for travel expenses.

2.3 | Measurements

2.3.1 | Yale Global Tic Severity Scale (YGTSS)

The YGTSS is a semi-structured clinician-rated instrument used to assess the characteristics and severity of motor and vocal tics in the week preceding the assessment (Leckman et al[30]). Global tic severity is established by summing the total scores of the vocal and the motor scale (number, frequency, intensity, complexity, interference with item score ranges between 0 and 5 for the motor and vocal tics separately), without the impairment item, creating a total score (range 0-50). The YGTSS is a reliable and valid instrument with excellent internal consistency.[31,32] Cronbach's alpha of the YGTSS in the current study was .95; the average score in our sample was 17.81 (SD = 10.11).

TABLE 1 Pearson correlations between EQ-VAS, BDI, BAI, Y-BOCS, and YGTSS

	EQ-VAS	BDI	BAI	Y-BOCS	YGTSS
EQ-VAS	1				
BDI	−0.626***	1			
BAI	−0.534***	0.658***	1		
Y-BOCS	−0.415***	0.440***	0.395***	1	
YGTSS	−0.211	0.170	0.117	0.191*	1

*P < .05 (2-tailed).
***P < .001 (2 tailed).

2.3.2 | Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

The SCID-I is a semi-structured interview designed to systematically diagnose the most prevalent DSM-IV Axis I disorders.[33] Research has shown excellent reliability for all disorders[34,35] and high validity.[36]

2.3.3 | Mini International Neuropsychiatric Interview (MINI), version 5.0.0

The MINI is a semi-structured interview to systematically diagnose the most prevalent DSM-IV axis I disorders.[37] Good to very good inter-rater reliability has been established[37]; sensitivity and specificity as well as test-retest reliability for all diagnoses has shown to be good, except for generalized anxiety disorder (GAD; κ = 0.36), agoraphobia (sensitivity = 0.59), and bulimia nervosa (κ = 0.53).[37-39]

2.3.4 | Beck Anxiety Inventory (BAI)

The BAI is a 21 item self-report scale designed to measure anxiety severity over the past week.[40] Items are rated on a 4-point scale ranging from 0 ("not at all") to 3 ("severe") and are added up to a total score (range 0-63). Numerous studies have supported the reliability, internal consistency and validity of this instrument.[40] In the current study, Cronbach's alpha was .91; the average score in our sample is 9.77 (SD = 9.28).

2.3.5 | Beck Depression Inventory-II (BDI-II)

The BDI-II is a self-report scale containing 21-items rated on a 4-point scale, ranging from 0 ("not at all") to 3 ("severely").[41,42] All items are added up to a total score (range 0-63) measuring severity of depressive symptoms over the past week. The internal consistency of the BDI is good to excellent.[42] Cronbach's alpha of the BDI in this study was .89; the average score in our sample is 9.64 (SD = 8.22).

2.3.6 | Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

The Y-BOCS is a 10 item (range 0-4) semi-structured interview used to assess the severity of obsessions (five items) and compulsions

(five items).[43] All items (time, distress, interference, resistance, and control measured separately for obsessions and compulsions) are added up to a total score (range 0-40). Goodman et al[44] found an excellent validity, high inter-rater reliability and internal consistency. The average score in our sample is 8.82 (SD = 8.90).

2.3.7 | Euro Qol-5D (EQ-5D)

The EQ-5D comprises five dimensions measuring QoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[45] Also, it contains a visual analogue scale (the EQ-VAS) that records the patient's self-rated health which can be used as a quantitative measure of health outcome according to the patient's own judgement. Convergent validity of the EQ-5D is moderate to strong and reliability has been found to be good; however, the EQ-5D seems to be better at detecting large than small changes in physical health.[46] Since the population in our study was relatively young with high physical health, the EQ-5D total score showed insufficient variability for the analyses in our study. Therefore, we decided to primarily use the EQ-VAS item. The wording of the EQ-VAS question is: "Please indicate on the line how good or bad your health is today." The scale ranges from 0 ("worst imaginable health") to 100 ("best imaginable health"). The EQ-VAS showed sufficient score variability, with an average score in our sample of 71.62 (SD = 17.99).

2.4 | Statistical analyses

All analyses were performed using the statistical software SPSS (version 22). A significance level of P ≤ .05 was adopted and two-tailed analyses were used. First, Pearson correlations were calculated between the BAI, BDI, Y-BOCS, YGTSS, and EQ-VAS. Second, stepwise linear regression analyses were used to analyze BAI, BDI, and Y-BOCS scores as predictors of EQ-VAS (QoL) and YGTSS (tic severity); all possible two-way interactions were calculated and added to the model, and R^2 change was evaluated for model selection. In order to evaluate the added value of each of the variables as well as the interactions separately, all variables were entered in the regression one by one according to their correlational strength with the dependent variable. Finally, PROCESS bootstrap mediation analyses were performed to test indirect effects of BAI, BDI, and Y-BOCS scores on EQ-VAS and YGTSS. To assess their effect on tic severity and QoL, variables that did not show significant effects in the linear regression were entered as predictors and variables that showed significant direct effects were entered as mediators in the bootstrap analyses.[47] The number of bootstraps was set to 50 000 with confidence intervals (CI) of 90%, 95%, and 99%. For the interpretation of the mediation effect the "index of mediation" was used, which is the completely standardized indirect effect. An index of mediation can be interpreted using Cohen's guidelines for squared correlation coefficients which defines a small, medium, and large effect as 0.01, 0.09, and 0.25.[48]

TABLE 2 Results on tic severity

Regression coefficients, β values, and P values for BDI, BAI, and Y-BOCS, as predictors of YGTSS and R^2 change for added predictors				
		YGTSS		
Predictor		**B**	**β**	**P**
Y-BOCS		.24	.20	.039
Model	**R^2**	**Adj R^2**	**R^2 change**	**P**
1: Y-BOCS	.04	.03	.04	.039
2: BDI added	.05	.03	.01	.323
3: BAI added	.05	.02	.00	.969
4: BDI*Y-BOCS added	.05	.01	.00	.665
5: BAI*Y-BOCS added	.05	.00	.00	.820
6: BDI*BAI added	.08	.02	.03	.100

Direct and indirect effects of BDI (model 1) and BAI (model 2) on YGTSS through Y-BOCS			
Model 1	**Coefficient**	**Model 2**	**Coefficient**
Direct effects		Direct effects	
BDI on Y-BOCS	0.46***	BAI on Y-BOCS	0.35***
Y-BOCS on YGTSS	0.19 NS	Y-BOCS on YGTSS	0.21*
BDI on YGTSS	0.13 NS	BAI on YGTSS	0.06 NS
Indirect effects		Indirect effects	
BDI on YGTSS through Y-BOCS	0.08 NS	BAI on YGTSS through Y-BOCS	0.08[a]
Index of mediation	0.06 NS		0.06[a]

Note: Coefficient: The change in the dependant variable with the increase of one point in the independent variable, assuming all other variables remain equal.

Abbreviation: NS, not significant.

[a]CI 99%.

*$P < .05$.

***$P < .001$.

3 | RESULTS

3.1 | Correlations

Table 1 shows correlations between anxiety severity (BAI), depression severity (BDI), OC symptom severity (Y-BOCS), tic severity (YGTSS), and QoL (EQ-VAS). All correlations between anxiety, depression, OC symptom severity, and QoL were significant, meaning that all comorbid symptoms except tic symptom severity were correlated. Depression, anxiety, and OC symptom severity were all negatively correlated with QoL, with depression severity showing the highest negative correlation with QoL ($r = -.626$), followed by anxiety severity ($r = -.534$) and OC symptom severity ($r = -.415$); tic severity did not correlate with QoL. Regarding relationships with tic severity only OC symptom severity was significantly correlated ($r = .191$), all other correlations with tic severity were not significant.

3.2 | Predictors of tic severity

As shown in Table 2, only OC symptom severity was a significant predictor of tic severity with a considerable effect ($b = .24$, $P < .05$).

Adding depression and anxiety severity did not result in a significant increase in explained variance in tic severity; that is, it did not result in a better model, leaving OC symptom severity as the only predictor of tic severity. To investigate whether OC severity scores interact with depression and anxiety severity, or if depression and anxiety severity combined act as predictors of tic severity, three interaction terms were added to the model (Table 2). However, adding interaction terms to the model did not cause a significant increase in explained variance in tic severity.

In order to test whether OC symptom severity mediates an effect of depression or anxiety severity on tic severity, two bootstrap mediation analyses were performed: a model with OC symptom severity as mediator of the effect of depression severity on tic severity (model 1) and a model with OC symptom severity as a mediator of the effect of anxiety severity on tic severity (model 2; see Table 2). In model 1, there was no indirect mediation effect of depression severity on tic severity through OC symptom severity. Interestingly, in model 2, there was a significant mediation effect of anxiety severity on tic severity through OC symptom severity, indicating that anxiety severity has a negative influence on tic severity through the negative effect on OC symptom severity (see Figure 1 for a graphical

representation of this indirect effect). With an index of mediation of 0.06 this was only a small effect.

3.3 | Predictors of QoL

As shown in Table 3 only depression severity significantly predicted QoL, with a considerable negative effect (b = −1.19, P <.001). Adding anxiety, OC symptom severity and tic severity to the model did not result in a significant improvement of the amount of variance explained by the model, leaving depression severity to be the only predictor of QoL. Adding interaction terms to the model did not yield a significant improvement of the model.

Table 3 shows the results of the bootstrap analyses with depression severity as a mediator of the effect of, respectively, OC symptom severity (model 1); anxiety severity (model 2); and tic severity (model 3) on QoL. Results indicate an effect of OC symptom severity (model 1), as well as anxiety severity (model 2) on QoL with depression severity as a mediator. The index of mediation of both effects is large with 0.32 for model 1 and 0.33 for model 2. Results showed no indirect effect of tic severity on QoL (see Figure 2 for a graphical representation of the indirect effects).

4 | DISCUSSION

In this study, the effects of OC, anxiety, and depression severity on tic severity and QoL in TD patients were investigated. This study is the first to use mediation analyses to study the combination of predictors of QoL and tic severity in concert.

In contrast to our expectations results indicate that only OC symptom severity significantly predicted tic severity. Further, OC symptoms did not interact with depression and anxiety severity, nor did they mediate the effect of depression severity on tic severity. This refines the specific role of anxiety and depression severity in TD patients and highlights the importance of OC symptoms in TD. There is a wealth of research that shows that anxiety and depression aggravate tic severity.[11,24] Our results nuance these findings by showing that this is not the result of a direct effect of anxiety or depression severity on tic severity. However, in line with our expectations we did find a small mediation effect of anxiety severity on tic severity through OC symptom severity, indicating that the more severe anxiety symptoms are, the higher the increase in OC symptom severity, resulting in higher tic severity.

We did not find a direct or indirect effect of depression severity on tic severity, nor was depression symptom severity associated with tic severity. We did find a strong correlation between depression severity and OC symptom severity, but an increase in depression severity did not result in an increase of the effect of OC symptom severity on tic severity. These findings strongly suggest that depression is more likely to be the result rather than a cause of OC symptom severity, a conclusion that should be confirmed in further studies using longitudinal data. One 2 year prospective study with between 4 and 24 measurements has specifically addressed
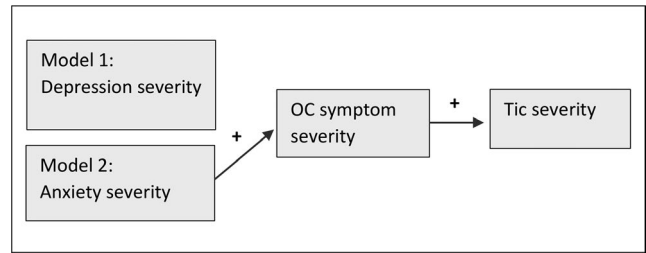

FIGURE 1 Graphic representation of the indirect effects of anxiety, OC symptom, and depression severity on tic severity. +, Positive effect

this issue: In 45 cases (age 7-17 years) with either TD, TD + OCD, or OCD, and in 41 matched controls, the temporal relationship between psychosocial stress and severity of tics, OC and depressive symptoms were studied. In line with the current study, OC symptom severity at baseline predicted future depressive symptoms. Further, and importantly, depression at baseline was an independent predictor of future tic symptom severity. Reversely, tic severity only very modestly predicted future depression. Thus, depressive symptoms in children and adolescents seem to be markers of later tic severity, rather than tic severity predisposing to later depressive symptoms.[49] In our study, the role of depression symptoms on QoL in TD was profound, showing that depression severity was a mediator of the effect of both anxiety and of OC symptom severity on QoL. This again suggests that depression in TD is a result of OC symptom and anxiety symptom disease burden, but not of tic severity.

In contrast to our expectations, depression severity rather than anxiety and OC symptom severity directly influenced QoL. However, depression severity was predicted by OC and anxiety severity and thus was a mediator in the effect on QoL. In other words, anxiety and OC symptom severity seem to result in a decrease in QoL by exacerbating depressive symptoms. These findings supplement previous findings[5,7,9] which showed that comorbid OCD was related to higher scores of depression and anxiety in patients with TD, and that in TD QoL was mostly influenced by comorbid depression and anxiety symptom severity.[28]

We did not find any direct or indirect effect of tic symptom severity on QoL. In line with this, Coffey et al[50] examined 156 young TD patients (between 5 and 20 years) on whether they needed hospitalization (as a proxy of disease severity). Of the 19 (12%) TD patients who required psychiatric hospitalization, major depression, bipolar disorder, panic disorder, and overanxious disorder were significant predictors of hospitalization, whereas tic severity only marginally predicted hospitalization. However, results of more recent studies suggest the opposite: Eddy et al[23] found impaired self-esteem and relations including lower QoL in young TD patients without comorbidity. A difference with our study is that Eddy et al defined "pure" cases as opposed to comorbid cases based on presence or absence of categorical comorbid diagnoses. As a result, TD cases with subtle or subthreshold OC, anxiety and/ or depressive symptoms below the threshold of a full comorbid diagnosis may well have been included in their group of "pure" TD cases, with the subthreshold comorbidities

TABLE 3 Results on QoL

Regression coefficients, β values, and P values for BDI, BAI, Y-BOCS, YGTSS, as predictors of EQ-VAS and R^2 change values for added interaction				
	EQ-VAS			
Predictor		**B**	**β**	**P**
BDI		−1.19	−.59	.000
Model	**R²**	**Adj R²**	**R² change**	**P**
1: BDI	.34	.33	.34	.000
2: BAI added	.37	.35	.03	.131
3: Y-BOCS added	.38	.34	.01	.543
4: YGTSS added	.38	.33	.00	.975
5: BDI*Y-BOCS added	.38	.31	.00	.883
6: BAI*Y-BOCS added	.42	.35	.04	.052
7: BDI*YGTSS added	.46	.38	.04	.104

Direct and indirect effects of Y-BOCS (model 1), BAI (model 2) and Tic severity (model 3) on EQ-VAS through BDI					
Model 1	**Coefficient**	**Model 2**	**Coefficient**	**Model 3**	**Coefficient**
Direct effects		Direct effects		Direct effects	
Y-BOCS on BDI	0.60***	BAI on BDI	0.64***	YGTSS on BDI	0.17 NS
BDI on EQ-VAS	−1.07***	BDI on EQ-VAS	−0.97***	BDI on EQ-VAS	−1.19***
Y-BOCS on EQ-VAS	−0.23 NS	BAI on EQ-VAS	−0.38 NS	YGTSS on EQ-VAS	−0.10 NS
Indirect effects		Indirect effects		Indirect effects	
Y-BOCS on EQ-VAS L through BDI	−0.64[a]	BAI on EQ-VAS through BDI	−0.62[a]	YGTSS on EQ-VAS through BDI	−0.21 NS
Index of mediation	−0.32[a]		−0.33[a]		−0.11 NS

Note: Coefficient: The change in the dependant variable with the increase of one point in the independent variable, assuming all other variables remain equal.
Abbreviation: NS, not significant.
[a]CI 99%.
*P < .05.
***P < .001.

resulting in lowered QoL. Another possible explanation of these apparent divergent results is that we examined adults, whereas Eddy et al examined children and adolescents. Especially, the adolescents may have been more prone to age-related insecurities as a result of tics than the adults of our sample. Further, our results are partly in contrast with Elstner et al[11] who found significantly lower QoL in TD patients as compared to the general population. Apparently, there

are qualitative differences in QoL between adults with persistent TD and healthy comparison subjects, with our study taking a different angle by investigating the effect of tic severity as a continuous predictor of QoL in a group of TD patients. However, in line with our findings, when comparing TD patients with high OC severity and depression scores versus low OC and depression severity scores they found that patients with high OC and depression severity had lower QoL scores. This highlights the importance of investigating
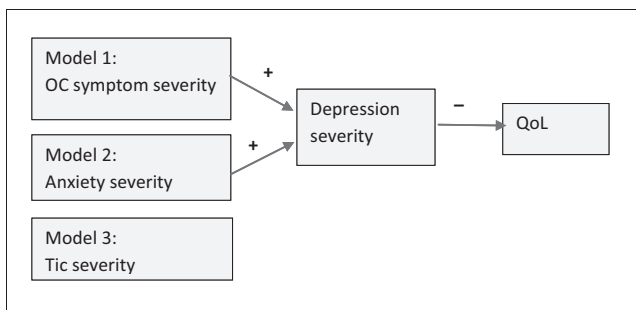

FIGURE 2 Graphic representation of the direct and indirect effects of anxiety, OC symptoms, and depression symptoms on QoL. +, Positive effect; −, Negative effect
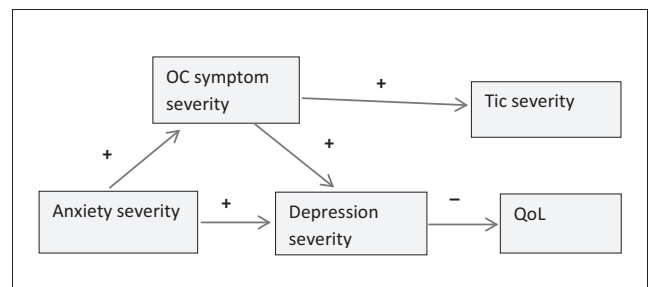

FIGURE 3 Graphic representation of a potential model combining the results of our study. +, Positive effect; −, Negative effect

comorbidities in TD in concert to unravel their combined effect on QoL.

The results of this study suggest that several mediators differentially form a network of anxiety, depression, and OC symptom severity influencing QoL in TD. Figure 3 shows what this network could look like. OC symptom severity seems to be crucial for the final outcomes on both tic severity and QoL. However, this full model cannot be tested using only mediation analyses but needs to be estimated using other statistical approaches, like structural equation modeling or network analyses. Our results merely show the structure of the mutual effects of the comorbidities, tic severity and QoL. Even though our results may reflect causal relations, extension of cross-sectional data to a longitudinal data approach is warranted to establish causal relationships. Prospective longitudinal studies can shed more light on the direction of the relationship between tic severity, anxiety, and depression.

4.1 | Limitations

Our study has several limitations. First, for the assessment of anxiety and depression symptom severity and QoL, only self-report instruments were used. Further, the data of this study are cross-sectional, and therefore directions of predictive effects are estimated in regression models, and may not necessarily reflect causality. Also, our study did not include a disorder-specific QoL measurement, and therefore may be unable to detect subtle and disorder related domains of QoL. And lastly this study did not take into account ADHD symptoms, although ADHD represents an important source of comorbidity both in children and adults, and earlier studies have reported ADHD symptoms to influence tic severity and QoL.[6,7,18,23]

4.2 | Implications for clinical practice and suggestions for future research

Our findings are of great importance for treatment of adult TD patients when it comes to improving QoL. Since tic severity was not predictive of QoL and has been only marginally predictive in other studies, treatment should focus predominantly on OC symptoms and depression, rather than on tic reduction; especially reduction of OC symptoms might be more important in contributing to decrease of tic severity than direct tic treatments, although this important issue has not been investigated in direct comparative prospective studies. Regarding the high percentage of comorbidities in clinical patients with TD, our results show that instead of focusing on diagnostic boundaries of disorders, much more attention should be given to the dynamics between symptoms across disorders. Furthermore, future studies should include ADHD symptoms in modeling their relationship with QoL in TD patients. Finally, in order to test causal relationships between symptoms, longitudinal studies in sufficiently large samples are needed.

To conclude, this study extends previous research and provides potential explanations for previous inconsistencies in the literature on the effects of OC symptom severity, anxiety, and depression severity on tic severity and QoL. Investigating the mutual relationships of the various comorbid symptoms in TD has provided more insight in the complex and crucial role of OC symptom severity on longer term TD outcome.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

In order to protect the privacy of the participating patients the data has not been made public.

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APPENDIX 1

Comorbid mental disorders in participants with TD (Measured with MINI, SCID, or Clinical Interview)

	Frequencies of mental disorders	
	TD participants	
	Current	Past
Disorders	n (%)	n (%)
Anxiety disorder	75 (50)	7 (4)
OCD	57 (38)	-
PTSD	5 (3)	-
GAD	25 (17)	-
Social phobia	21 (14)	-
Panic disorder		
With agoraphobia	5 (3)	2 (1)
Without agoraphobia	8 (5)	5 (3)
Agoraphobia	-	-
Hypochondria	2 (1)	-
Specific phobia[a]	16 (11)	-
Mood disorder	37 (25)	32 (21)
Depression	27 (18)	30 (20)
Depression with melancholic features	5 (3)	-
Dysthymia	7 (5)	-
Bipolar 1	1 (<1)	-
Bipolar 2	1 (<1)	-
Hypomania episode	-	2 (1)
Manic	-	-
Dependency and abuse	19 (13)	12 (8)

	Frequencies of mental disorders	
	TD participants	
	Current	Past
Disorders	n (%)	n (%)
Substance abuse and dependency	19 (13)	10 (7)
Abuse	8 (5)	4 (3)
Alcohol	6 (4)	3 (2)
Drugs	2 (1)	2 (1)
Dependency	14 (9)	8 (5)
Alcohol	9 (6)	3 (2)
Drugs	6 (4)	7 (5)
Drug induced disorders	-	3 (2)
Eating disorders	4 (3)	1 (<1)
Anorexia nervosa	1 (<1)	1 (<1)
Bulimia nervosa	1 (<1)	1 (<1)
Binge eating disorder	2 (1)	-
Other disorders	6 (4)	2 (1)
Psychotic disorders	1 (<1)	-
Psychotic disorder NAO	1 (<1)	1 (<1)
Cyclothymia	1 (<1)	-
Undifferentiated Somatoform disorder	-	-
Pain disorder	1 (<1)	-
Impulse control disorders[a]	2 (1)	1 (<1)

[a]Diagnoses were only assessed in the SCID but not in the MINI.