Anxiety Symptoms Differ in Youth With and Without Tic Disorders

Jennifer Vermilion[1,9], Carolina Pedraza[2], Erika F. Augustine[1], Heather R. Adams[1], Amy Vierhile[1], Adam B. Lewin[3], Alyssa T. Collins[4], Michael P. McDermott[5], Thomas O'Connor[6], Roger Kurlan[7], Edwin van Wijngaarden[8], Tanya K. Murphy[3], Jonathan W. Mink[1]

[1]Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA

[2]Byram Hills High School, Armonk, NY, USA

[3]Department of Pediatrics, University of South Florida, Tampa, FL, USA

[4]Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA

[5]Department of Biostatistics and Computational Biology, University of Rochester Medical Center, Rochester, NY, USA

[6]Department of Psychiatry, University of Rochester Medical Center, Rochester, NY, USA

[7]Center for Neurological and Neurodevelopmental Health, Voorhees, NJ, USA

[8]Department of Public Health Sciences, University of Rochester Medical Center, Rochester, NY, USA

[9]Division of Child Neurology, Department of Neurology, Box 631, 601 Elmwood Ave, Rochester, NY 14642, USA

Abstract

We compared anxiety symptoms in youth with and without tic disorders by comparing scores on the Multidimensional Anxiety Scale for Children (MASC) in youth with tic disorders to those in a concurrent community control group and in a group of treatment-seeking anxious youth from the Child/Adolescent Anxiety Multimodal Study (CAMS). Data from 176 youth with tic disorders, 93 control subjects, and 488 CAMS participants were included. Compared to youth with tic disorders, controls had lower total MASC scores (p < 0.0001) and CAMS participants had similar total MASC scores (p = 0.13). Separation Anxiety (p = 0.0003) and Physical Symptom (p < 0.0001) subscale scores were higher in youth with tic disorders than in CAMS participants. We conclude that the anxiety symptom profile differs in youth with and without tic disorders, which may have important implications for targeting treatment of anxiety in youth with tic disorders.

Keywords

Tics; Tourette; Anxiety; Separation anxiety

✉ Jennifer Vermilion, jennifer_vermilion@urmc.rochester.edu.

Introduction

Chronic tic disorders (CTDs) such as Tourette syndrome (TS) are common, affecting 1–3% of youth [1]. Anxiety disorders are diagnosed in approximately half of individuals with a CTD [2–4]. The proportion of individuals with a CTD impacted by anxiety symptoms is likely even greater than these estimates; patients who do not meet criteria for formal diagnosis of an anxiety disorder may nonetheless have impairing anxiety symptoms [5–7]. For example, in a sample of youth with TS, fewer than 2% met formal diagnostic criteria for a diagnosis of separation anxiety disorder based on interview but over 30% met the criterion for clinical significance of these symptoms [7] based on the Multidimensional Anxiety Scale for Children (MASC) [8].

It is not known if anxiety in CTDs differs from anxiety in the general pediatric population. For example, in childhood anxiety disorders not associated with tics, separation anxiety decreases with age, and social phobia becomes more prevalent [9–11]. However, we do not know if this same age-related transition occurs in youth with CTDs. There is evidence that other psychiatric comorbidities manifest differently in CTDs. For example, obsessive-compulsive disorder (OCD) differs phenotypically between patients with and without tics [12–14]. Patients with tics report more tapping, rubbing, and touching compulsions while non-tic patients report more cleaning compulsions [12]. There are also treatment implications for these distinctions as the presence of tics in OCD may moderate response to OCD treatment [15–17]. Similar studies comparing the phenotype of anxiety in patients with vs. without tics have not been done, but we hypothesize that anxiety differs between patients with and without tics. In a study of anxiety symptoms in boys with ADHD, the presence of comorbid tics was associated with differences in anxiety symptoms [18]. Individuals with tics had increased separation anxiety severity compared to those without tics.

Whether tic-related anxiety is distinct from non-tic-related anxiety has not been fully assessed in the tic disorder population. Prior estimates of anxiety prevalence in tic disorders have focused on individuals meeting diagnostic criteria for specific anxiety disorders. This approach likely misses individuals with sub-threshold symptoms or symptom combinations that may still be impairing [5–7, 19]. The concept of framing anxiety as a spectrum disorder rather than as discrete categorical diagnoses is consistent with the NIMH-initiated Research Domain Criteria (RDoC) Framework [20]. We set out to evaluate anxiety symptoms in youth with tic disorders and to evaluate if youth with tics have a similar anxiety symptom profile to that in youth without tics. We hypothesized that, compared to community control subjects, youth with tic disorders would have greater anxiety symptom severity. We further hypothesized that, compared to treatment-seeking youth with anxiety disorders but without tic disorders, youth with tic disorders would have lower anxiety symptom severity since the tic disorder sample was not selected for presence of anxiety disorders.

Method

We conducted the Centers for Disease Control (CDC) Tic Impact Study, a cross-sectional study of children with tic disorders, community control children, and their caregivers at the

University of Rochester (UR; Rochester, New York) and the University of South Florida (USF; St. Petersburg, Florida). Both sites are tertiary care centers for individuals with tic disorders. Each site submitted independent applications to the CDC and were awarded cooperative agreements. Although both sites collaborated to align study plans, some aspects of the study differed. The study design and data collection methods have been published [21]. Local IRB approval was obtained at both sites prior to subject recruitment and enrollment (UR RSRB#30985; USF IRB# 09–0209). Parent permission, parent consent, and child assent were obtained for each participant.

The following sections describe methods specific to the evaluation of anxiety symptom severity. As a comparison, we evaluated archival data on baseline anxiety symptom severity from the Child/Adolescent Anxiety Multimodal Study (CAMS), the largest randomized controlled treatment trial of pediatric anxiety. This study compared cognitive behavioral therapy (CBT), sertraline, the combination, or placebo in a sample of 488 treatment-seeking youth with anxiety disorders [22]. CAMS study data were available through the National Institute of Mental Health (NIMH) data archive.

Subjects

At UR, subjects with TS were recruited in-person at clinic visits or by mail. Children and adolescents ages 8–18 years with a physician-confirmed diagnosis of TS by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [23] criteria were included, per the diagnostic criteria current at the time of the study. Community control subjects were recruited at UR by distributing study recruitment materials at local pediatric practices, community organizations, and local websites. At USF, subjects with a clinician-confirmed tic disorder for at least 6 months by DSM-IV-TR criteria were recruited in-person at clinic visits. The majority of participants at UR and USF had TS. At both sites, recruitment information was also distributed at local Tourette Association of America chapter events. Control subjects were not enrolled at USF. Demographics of subjects with tic disorders recruited at the two study sites were similar [21].

The CAMS trial enrolled youth ages 7–17 years who met DSM-IV-TR criteria for separation anxiety disorder, social phobia, or generalized anxiety disorder (GAD) with clinically significant anxiety who were seeking anxiety treatment but were not on an anti-anxiety medication at the time of enrollment. Detailed eligibility criteria have been published [22].

Study Measures

In our cross-sectional study, participation at both sites involved a single research visit consisting of structured and semi-structured interviews, child and parent self-report assessments, and parent proxy-report assessments. Diagnosis of comorbid GAD was determined in accordance with the DSM-IV-TR criteria using the Columbia Diagnostic Interview Schedule for Children-Fourth Edition (C-DISC-IV) [24]. GAD was considered present if criteria were met by either parent or child report. Formal diagnoses of separation anxiety disorder and social phobia were not made as we did not administer these modules. Anxiety symptom severity was measured with the MASC [8], a child self-report instrument that evaluates for the presence and severity of a wide spectrum of anxiety symptoms. It

comprises multiple subscales including Physical Symptoms, Harm Avoidance, Separation Anxiety, and Social Phobia (Table 1). Raw scores were age- and sex-normalized to T scores (mean = 50, standard deviation (SD) = 10). Higher scores reflect greater symptom severity, and T scores 65 are consistent with "elevated" scores that suggest clinically significant problems in relation to peers of the same age and sex. In the CAMS trial, subjects completed the MASC at their baseline evaluation.

Tic symptom severity was measured by the Yale Global Tic Severity Scale (YGTSS) for tics [25], a validated, clinician-administered assessment of tic severity over the past week. The Total Tic Score (TTS; range 0–50) measures motor and phonic tic severity over the previous week; higher scores indicate greater severity. OCD symptom severity was measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) for OCD [26]. The CY-BOCS is reliable and valid clinician-administered, semi-structured tool that assesses OCD symptom severity over the past week [26]. Scores range from 0 to 40, with higher scores reflecting greater symptom severity. Global function was measured by the Children's Global Assessment Scale (CGAS) [27], a clinician rating of overall functioning. Scores range from 1 to 100, with higher scores indicating better function. CY-BOCS scores were not available in the CAMS trial database.

Statistical Analysis

Subjects were categorized into the tic disorder, community control or CAMS groups. Data from USF and UR tic disorder subjects were combined for all analyses involving the "tic disorder" group. Demographic variables were compared between groups using Wilcoxon rank sum tests or χ^2 tests, as appropriate. Age was rounded to the nearest integer. Comparisons between the tic disorders and control groups and between the tic disorders and CAMS groups with respect to MASC total and subscale scores were performed using Wilcoxon rank sum tests, with adjustment for multiple comparisons using Holm's method [28]. Group comparisons with respect to the proportions of subjects with MASC total T scores above the clinically significant threshold (T 65) were performed using χ^2 tests. MASC total and subscale scores were also compared between children (age < 13) and adolescents (age 13) separately in the tic disorder and CAMS groups using Wilcoxon rank sum tests, with adjustment for multiple comparisons using Holm's method.

Comparisons between the tic disorder and CAMS groups with respect to MASC total and subscale scores were similarly performed separately in children and adolescents using Wilcoxon rank sum tests, with adjustment for multiple comparisons using Holm's method. Bivariate correlation analyses were used to evaluate relationships among continuous variables (age, anxiety severity, tic severity, OCD severity, global function) in the tic disorders group. Analyses were performed using JMP Pro 14.0.

Results

Study participants

The MASC was completed by 176 youth with tic disorders and 93 control subjects enrolled in the CDC Tic Impact Study and 488 CAMS trial participants (Table 2). The median age

was 11 years in each group. There were more boys in the tic disorder group (75%) than in the community control (60%) or CAMS trial (50%) groups.

Anxiety in Youth with Tic Disorders Compared to Community Control Subjects

Of those participants who completed the MASC, 15.3% (n = 27) of youth with tic disorders and 2.2% (n = 02) of control youth had GAD based on the C-DISC-IV (p = 0.009). Youth with tic disorders reported greater overall anxiety symptom severity compared to community control subjects. The median total MASC scores were 52.0 (interquartile range (IQR) 45.5–61.0) in youth with tic disorders and 46.0 (IQR 38.0–52.0) in community control subjects (p < 0.0001; Fig. 1). Youth with tic disorders also reported higher symptom severity than community control subjects in the Physical Symptom (p < 0.0001), Social Phobia (p < 0.0001), and Separation Anxiety (p < 0.0001) domains (Table 3). Youth with tic disorders reported lower anxiety severity than community control subjects in the Harm Avoidance domain (p = 0.02). There was a significantly greater proportion of subjects in the tic disorder group (15.9%, n = 28) with a MASC total T score 65 compared to the community control group (3.2%, n = 03) (p = 0.002). Of those tic disorder subjects with MASC total T score 65, only 8 (28.6%) had GAD based on the C-DISC-IV.

Youth with tic disorders had worse clinician-rated global function than community control subjects. The median global function score (CGAS) was 60 (interquartile range (IQR) 52–65) in youth with tic disorders and 81 (IQR 63–90) in community control subjects (p < 0.0001). Higher anxiety severity was weakly but significantly associated with worse global function in the tic disorder group (r = 0.14, p = 0.02). In those individuals with tic disorders and clinically significant MASC scores (total MASC 65), anxiety severity was negatively correlated with global function (r = − 0.35, p = 0.05).

Anxiety, OCD and Tic Severity in Youth with Tic Disorders

Youth with tic disorders had a mean YGTSS TTS score of 21.8 (SD 9.4), representing moderate severity. Tic severity was positively correlated with overall anxiety symptom severity (r = 0.24, p = 0.0007). Tic severity was also associated with symptom severity in the Physical Symptoms (r = 0.30, p < 0.0001; Fig. 2) and Social Phobia (r = 0.20, p = 0.006) domains. Tic severity was not associated with Harm Avoidance (r = − 0.04, p = 0.41) or Separation Anxiety (r = 0.10, p = 0.08) symptom severities.

Youth with tic disorders had a median total CY-BOCS score of 13.0 (IQR 4.0–20.0), indicating a mild but clinically significant degree of OCD severity. OCD severity was associated with both anxiety severity (r = 0.33, p < 0.0001) and tic severity (r = 0.24, p = 0.0004).

Anxiety in Youth with Tic Disorders Compared to Treatment-seeking Anxious Youth

Table 4 provides the MASC total and subscale scores for the tic disorder and CAMS participant groups. Youth with tic disorders had similar total MASC scores as the CAMS participants (p = 0.13, Fig. 1). Youth with tic disorders had higher symptom severity compared to the CAMS participants in the Physical Symptoms (p < 0.0001) and Separation Anxiety (p = 0.0003) domains. Harm Avoidance symptom severity was higher in the CAMS

trial group compared to the tic disorder group (p < 0.0001). Youth with tic disorders and CAMS participants did not significantly differ with respect to Social Phobia symptom severity (p = 0.06). The proportions of subjects with a MASC total score of at least 65 were similar in the tic disorder group (13.6%, n = 24) and the CAMS participants (14.3%, n = 70; p = 0.82).

Associations Between Age and Anxiety Symptoms in Youth with Tic Disorders

Age and anxiety symptom severities were not related in the tic disorders group. There was no relationship between age and MASC total score (r = − 0.08, p = 0.91). There were also no relationships between age and the Physical Symptoms (r = − 0.08, p = 0.94), Harm Avoidance (r = − 0.08, p = 0.84), Social Phobia (r = − 0.04, p = 0.44), or Separation Anxiety (r = − 0.08, p = 0.99) domains. In youth with tic disorders who had clinically significant anxiety (MASC total T score 65), half of individuals (n = 14) were children (age under 13 years), and half (n = 14) were adolescents (age 13 years and older).

Table 5 provides MASC scores for children and adolescents with tic disorders. Children with tic disorders had similar total and subscale MASC scores compared to adolescents with tic disorders.

Associations Between Age and Anxiety Symptoms in Treatment-Seeking Anxious Youth

There were generally weak relationships between age and anxiety symptom severity in the CAMS group. Older age was associated with worse MASC total scores (r = 0.14, p = 0.002). Older age was also associated with higher Physical Symptoms severity (r = 0.17, p < 0.0001) and higher Social Phobia severity (r = 0.39, p < 0.0001). Younger age was negatively correlated with Harm Avoidance symptom severity (r = − 0.1, p = 0.01) and Separation Anxiety severity (r = − 0.17, p < 0.0001).

Table 5 also provides MASC scores for children and adolescents in the CAMS trial. Treatment-seeking anxious children from the CAMS trial had worse Separation Anxiety scores (p = 0.0009) and lower total MASC (p < 0.0001), Physical Symptoms (p < 0.0001), and Social Phobia (p < 0.0001) scores than adolescents in the CAMS trial. Children and adolescents in the CAMS trial had similar Harm Avoidance scores (p = 0.15).

Anxiety in Youth with Tic Disorders Compared to Treatment-Seeking Anxious Youth in Both Children and Adolescents

When comparing children with tic disorders to children in the CAMS trial (Table 5), the groups did not differ significantly with respect to the Separation Anxiety score (p = 0.07). Children with tic disorders had higher severity in the total MASC score (p = 0.01) and scores in the Physical Symptoms (p < 0.0001) and Social Phobia (p < 0.0001) domains but lower symptom severity in the Harm Avoidance domain (p < 0.0001) compared to children from the CAMS trial.

When comparing adolescents with tic disorders to adolescents in the CAMS trial (Table 5), the groups did not differ significantly with respect to the total MASC score (p = 0.35) and the Physical Symptoms domain (p = 0.39). Adolescents with tic disorders had higher

severity in the Separation Anxiety (p = 0.0005) domain and lower severity in the Harm Avoidance (p = 0.01) and Social Phobia (p = 0.002) domains compared to adolescents in the CAMS trial.

Discussion

Our study compared anxiety symptom severity in a sample of youth with tic disorders to both a community control sample and to a previously published sample of treatment-seeking youth with anxiety disorders (CAMS participants). We found that youth with tic disorders had significantly greater anxiety severity compared to youth from the community. This difference was less than one standard deviation, which may suggest it is not a highly clinically meaningful difference. However, there was also a greater proportion of subjects in the tic disorder group compared to the community control group with clinically significant anxiety severity scores. Youth with tic disorders and CAMS participants had overall similar anxiety symptom severity, and both groups had a similar proportion of subjects with total MASC scores suggesting clinically significant anxiety. Separation anxiety severity was similar between children and adolescents with tic disorders, but it was significantly lower in adolescents compared to children from the CAMS trial. Although this is a cross-sectional study and not longitudinal, this may suggest that, in tic-related anxiety, separation anxiety symptoms may persist into adolescence.

In our sample, there was a weak but significant relationship between tic severity and anxiety symptom severity. Conelea et al. evaluated 232 youth with CTDs and found a stronger relationship between anxiety symptom severity and tic severity (r = 0.55, p < 0.01) [29]. This stronger association may be related to different measurement tools: Conelea et al. developed a child-reported tic scale to measure tic severity rather than the clinician-rated YGTSS that we used in this study. Children who are highly anxious may be more aware of, and more bothered by, their tics so may rate tic severity as higher. Despite the weak relationship between anxiety and tic severity that we found, there does seem to be a relationship between tic severity and anxiety. For example, anxiety disorders, particularly separation anxiety, have been associated with increased tic severity [3]. In addition, state anxiety—a heightened sense of anxiety in response to a stressor—is associated with worsened tics [30].

Our study also found a weak but significant relationship between total MASC score and clinician-rated global function in our sample of youth with tic disorders. This relationship was stronger when excluding subjects below the threshold for clinically significant symptom severity. This may suggest that, while minimal or mild anxiety symptoms may not contribute significantly to global function, greater anxiety symptom severity does affect overall function. It is also possible that we do not see a relationship between anxiety and overall function because individuals with tic disorders often have multiple other factors that can contribute to function (i.e., other comorbid psychiatric disorders), which we did not control for in this study. In addition, anxiety symptoms may contribute more significantly to specific aspects of function (i.e., school or social) rather than global function. For example, youth with GAD tend to have better social function than youth with separation anxiety disorder [31]. It is also possible that specific anxiety symptoms contribute more significantly to

global function rather than overall anxiety severity. In this study, we did not do a factor analysis of specific anxiety symptoms or evaluate context-specific function. Therefore, future studies focused on specific symptoms and functional impairment are needed to explore these questions.

We assessed anxiety as a dimensional measurement, focusing on symptom severity rather than specific diagnoses. Taking a dimensional approach to evaluating anxiety is important because youth with clinically significant anxiety symptoms may not meet criteria for a specific anxiety disorder. For example, we found that the majority of tic disorder subjects with clinically significant total anxiety severity did not meet diagnostic criteria for GAD, the most common anxiety disorder reported in youth with tic disorders. Using the MASC, Marwitz et al. took a similar approach when evaluating the benefit of screening for anxiety in a clinic sample of 126 youth with tic disorders [7]. Mean total and specific subscale scores were similar to those in our sample of youth with tics, with the exception of the Harm Avoidance subscale [7]. As in the current study, Marwitz et al. found the highest severity scores for the Separation Anxiety domain. In contrast, Harm Avoidance severity was higher (by more than 10 points) in Marwitz et al. compared to the current sample of youth with tic disorders. The reason for this difference is unclear but may be related to problems with the scale itself. The Harm Avoidance domain on the MASC has lower internal reliability than the other scales and is not predictive of one specific anxiety disorder [32, 33].

Other studies assessing anxiety in tic disorders have reported that anxiety is more common in individuals with tic disorders than in the general population. In a community-based study evaluating behavioral symptoms in tic disorders, diagnoses of overanxious disorder, social phobia, and separation anxiety disorder were significantly more common in youth with tics compared to youth without tics [2]. Indeed, individuals with tic disorders have increased rates of anxiety disorders throughout life. The estimated lifetime risk of anxiety disorders in TS is 36%, and the estimated lifetime risk is 62% in individuals with comorbid OCD [34]. Children with tic disorders tend to have an earlier age at onset of anxiety, with the high-risk age at onset starting at 4 years and continuing into adolescence [34].

Based on previous studies, we expected anxiety severity to be increased in youth with tic disorders compared to children from the community. However, we were surprised to find that youth with tic disorders had overall total anxiety severity similar to that of the CAMS participants. Our sample of youth with tic disorders was not selected for comorbid anxiety and were not seeking treatment for anxiety. In the CAMs trial, a diagnosis of GAD, social phobia or separation anxiety disorder was required for inclusion and participants were seeking treatment. Our tic disorder sample had worse Physical Symptoms and Separation Anxiety domain scores than the CAMS participants. Although these differences are statistically significant, it is not clear if they are clinically meaningful because a minimal clinically significant difference has not been established for the MASC. However, these findings suggest that, while overall anxiety symptom severity may be similar, the anxiety phenotype may differ between youth with vs. without tic disorders. For example, in childhood anxiety disorders not associated with tics, separation anxiety typically improves with age and social phobia becomes more prevalent [9–11]. Data from the CAMS cohort support this finding: Separation Anxiety severity was higher in the child group compared

to the adolescent group, and Social Phobia severity was higher in the adolescent group compared to the child group. However, this same age-related difference was not seen in youth with tic disorders. In our tic disorder sample, Social Phobia and Separation Anxiety severities were similar in the child and adolescent groups. Social Phobia severity was higher in children with tics compared to children from the CAMS trial. Higher Social Phobia in children with tics may be related to embarrassment over tics. On average, tic disorders start around 7 years of age and are often most severe around ages 10–12 years [35]. Thus, while clinician-rated tic severity was not correlated with Social Phobia severity, children may experience embarrassment over their tics, regardless of tic severity.

Although the relationship between the pathophysiologies of anxiety and tics is not well understood, the severities of anxiety symptoms and tics may be related [3, 7, 36–38]. Youth with severe tic disorders are more likely to have at least one anxiety disorder [3]. In particular, a diagnosis of separation anxiety disorder has been shown to most strongly predict tic severity [3, 38]. In our study, we found a weak but positive relationship between severity of anxiety symptoms and tic severity; a similar relationship was demonstrated in the Marwitz et al. study [7]. These findings suggest that, while there is a relationship between anxiety and tic severity, other factors contribute to anxiety in youth with tic disorders.

Study limitations should be recognized. First, our tic disorder group was recruited from tertiary care centers which may affect the generalizability of our tic disorder sample to the general tic disorder population. Second, this study was cross-sectional so we are not able to draw any conclusions on the longitudinal nature of anxiety symptoms. The results of the analyses concerning the relationship between age and anxiety symptoms should be interpreted with this in mind. Third, anxiety severity was based on child self-report alone. Relying only on self-report may underestimate the severity of anxiety symptoms. Only 14.3% of CAMS participants had total MASC scores 65 and 60% of CAMS participants had a score 65 in at least one domain. However, to be eligible for the trial, CAMS participants had to have anxiety severity significant enough to warrant treatment, based on an Anxiety Disorders Interview Schedule Clinical Severity Rating of at least 4. Parent-child agreement on the MASC tends to be low, but each informant provides valuable and unique information; thus, inclusion of multiple informants would strengthen the study [39]. This may also suggest that the cutoffs for MASC scores may miss some individuals with clinically significant anxiety disorders. Finally, our anxiety disorder control group was drawn from previously published data and was not a concurrent sample. The studies were conducted in different years: the CAMS trial ran from 2003 to 2008 while our study took place from 2010 to 2012. Since rates of anxiety disorders have increased in youth over time [40], it is possible that this may affect our ability to compare these groups. In addition, the CAMS participants had been enrolled in a clinical trial, so this group may not be representative of those with pediatric anxiety disorders in the general population.

Despite these limitations, these findings do provide interesting and important information regarding anxiety symptoms in youth with tic disorders. Prior studies suggest that anxiety in tic disorders can be severe and cause significant impairment for affected youth [33, 41]. Tics often improve by young adulthood, but anxiety may persist [42] and even increase over time [43]. In the general population, childhood-onset anxiety disorders are associated with

Author Manuscript

low overall function and increased future suicidality [44]. It is important to identify and treat anxiety in youth with tic disorders early in the course. As suggested in the CAMS study, identifying the specific underlying disorder diagnosis may be important for determining treatment and prognosis. Clinicians treat anxiety in tic disorders as they would in individuals without tics, but a more targeted treatment approach may lead to better outcomes, as already seen for treatment of tic-related OCD [15, 16].

The current results suggest that anxiety symptoms in youth with tic disorders are common, can be severe and may differ from that of anxiety in the general population. These results may have important clinical implications. For example, they underscore the importance of screening for anxiety symptoms in every child with a tic disorder to determine who may benefit from anxiety treatment. While specific treatment recommendations based on these findings would be speculative and premature at this time, but these findings do highlight the importance of further investigation into the topic. For example, studies of treatments for anxiety specifically in the tic disorder population may be warranted. Prior to designing treatment studies for anxiety in youth with tic disorders, it is important to first address some of the limitations discussed above. Future studies of anxiety in youth with tic disorders should incorporate multiple informants to measure anxiety symptoms, include a concurrent control sample of anxious youth without tics, and follow the natural history over time to broaden our understanding of tic-related anxiety.

Summary

Overall, we found that youth with tic disorders have higher total anxiety symptom severity compared to youth from the community, and similar total anxiety symptom severity compared to treatment-seeking anxious youth (CAMS participants). However, there were differences in the severity of symptom subscales between the tic disorder and CAMS groups. The tic disorder group had higher Separation Anxiety and Physical Symptoms scores compared to the CAMS group. In addition, while older age was associated with lower Separation Anxiety and higher Social Phobia subscale scores in the CAMS group, these age-related relationships were not seen in the tic disorder group. These findings suggest that the anxiety symptom phenotype may differ in youth with and without tic disorders, which may have implications for targeting anxiety treatment in youth with tic disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

References

1. Knight T, Steeves T, Day L, Lowerison M, Jette N, Pringsheim T (2012) Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr Neurol 47:77–90 [PubMed: 22759682]

2. Kurlan R, Como PG, Miller B, Palumbo D, Deeley C, Andresen EM, Eapen S, McDermott MP (2002) The behavioral spectrum of tic disorders: a community-based study. Neurology 59:414–420 [PubMed: 12177376]

3. Coffey BJ, Biederman J, Smoller JW, Geller DA, Sarin P, Schwartz, Kim GS (2000) Anxiety disorders and tic severity in juveniles with Tourette's disorder. J Am Acad Child Adolesc Psychiatry 39:562–568 [PubMed: 10802973]

4. Bitsko RH, Holbrook JR, Visser SN, Mink JW, Zinner SH, Ghandour RM, Blumberg SJ (2014) A national profile of Tourette syndrome, 2011–2012. J Dev Behav Pediatr 35:317–322 [PubMed: 24906033]

5. Safer DJ, Rajakannan T, Burcu M, Zito JM (2015) Trends in sub-threshold psychiatric diagnoses for youth in community treatment. JAMA Psychiatry 72:75–83 [PubMed: 25426673]

6. Lewinsohn PM, Shankman SA, Gau JM, Klein DN (2004) The prevalence and co-morbidity of subthreshold psychiatric conditions. Psychol Med 34:613–622 [PubMed: 15099416]

7. Marwitz L, Pringsheim T (2018) Clinical utility of screening for anxiety and depression in children with tourette syndrome. J Can Acad Child Adolesc Psychiatry 27:15–21 [PubMed: 29375629]

8. March JS, Parker JD, Sullivan K, Stallings P, Conners CK (1997) The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. J Am Acad Child Adolesc Psychiatry 36:554–565 [PubMed: 9100431]

9. Waite P, Creswell C (2014) Children and adolescents referred for treatment of anxiety disorders: differences in clinical characteristics. J Affect Disord 167:326–332 [PubMed: 25016489]

10. Weems CF, Costa NM (2005) Developmental differences in the expression of childhood anxiety symptoms and fears. J Am Acad Child Adolesc Psychiatry 44:656–663 [PubMed: 15968234]

11. Kendall PC, Cummings CM, Villabo MA, Narayanan MK, Treadwell K, Birmaher B, Compton S, Piacentini J, Sherrill J, Walkup J, Gosch E, Keeton C, Ginsburg G, Suveg C, Albano AM (2016) Mediators of change in the Child/Adolescent Anxiety Multimodal Treatment Study. J Consult Clin Psychol 84:1–14 [PubMed: 26460572]

12. Holzer JC, Goodman WK, McDougle CJ, Baer L, Boyarksky BK, Leckman FJ, Price LH (1994) Obsessive-compulsive disorder with and without a chronic tic disorder. A comparison of symptoms in 70 patients. Br J Psychiatry 164:469–473 [PubMed: 8038934]

13. de Vries FE, Cath DC, Hoogendoorn AW, van Oppen P, Glas G, Veltman DJ, van den Heuval OA, van Balkom AJ (2016) Tic-related versus tic-free obsessive-compulsive disorder: clinical picture and 2-year natural course. J Clin Psychiatry 77:e1240–e1247 [PubMed: 27631146]

14. George MS, Trimble MR, Ring HA, Sallee FR, Robertson MM (1993) Obsessions in obsessive-compulsive disorder with and without Gilles de la Tourette's syndrome. Am J Psychiatry 150:93–97 [PubMed: 8417588]

15. Masi G, Pfanner C, Brovedani P (2013) Antipsychotic augmentation of selective serotonin reuptake inhibitors in resistant tic-related obsessive-compulsive disorder in children and adolescents: a naturalistic comparative study. J Psychiatr Res 47:1007–1012 [PubMed: 23664673]

16. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF (2006) A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry 11:622–632 [PubMed: 16585942]

17. Skarphedinsson G, Compton S, Thomsen PH, Weidle B, Dahl K, Nissen JB, Torp NC, Hybel K, Melin KH, Valderhaug R, Wentzel-Larsen T, Ivarsson T (2015) Tics moderate sertraline, but not cognitive-behavior therapy response in pediatric obsessive-compulsive disorder patients who do not respond to cognitive-behavior therapy. J Child Adolesc Psychopharmacol 25:432–439 [PubMed: 26091197]

18. Schneider J, Gadow KD, Crowell JA, Sprafkin J (2009) Anxiety in Boys with Attention-Deficit/Hyperactivity Disorder with and without Chronic Multiple Tic Disorder. J Child Adolesc Psychopharmacol 19:737–748 [PubMed: 20035592]

19. Rozenman M, Johnson OE, Chang SW, Woods DW, Walkup JT, Wilhelm S, Peterson A, Scahill L, Piacentini J (2015) Relationships between premonitory urge and anxiety in youth with chronic tic disorders. Child Health Care 44:235–248 [PubMed: 27110050]

20. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Saniislow C, Wang P (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 167:748–751 [PubMed: 20595427]

21. Augustine EF, Adams HR, Bitsko RH, van Wijngaarden E, Claussen AH, Thatcher A, Hanks CE, Lewin AB, O'Connor TG, Vierhlie A, Danielson ML, Kurlan R, Murphy TK, Mink JW (2017) Design of a multisite study assessing the impact of tic disorders on individuals, families, and communities. Pediatr Neurol 68:49–58 [PubMed: 28254245]

22. Compton SN, Walkup JT, Albano AM, Piacentini JC, Birmaher B, Sherrill JT, Gnisburg GS, Rynn MA, McCracken JT, Waslick BD, Iyengar S, KEndall PC, March JS (2010) Child/Adolescent Anxiety Multimodal Study (CAMS): rationale, design, and methods. Child Adolesc Psychiatry Ment Health 4:1 [PubMed: 20051130]

23. American Psyciatric Association (2000) Diagnostic and statistical manual of mental disorder, 4th edn. American Psychiatric Association, Washington

24. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000) NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 39:28–38 [PubMed: 10638065]

25. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ (1989) The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 28:566–573 [PubMed: 2768151]

26. Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, Cicchetti D, Leckman JF (1997) Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 36:844–852 [PubMed: 9183141]

27. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S (1983) A children's global assessment scale (CGAS). Arch Gen Psychiatry 40:1228–1231 [PubMed: 6639293]

28. Holm S (1979) A simple sequentially rejective multiple test procedure. Scand J Stat 6:65–70

29. Conelea CA, Woods DW, Zinner SH, Budman C, Murphy T, Scahill LD, Compton SN, Walkup J (2011) Exploring the impact of chronic tic disorders on youth: results from the Tourette Syndrome Impact Survey. Child Psychiatry Hum Dev 42:219–242 [PubMed: 21046225]

30. Cohen SC, Leckman JF, Bloch MH (2013) Clinical assessment of Tourette syndrome and tic disorders. Neurosci Biobehav Rev 37:997–1007 [PubMed: 23206664]

31. Scharfstein L, Alfano C, Beidel D, Wong N (2011) Children with generalized anxiety disorder do not have peer problems, just fewer friends. Child Psychiatry Hum Dev 42:712–723 [PubMed: 21739298]

32. Wei C, Hoff A, Villabo MA, Peterman J, Kendall PC, Piacentini J, McCracken J, Walkup JT, Albano AM, Rynn M, Sherrill J, Sakolsky D, Birmaher B, Ginsburg G, Keeton C, Gosch E, Compton SN, March J (2014) Assessing anxiety in youth with the multidimensional anxiety scale for children. J Clin Child Adolesc Psychol 43:566–578 [PubMed: 23845036]

33. Baldwin JS, Dadds MR (2007) Reliability and validity of parent and child versions of the multidimensional anxiety scale for children in community samples. J Am Acad Child Adolesc Psychiatry 46:252–260 [PubMed: 17242629]

34. Hirschtritt ME, Lee PC, Pauls DL, Dion Y, Grados MA, Illmann C, King RA, Sandor P, McMahon WM, Lyon GJ, Cath DC, Kurlan R, RObertson MM, Osiecki L, Scharf JM, Mathews CA; Tourette Syndrome Association International Consortium for Genetics (2015) Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry 72:325–333 [PubMed: 25671412]

35. Leckman J, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, Kim YS, Peterson BS (1998) Course of tic severity in Tourette syndrome: the first two decades. Pediatrics 102:14–19 [PubMed: 9651407]

36. Conelea CA, Woods DW (2008) The influence of contextual factors on tic expression in Tourette's syndrome: a review. J Psychosom Res 65:487–496 [PubMed: 18940379]

37. Lewin AB, Storch EA, Conelea CA, Woods DW, Zinner SH, Budman CL, Scahill LD, Compton SN, Walkup JT, Murphy TK (2011) The roles of anxiety and depression in connecting tic severity and functional impairment. J Anxiety Disord 25:164–168 [PubMed: 20889290]

38. Eaton CK, Jones AM, Gutierrez-Colina AM, Ivey EK, Carolson O, Melville L, Kardon P, Blount RL (2017) The influence of environmental consequences and internalizing symptoms on children's tic severity. Child Psychiatry Hum Dev 48:327–334 [PubMed: 27044052]

39. Villabo M, Gere M, Torgersen S, March JS, Kendall PC (2012) Diagnostic efficiency of the child and parent versions of the Multidimensional Anxiety Scale for Children. J Clin Child Adolesc Psychol 41:75–85 [PubMed: 22233247]

40. Bitsko RH, Holbrook JR, Ghandour RM, Blumberg SJ, Visser SN, Perou R, Walkup JT (2018) Epidemiology and impact oof health care provider-disagnosed anxiety and depression among US children. J Dev Behav Pediatr 39:395–403 [PubMed: 29688990]

41. Ezpeleta L, Keeler G, Erkanli A, Costello EJ, Angold A (2001) Epidemiology of psychiatric disability in childhood and adolescence. J Child Psychol Psychiatry 42:901–914 [PubMed: 11693585]

42. Hovik KT, Plessen KJ, Cavanna AE, Skogli EW, Andersen PN, Oie M (2015) Cognition, emotion and behavior in children with tourette's syndrome and children with ADHD-combined subtype-a two-year follow-up study. PLoS ONE 10:e0144874

43. Hoekstra PJ, Lundervold AJ, Lie SA, Gillberg C, Plessen KJ (2013) Emotional development in children with tics: a longitudinal population-based study. Eur Child Adolesc Psychiatry 22:185–192 [PubMed: 23064999]

44. Wehry AM, Beesdo-Baum K, Hennelly MM, Connolly SD, Strawn JR (2015) Assessment and treatment of anxiety disorders in children and adolescents. Curr Psychiatry Rep 17:52 [PubMed: 25980507]
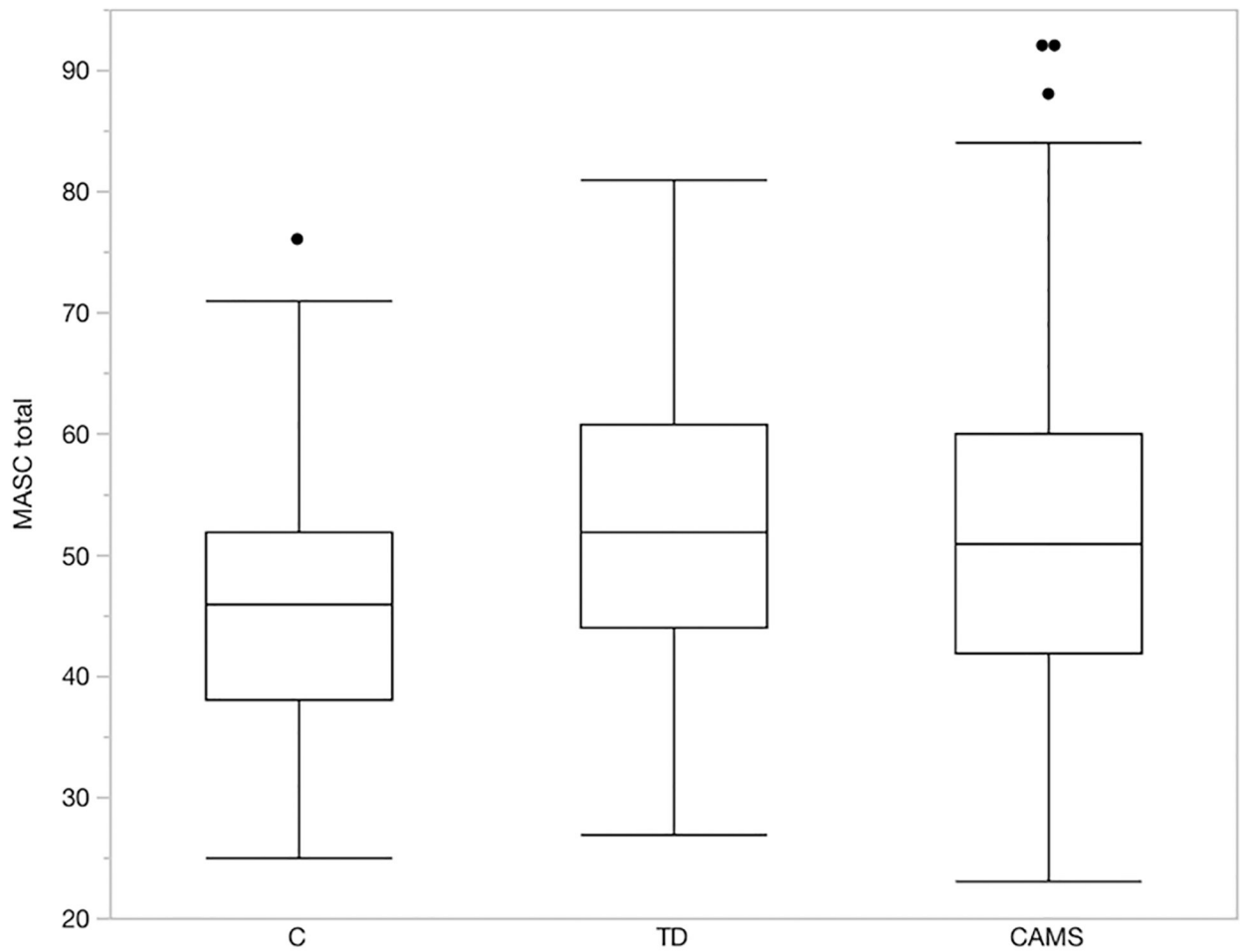
Fig. 1.
Youth with tic disorders had higher MASC total scores than community control youth and similar MASC total scores to those of treatment-seeking anxious youth in the CAMS trial. The box represents the interquartile range and the horizontal line inside the box represents the median. The whiskers represent minimum and maximum scores, excluding outliers (black dot). *C* community control subjects, *TD* Tic disorder subjects, *CAMS* CAMS trial participants
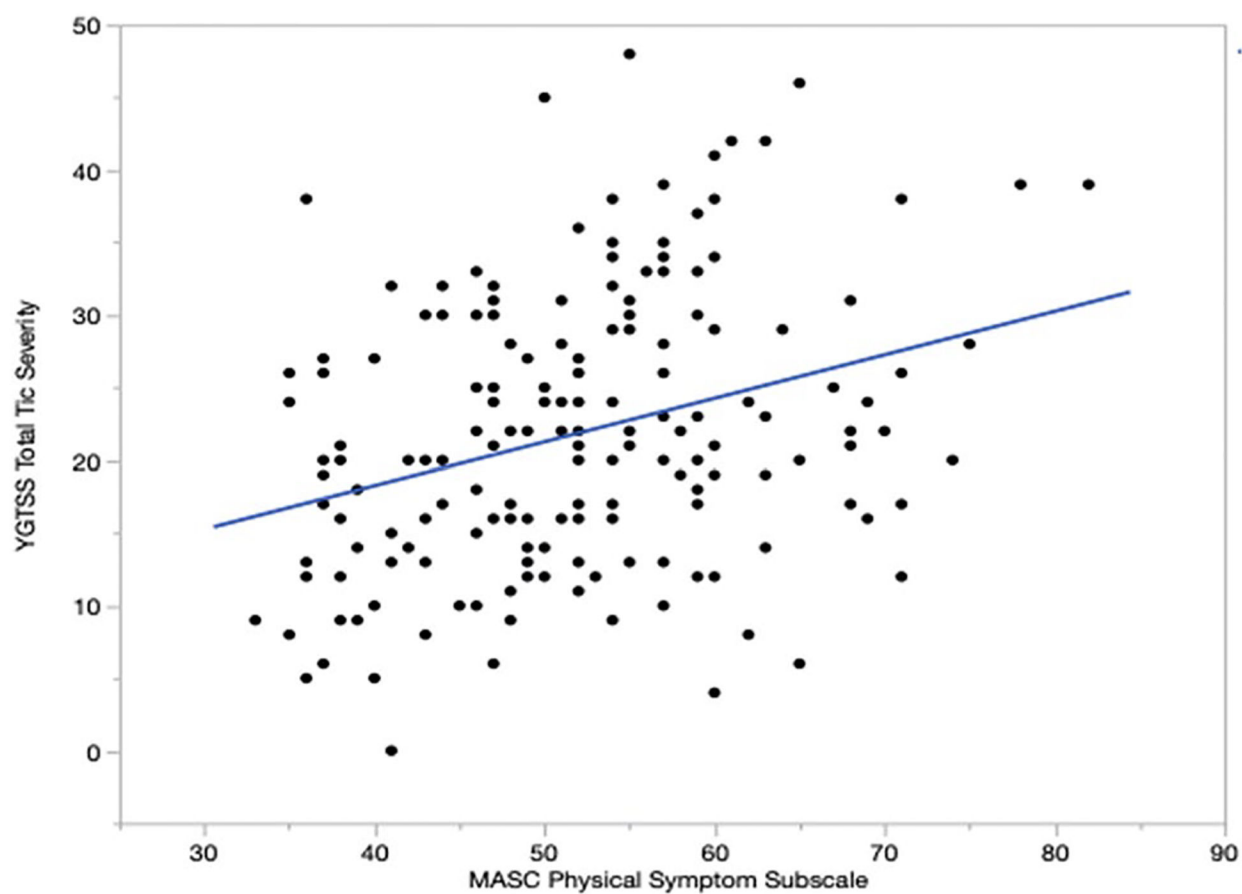
Fig. 2.
Tic severity was associated with physical anxiety symptoms (r = 0.30 p < 0.0001)

Table 1

MASC subscales

	Subscale components	**Symptom example(s)**
Physical symptoms	Panic + tense/restless	Feeling shaky or sweaty
Harm avoidance	Perfectionism + anxious coping	Always obeying the rules
Separation anxiety/phobias	N/A	Scared to be alone

MASC Multidimensional Anxiety Scale for Children

Table 2

Subject demographics

	n	Age median (IQR)[a]	Male sex n (%)
Tic disorders	176	11.0 (10.0–14.0)	132 (75%)
Community control	93	11.0 (9.0–13.0)[a]	56 (60%)[c]
CAMS participants	488	11.0 (9.0–13.0)[b]	246 (50%)[d]

IQR interquartile range

Compared to the Tic Disorders group:

[a] p=0.27 on Wilcoxon rank sum test;

[d] $\chi^2 = 31.90$ p < 0.0001

[b] p=0.01 on Wilcoxon rank sum test

[c] $\chi^2 = 6.32$, p = 0.01

Table 3

MASC total and subscale scores in youth with tic disorders and community control subjects

	Tic disorder median (IQR) (n = 176)	Community control median (IQR) (n = 93)	p value
MASC total	52.0 (44.0–60.8)	46.0 (38.0–52.0)	< 0.0001
MASC physical symptoms	52.0 (44.3–58.0)	41.0 (37.0–47.0)	< 0.0001
MASC harm avoidance	43.5 (31.3–53.0)	48.0 (37.0–55.0)	0.02
MASC social phobia	53.0 (47.3–62.0)	46.0 (38.0–54.5)	< 0.0001
MASC separation anxiety	59.0 (51.3–70.0)	49 (43.0–55.5)	< 0.0001

MASC Multidimensional Anxiety Scale for Children, *IQR* interquartile range

Table 4

MASC scores in youth with tic disorders and youth in the CAMS trial

	Tic disorder median (IQR) (n = 176)	CAMS median (IQR) (n = 488)	p value
MASC total	52.0 (44–60.8)	51.0 (42.0–60.0)	0.13
MASC physical symptoms	52.0 (44.3–58.0)	46.0 (37.0–55.0)	< 0.0001
MASC harm avoidance	43.5 (31.3–53.0)	49.0 (40.0–57.0)	< 0.0001
MASC social phobia	53.0 (47.3–62.0)	51.5 (41.0–63.0)	0.06
MASC Separation Anxiety	59.0 (51.3–70.0)	55.0 (47.0–66.0)	0.0003

MASC Multidimensional Anxiety Scale for Children, *IQR* interquartile range

Table 5

Impact of age on MASC scores in tic disorders and CAMS trial groups

	n	MASC total median (IQR)	Physical Symptoms median (IQR)	Harm Avoidance median (IQR)	Social Phobia median (IQR)	Separation Anxiety median (IQR)
Tic disorders						
Children (< 13 years)	116	52.0 (44.5–60.0)	51.0 (44.5–57.0)	45.0 (32.0–53.0)	53.5 (48.0–62.0)	59.0 (51.0–68.0)
Adolescents (13 years)	60	52.0 (44.0–62.5)	52.0 (42.8–59.0)	42.5 (31.0–51.8)	53.0 (46.0–62.0)	59.0 (52.0–71.5)
p-value		0.98	0.76	0.68	0.85	0.74
CAMS trial						
Children (< 13 years)	335	49.0 (41.0–58.0)	43.0 (37.0–52.0)	49.0 (42.0–57.0)	48.0 (39.0–58.0)	57.0 (49.0–68.0)
Adolescents (13 years)	153	55.0 (45.0–64.0)	49.0 (42.0–58.0)	48.0 (39.0–56.0)	61.0 (52.0–71.0)	52.0 (44.0–62.0)
p-value		< 0.0001	< 0.0001	0.15	< 0.0001	0.0009

MASC Multidimensional Anxiety Scale for Children, *IQR* interquartile range