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Relationship between adverse childhood experiences and symptom severity in adult men with Tourette Syndrome

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ABSTRACT

Childhood adversity is associated with the development or expression of many neuropsychiatric disorders, including those with strong genetic underpinnings. Despite reported associations between perceived stress and tic severity, the relationship between potentially traumatic events in childhood and Tourette Syndrome (TS), a highly heritable neuropsychiatric disorder, is unknown. This study aimed to assess whether exposure to eight categories of adverse childhood experiences (ACEs) is associated with TS severity and impairment, and whether TS genetic risk modifies this association. Online survey data were collected from 351 adult males with TS who previously participated in genetic studies. Participants completed the ACE questionnaire and a lifetime version of the Yale Global Tic Severity Scale (YGTSS). Demographic and relevant health data were assessed; polygenic risk scores (PRS) measuring aggregated TS genetic risk were derived using genome-wide association data. Univariable and multivariable linear regressions examined the relationships between childhood adversity and retrospectively recalled worst-ever tic severity and impairment, adjusting for covariates. Potential gene-by-environment (GxE) interactions between ACE and PRS were estimated. After covariate adjustment, there was a significant graded dose-response relationship between ACE Scores and increases in lifetime worst-ever tic severity and impairment. There was some evidence that TS genetic risk moderated the relationship between ACE Score and tic impairment, but not tic severity, particularly for individuals with higher TS polygenic risk. We provide evidence that childhood adversity is associated with higher lifetime TS severity and impairment, although future longitudinal studies with genetically-sensitive designs are needed to determine whether these relationships are causal and/or directional.

Abbreviations: TS, Tourette syndrome; ACE, Adverse Childhood Experiences; YGTSS, Yale Global Tic Severity Scale.

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1. Introduction

Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by multiple, involuntary, repetitive motor movements and vocalizations (tics) that are present for at least one year. Tics frequently wax and wane and can vary widely in severity and associated impairment; at best they are unnoticeable, while at worst they result in poor quality of life and even self-injury (Robertson et al., 2017). TS affects approximately 0.6% of children (Scharf et al., 2015), and persists into adulthood in greater than 30% of affected youth (Groth et al., 2017). In adults with non-remitting tics, tic severity is associated with disrupted social functioning, job instability, and other signs of functional impairment (Conelea et al., 2013).

TS has a complex etiology, with multiple genetic and environmental factors implicated in its development and expression (Robertson et al., 2017). While highly familial, few individual TS risk genes have been identified. Current research suggests that a significant proportion of TS genetic risk arises from an aggregated sum of common, small effect-size variants (Davis et al., 2013). This genome-wide 'polygenic burden' of TS genetic risk varies across individuals, and recent studies have demonstrated that TS polygenic risk correlates with higher lifetime, worst-ever tic severity in those with a family history of tics (Yu et al., 2019). Family studies have also demonstrated that TS has overlapping genetic risk with obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD), such that individuals with TS and their first-degree relatives have higher rates of OCD and ADHD compared to the general population (Browne et al., 2015; Hirschtritt et al., 2015; Mataix-Cols et al., 2015). With respect to environmental contributions, daily psychosocial stressors have emerged as an important factor shaping tic severity in a handful of studies (Buse et al., 2014; Hoekstra et al., 2004; Steinberg et al., 2013). In a prospective study on the effects of stress in 37 children and adolescents with TS, higher levels of self-reported psychosocial stress at baseline were predictive of worse tic severity two years later (Lin et al., 2007), even when antecedent tic severity was included in the predictive model. However, few studies have examined the impact of exposure to major, potentially traumatic childhood experiences (Horesh et al., 2018), which are estimated to affect as many as 70% of the world's population (Benjet et al., 2016), including 40% of children under age thirteen (Koenen et al., 2010).

Childhood adversity is associated with poor physical and mental health outcomes across the life course (Dunn et al., 2013; Teicher and Samson, 2013). The Adverse Childhood Experiences (ACE) Study (Felitti et al., 1998) was among the first large-scale efforts to demonstrate a clear dose-response relationship between exposure to multiple categories of potentially traumatic events in childhood and risk factors for some of the leading causes of death in adults, including ischemic heart disease and cancer. Exposure to four or more categories of childhood adversity (emotional, physical, or sexual abuse, substance abuse, mental illness in the household, parental separation, domestic violence, having a family member in prison) was associated with a 4-12-fold increased risk of substance abuse and depression in adulthood. Subsequent research has documented a similar dose-response relationship with many adult outcomes including suicide (Dube et al., 2001; Shonkoff et al., 2012). Although no work has yet been done for TS, numerous studies have since replicated this finding with other mental health problems, including ADHD and obsessive-compulsive disorders (Brown et al., 2017; Visser et al., 2014), both of which commonly co-occur with TS (Hirschtritt et al., 2015).

Prior studies also suggest that pre-existing genetic vulnerability may exacerbate the effects of childhood adversity on mental health (Dunn et al., 2011; Trotta et al., 2016). For TS, a combination of genetic risk and exposure to environmental factors may explain the marked heterogeneity in clinical manifestations and tic progression (Robertson et al., 2017). However, to our knowledge no studies have tested this hypothesis.

To address these gaps, the goals of the current study were to: (1) investigate the association between exposure to childhood adversity and lifetime worst-ever tic severity and impairment in a sample of 351 adult males with TS who previously participated in a TS genetic study and completed an online re-contact study that included the ACE Study Questionnaire and (2) conduct an exploratory examination into the extent to which TS genetic risk modifies any observed association between retrospectively-reported childhood adversity and TS symptom severity.

2. Material and methods

2.1. Participants

This study included 351 adult males with TS who previously participated in genetic studies of TS (Darrow et al., 2015; Egan et al., 2012; Yu et al., 2019) from whom ACE data were collected retrospectively in a subsequent follow-up study on potential relationships between the androgen pathway and tic severity (Muroni et al., 2011). Participants who reported intellectual disability, epilepsy, or genetic or neurological disorders that could confound a TS diagnosis were excluded.

2.2. Study procedure

All study procedures were reviewed and approved by the Mass General Brigham Healthcare Institutional Review Board. Self-report surveys were distributed to interested participants via email or direct mail. All participants provided informed consent to participate in this study.

2.3. Measures

2.3.1. Adverse Childhood Experiences

Childhood adversity was assessed using the Adverse Childhood Experiences (ACE) questionnaire (Dube et al., 2001), which was designed as a retrospective, self-report measure to assess exposure to eight categories of childhood adversity: emotional, physical, and sexual abuse; parental domestic violence and divorce/separation; substance abuse, mental illness in the household, and incarceration of a family member. The prevalence of each category was calculated, and summed ACE Scores (range, 0–8) were generated using the procedures in Dube et al. to define the number of specific ACEs endorsed by each participant (Supporting **Information, Fig. S1).**

2.3.2. TS, OCD, and ADHD diagnoses

TS, OCD, and ADHD diagnoses were assigned using the Tourette Internet-implemented Questionnaire (TIQue), a validated web-based phenotypic assessment tool (Darrow et al., 2015; Egan et al., 2012).

2.3.3. Tic severity and impairment

TS symptoms, lifetime ("worst ever") tic severity and impairment were assessed retrospectively by self-report using a modified form of the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989), as implemented in previous clinical and genetic research studies of TS (Hirschtritt et al., 2015; Tourette Syndrome Association International Consortium for Genetics, 2007). Two outcomes were examined, each scored on a 0–50 scale: tic severity (YGTSS Total Tic Severity Score) and impairment (YGTSS Impairment Score). Worst ever tic severity and impairment scores were analyzed as separate outcomes, as each captures a different aspect of TS disease severity (Storch et al., 2011). While the tic severity score is based on the number, frequency, intensity, and complexity of one's motor and vocal tics, the impairment score captures the inability to perform routine or other age-appropriate tasks in various domains of life and is thought to be driven by the presence of co-occurring neuropsychiatric disorders (Robertson et al., 2017; Storch et al., 2007).

2.3.4. Covariates

Participants reported their race and ethnicity, age at the time of interview, and retrospective recollection of age at tic onset, age at first ACE, and age at worst-ever tic severity. For analysis, due to low diversity among participants, race and ethnicity data were collapsed into a dichotomous variable (Non-Hispanic White; Non-White, Hispanic White, or Other/Unknown).

2.3.5. Genetic risk

Genetic analyses were conducted in European ancestry participants only (n = 304), as these were the participants for whom genome-wide genotype data were available. TS genetic risk was defined as the aggregate effect of multiple TS risk variants across the genome, and was captured using standardized, genome-wide ancestry-adjusted polygenic risk scores (aPRS) derived from the previously published TS genome-wide association study (GWAS) of 4819 TS cases and 9488 controls (Abdulkadir et al., 2019; Purcell et al., 2009; Yu et al., 2019). PRS per subject was calculated from GWAS data using a cross-validation method (Supplementary Methods) (Yu et al., 2019).

2.4. Statistical analyses

A schematic diagram outlining the statistical plan for primary, secondary, and exploratory statistical analyses is provided in Fig. 1. Two outcome measures - worst-ever tic severity and impairment – were used for all univariable and multivariable analyses. Statistical analyses were conducted using Stata 14. Of note, a 5-point change on both outcome measures corresponds to a 10% or greater change on the 50-point YGTSS Severity and YGTSS Impairment scales.

Univariable linear regression was used to examine unadjusted associations between ACE Score and the two outcome variables: worst-ever tic severity and impairment scores. Additional univariable regressions were then conducted between each candidate covariate and worst-ever tic severity and impairment. Covariates that met a p-value threshold of $p \leq 0.10$ in univariable analyses were retained for primary multivariable analyses. In selecting covariates to retain, pairwise relationships between covariates, predictor, and outcome variables were examined to prevent potential collinearity within the final models.

2.5. Gene x environment analysis

After estimating the final multivariable models, an exploratory analysis was conducted to investigate potential effects of gene-by-environment (GxE) interactions, focusing on TS genetic risk (aPRS) and childhood adversity (ACE Score) on worst-ever tic severity and impairment in the 304 participants of European ancestry for which GWAS data were available. TS aPRS was entered into the final multivariable models for tic severity and impairment, and subsequently an aPRS x ACE Score interaction term was introduced. For the final GxE models, adjustments were made to create a fully-saturated model to include all gene-by-covariate and environment-by-covariate interaction terms to minimize the risk of false positives due to confounders (Keller, 2014). In addition, the gene-environment correlation between aPRS and ACE Score was calculated (Dick et al., 2015).

Two sensitivity analyses were also conducted. 1) Given an observed correlation between ACE Score and both OCD and ADHD, the primary multivariable and exploratory, fully-saturated GxE models for tic severity and impairment were repeated excluding OCD and ADHD terms to evaluate the degree to which these two comorbidities might attenuate the association between ACE Score and tic severity or impairment. 2) The primary and exploratory GxE multivariable models were also re-examined after removing 19 subjects whose retrospective, self-reported age of worst tics preceded their reported age of first ACE exposure.

Finally, to evaluate the relative influence of individual ACE categories on tic severity and impairment, a set of secondary analyses were performed. First, associations between each individual ACE category and tic severity/impairment were assessed using linear regression after adjusting for race/ethnicity and age at tic onset for tic severity and only race/ethnicity for tic impairment, as these were the nominally-significant covariates in univariable analyses. Men who reported no childhood adversity were used as a reference for all analyses. Second, each of the eight ACE categories were introduced simultaneously into a single model that also included race/ethnicity, age at tic onset, OCD and ADHD, followed by stepwise, backward elimination of any ACE category with an association p-value <0.05 while adjusting for the other ACEs in the model.

3. Results

3.1. Sample characteristics

351 of 647 eligible adult males from the initial TS genetic study completed the follow-up survey (54.3% response rate). The mean age of the sample at interview was 38.5 (SD = 16.0) years. 92.9% of subjects self-reported as Non-Hispanic White, and 31 (7.1%) self-reported as Non-White and/or Hispanic or Other/Unknown. The mean age of tic onset was 7.4 (SD = 3.1) years; the mean age of worst-ever tics was 18

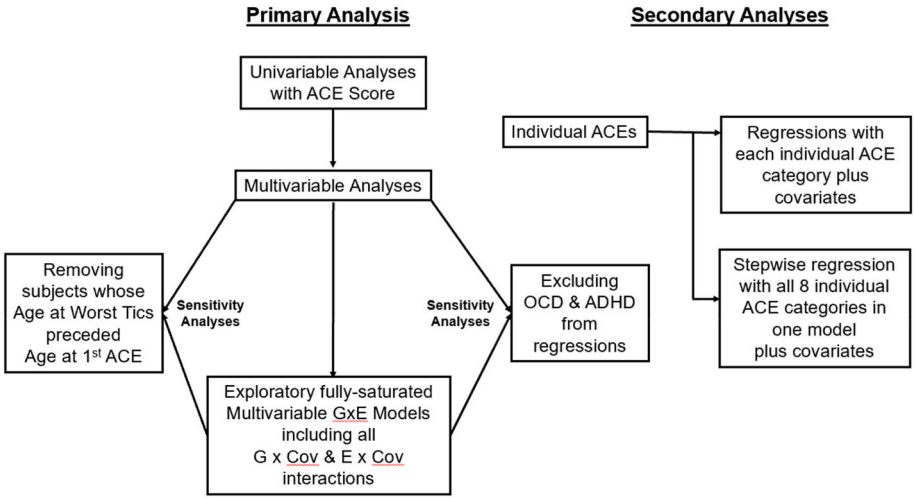

Fig. 1. Diagram of Statistical Analysis Plan. All primary, secondary and exploratory analyses were conducted with two outcome measures - worst-ever Yale Global Tic Severity Scale (YGTSS) Total Tic Score (0–50) and YGTSS Impairment Score (0–50).

(SD = 11) years (Table 1). 29% of subjects reported experiencing their worst-ever tics in adulthood (18+), while 43% experienced their worst tics between ages 12–18, and 28% reported their age of worst tics occurred prior to age 12. There were no significant differences in retrospectively-recalled mean worst-ever tic severity or impairment across these three groups (data not shown). 59% of men met DSM-5 criteria for OCD, 33% met DSM-5 criteria for ADHD, 28% met criteria for both, and 35% had neither. Men who did not respond to the re-contact survey request had similar rates of OCD (61%) and ADHD (39%) at the time of initial interview. Mean lifetime worst-ever YGTSS Total Tic Severity score was 29.4 (SD = 8.6), while mean lifetime worst-ever YGTSS Impairment score was 29.3 (SD = 13.4), consistent with moderate TS severity.

3.2. Childhood adversity

Exposure to childhood adversity was common in this sample, with 59.8% of men with TS reporting exposure to one or more ACEs prior to age 18 (Fig. S1, Table S1). This rate was not significantly elevated compared to those in the general population (61.8%; $\chi^2 = 0.56$, p = 0.5) (Dube et al., 2001). Mental illness in the household was the most commonly reported ACE (35%), while incarceration of a member of the household was the least common (1.6%) (Table S1). With the exception of mental illness in the household (35%) and emotional abuse (17.8%), the prevalence of each adversity category was lower than or similar to that reported previously for a general population sample of men (Dube et al., 2001).

3.3. Adverse childhood experiences and worst-ever tic severity

In univariable analyses, there was a graded relationship between ACE Score and tic severity, in which each additional ACE Score unit increase was associated with a 1.4-point increase in lifetime worst-ever YGTSS Total Tic Severity (β = 1.4, 95% CI = 0.8–2.1, p < 0.001) (Table S2). OCD and ADHD were associated with 6.9 point and 4.0 point increases in worst-ever tic severity, respectively, while race/ethnicity other than Non-Hispanic White was associated with a 3.8 point increase in tic severity (β = 3.8, 95% CI = 0.3–7.3, p = 0.03). Age of tic onset also qualified for inclusion in the final multivariable model. Of note, both OCD (OR = 1.2, 95% CI (1.1–1.5), p = 0.01) and ADHD (OR = 1.4, 95% CI (1.2–1.6), p < 0.001) were also significantly associated with ACE Score.

In the final primary multivariable model, the graded relationship between ACE Score and worst-ever tic severity remained, although the effect size was attenuated. Each ACE Score unit increase was associated with a 1.1-point increase in worst-ever YGTSS Total Tic Severity (β = 1.1, 95% CI = 0.5–1.7, p < 0.001) (Table S3); ACE Score accounted for 3% of the variance in this model. OCD was independently associated with a 6-point increase in tic severity (β = 6.0, 95% CI = 4.1–7.8, p < 0.001) and accounted for 11.5% of the variance. In contrast, comorbid ADHD was not significant in the final adjusted multivariable model.

Table 1
Descriptive statistics of all measures included in the study. *Age at first ACE is limited only to the 210 participants who reported experiencing at least one ACE prior to age 18. ACE, Adverse Childhood Experience; YGTSS, Yale Global Tic Severity Scale; Adjusted TS PRS, Ancestry-adjusted Tourette syndrome Polygenic Risk Scores.

Variable	Number	Mean (SD)	Median (IQR)	Range	Distribution
Age of subject	351	38.5 (16.0)	35 (24, 51)	[18, 76]	Right-skew
Age of tic onset	350	7.4 (3.1)	7 (5, 10)	[0, 17]	Right-skew
Age of worst tics	338	17.6 (11.0)	14 (11, 19)	[5, 60]	Right-skew
Age at first ACE	210*	7.9 (3.7)	7.5 (6,11)	[0, 16]	Normal
ACE Score (0–8)	351	1.2 (1.4)	1 (0, 2)	[0, 8]	Right-skew
YGTSS Tic Severity (0–50)	332	29.4 (8.6)	29 (23, 35)	[4, 50]	Normal
YGTSS Tic Impairment (0–50)	348	29.3 (13.4)	30 (20, 40)	[0, 50]	Normal
Adjusted TS PRS	304	0 (1.00)	0.08 (−0.58, 0.63)	[-2.93, 2.46]	Left-skew

3.4. Adverse childhood experiences and worst-ever impairment

Similar results were observed when examining worst-ever impairment as the outcome. In univariable analyses, ACE Score was associated with a 2.3-point increase in worst-ever YGTSS Impairment for each additional ACE Score unit exposure in childhood (β = 2.3, 95% CI = 1.3–3.3, p < 0.001) (Table S2). In the primary multivariable model including OCD and ADHD, worst-ever impairment was positively associated with ACE Score (β = 1.9, 95% CI = 0.9–2.9, p < 0.001) and explained 6% of the variance (Table S3). Co-occurring OCD, but not ADHD, was also independently associated with worst-ever impairment (β = 7.0, 95% CI = 4.1–9.9, p < 0.001). The final multivariable model predicted approximately 13% of the variance (adjusted $R^2 = 0.13$, $F_{4, 338} = 13.74$, $P < 0.001$).

3.5. Individual ACE categories and tic severity/impairment

Secondary analyses suggested that all eight categories of childhood adversity were associated with both tic severity and impairment (Table S4). Therefore, additional analyses were conducted which introduced all individual ACE categories into a multivariable model simultaneously including significant covariates from univariable analyses, followed by stepwise backward elimination of ACEs without nominally significant associations after adjusting for the remaining ACEs. Domestic violence in the home (β = 5.7(1.8–9.8), p = 0.005) and incarceration of a family member(β = 5.8(−1.1-12.6), p < 0.001) were the two ACEs that remained in the model with worst-ever tic severity (Table S5). In contrast, household mental illness (β = 3.3(0.5–6.2), p = 0.02) and emotional abuse (β = 5.6(2.1–9.1), p = 0.002) remained in the multivariable model of worst-ever impairment **(Table S6)**.

3.6. Impact of gene-by-environment interactions on tic severity and impairment

TS genetic risk, as measured by genome-wide, ancestry-adjusted polygenic risk scores (aPRS), was not significantly associated with either lifetime worst-ever tic severity or impairment in univariable analysis (Table S2). However, since TS aPRS was recently demonstrated to be associated with lifetime, worst-ever tic severity in TS-affected individuals with a positive family history of TS or chronic tics in a large TS genetic study that included this sample (Yu et al., 2019), an exploratory, multivariable gene-by-environment (GxE) analysis was performed for both tic severity and impairment.

In the fully-saturated GxE model for tic severity that included all gene-by-covariate and environment-by-covariate interaction terms, increased TS genetic risk (aPRS) was associated with additional increases in worst-ever tic severity for each unit increase in ACE Score, although the aPRS × ACE interaction term did not meet the pre-specified threshold for significance (β = 0.6, 95% CI(-0.1, 1.4), p = 0.09, Table 2). The OCD x ACE Score (environment-by-covariate) interaction was nominally significant (β = −1.6, 95% CI(-3.1, −0.04), p = 0.04), resulting in a 1.6 point attenuation of the effect of each ACE Score unit increase on worst-ever tic severity from 3.1 to 1.5 points while also increasing baseline worst-ever tic severity by 6.8 points due to the main effect of OCD (β = 6.8, 95% CI (4.2–9.5), p < 0.001), Table 2, Fig. 2A).

In contrast, the fully-saturated multivariable GxE model for worst-ever YGTSS Impairment scores demonstrated a significant ACE ×

Table 2
Final multivariable Gene-by-Environment (GxE) regression model for YGTSS worst-ever Total Tic Severity including all Gene x Covariate and Environment × Covariate interactions. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. R^2, Effect size estimate for each predictor in the model. The prespecified significance threshold for each covariate in the multivariable models was $p < 0.05$, as indicated with a dagger symbol (†). Model statistics: $F_{12,\ 266} = 5.49$, $P < 0.001$; Overall model $R^2 = 0.20$; Adjusted $R^2 = 0.162$; N = 279.

Predictor	β-Coefficient (95% CI)	SE	Standardized β-Coefficient (95% CI)	SE	p-value	R^2
OCD	6.8 (4.2, 9.5)	1.3	0.39 (0.24, 0.54)	0.08	<0.001†	0.085
ADHD	0.9 (−2.1, 3.9)	1.5	0.05 (−0.11, 0.21)	0.08	0.5	0.029
ACE Score	3.1 (0.6, 5.6)	1.3	0.50 (0.10, 0.90)	0.21	0.02†	0.050
Age of Tic Onset	0.1 (−0.4, 0.6)	0.2	0.03 (−0.13, 0.19)	0.08	0.7	0.003
aPRS	−2.0 (−4.8, 0.8)	1.4	−0.23 (−0.56, 0.09)	0.17	0.2	<0.001
ACE Score x aPRS	0.6 (−0.1, 1.4)	0.4	0.14 (−0.02, 0.30)	0.08	0.09	0.013
ADHD x aPRS	0.1 (−2.1, 2.2)	1.1	0.006 (−0.14, 0.15)	0.08	0.9	<0.001
OCD x aPRS	0.6 (−1.5, 2.7)	1.1	0.06 (−0.13, 0.24)	0.09	0.6	<0.001
Age of Tic Onset x aPRS	0.1 (−0.2, 0.4)	0.1	0.09 (−0.19, 0.37)	0.14	0.5	0.001
ADHD x ACE Score	0.4 (−1.2, 1.9)	0.8	0.05 (−0.16, 0.25)	0.10	0.7	<0.001
OCD x ACE Score	−1.6 (−3.1, −0.04)	0.8	−0.24 (−0.46, −0.01)	0.12	0.04†	0.01
Age of Tic Onset x ACE Score	−0.2 (−0.4, 0.1)	0.1	−0.22 (−0.57, 0.14)	0.18	0.2	0.004

aPRS interaction (β = 1.1, 95% CI(0.1–2.2), p = 0.04, Table 3, Fig. 2B). No gene-by-covariate or environment-by-covariate interaction terms were significant in this model. There was also no evidence of a gene-environment correlation between TS aPRS and ACE Scores (r = −0.0003, p = 0.99).

3.7. Sensitivity analyses

After excluding OCD and ADHD from the analyses, the proportion of variance attributable to ACE Score in the primary multivariable models of tic severity increased from 3% to 7%(β = 1.5, 95% CI(0.8–2.1), p < 0.001) (Table S4). Each ACE Score unit exposure was also associated with a 2.4 point increase in worst-ever tic impairment (β = 2.4, 95% CI (1.4–3.4), p < 0.001) **(Table S4)** compared to a 1.9 point increase (β = 1.9, 95% CI(0.9–2.9), p < 0.001) when OCD and ADHD were include in the model (Table S3).

In the fully-saturated multivariable GxE model for tic severity excluding OCD and ADHD, both the main effect for ACE Score (β = 2.3, 95% CI(0.3–4.4), p = 0.03) and the ACE × aPRS interaction (β = 0.8, 95% CI(0.1–1.6), p = 0.03) were significant (Table S7). Similarly, in the multivariable GxE model for impairment without OCD and ADHD, the main effect for ACE Score (β = 2.1, 95% CI(1.0–3.1), p < 0.001) and the ACE × aPRS interaction (β = 1.3, 95% CI(0.2–2.4), p = 0.02) were also significant (Table S7).

In the sensitivity analyses removing 19 subjects whose age at worst tics occurred before their age of first ACE exposure, ACE Score was still significantly associated with both outcomes in the primary multivariable analyses (Table S8), and the fully-saturated GxE model of tic severity also demonstrated a significant ACE × OCD interaction (Table S9). Similar results were observed for tic impairment, though the ACE × aPRS interaction was no longer significant (p = 0.1) (Tables S9 and S10).

4. Discussion

Childhood adversity, as assessed by the ACE Study Questionnaire, has been consistently associated with myriad negative health outcomes, ranging from cardiovascular disease (Musselman et al., 1998) to neuropsychiatric illness (Anda et al., 2006; Teicher and Samson, 2013). While childhood adversity is correlated with OCD and ADHD (Brown et al., 2017; Mathews et al., 2008), both of which commonly co-occur with TS (Hirschtritt et al., 2015), few studies have explicitly explored the relationship between major childhood life events and TS severity (Findley et al., 2003; Horesh et al., 2018). Here, we demonstrate that ACE Score, representing the cumulative exposure to eight potentially traumatic events prior to age 18, has a significant, graded relationship with 'worst ever' YGTSS Total Tic Severity and Impairment. These effects were retained even when adjustments are made for the presence of comorbid OCD and ADHD, both of which have been shown previously to contribute to TS disease severity (Hirschtritt et al., 2015).

The prevalence of at least one ACE exposure in our sample is consistent with those reported for males in the general population (Felitti et al., 1998), indicating that exposure to childhood adversity is not elevated in individuals with TS. However, childhood adversity might be associated with the *expression* of TS, and particularly with higher worst-ever tic severity and impairment. We demonstrate that, even after adjusting for covariates including comorbid OCD and ADHD, each additional ACE Score unit exposure is associated with a 1.1-point increase in lifetime tic severity scores and a 1.9-point increase in lifetime tic-related impairment.

While the YGTSS Impairment score was initially designed to capture tic-related impairment, subsequent studies have demonstrated that YGTSS Impairment scores are also sensitive to effects of psychiatric comorbidities and life circumstances (Storch et al., 2007). Although our analyses controlled for OCD and ADHD, we did not assess for anxiety, depression, or other psychiatric comorbidities, which also contribute to impairment (Hirschtritt et al., 2015). Therefore, it is possible that the stronger relationship between ACEs and worst-ever impairment scores reported here could be explained partly by other unmeasured psychiatric symptoms which could present additional challenges for a child attempting to develop healthy coping mechanisms.

Multiple lines of evidence support an additional relationship

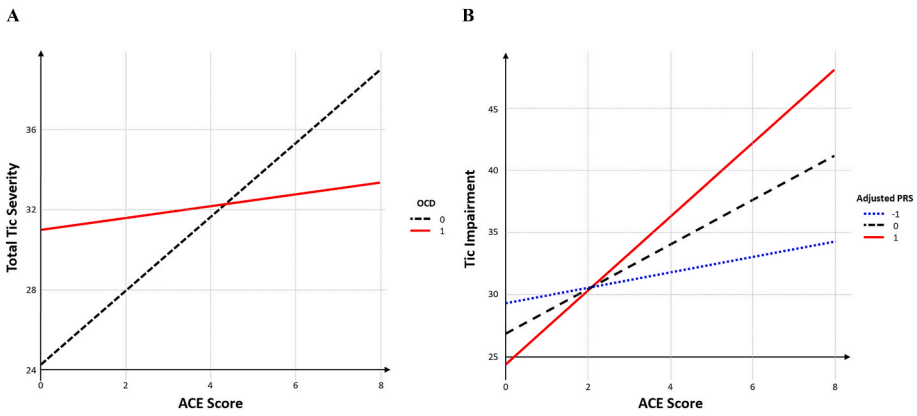

Fig. 2. Covariate-by-environment and gene-by-environment interactions for tic severity and tic impairment. A. Plot of the relationship between ACE Score and worst-ever YGTSS Total Tic Severity Score in subjects with (red) and without (black) comorbid OCD. **B.** Plot of the relationship between ACE Score and YGTSS Impairment score in subjects with three levels of genome-wide, ancestry-adjusted TS polygenic risk scores (PRS). YGTSS, Yale Global Tic Severity Scale; ACE, Adverse Childhood Experiences; OCD, Obsessive-Compulsive Disorder. Genome-wide ancestry adjusted TS PRS was standardized across cases with mean of zero and each unit representing one standard deviation above (red) or below (blue) the case mean PRS. OCD × ACE interaction term for tic severity: β = −1.6, 95% CI(-3.1, −0.04), R^2 = 0.01, p = 0.04. aPRS × ACE interaction term for tic impairment: β = 1.1, 95% CI(0.1, 2.2), R^2 = 0.012, p = 0.04.

Table 3
Final multivariable Gene-by-Environment (GxE) regression model for worst-ever YGTSS Impairment Score including all Gene x Covariate and Environment × Covariate interactions. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. R^2, Effect size estimate for each predictor in the model. The prespecified significance threshold for each covariate in the multivariable models was $p < 0.05$, as indicated with a dagger symbol (†). Model Statistics: $F_{9, 286} = 5.46$, $P < 0.001$; Overall model $R^2 = 0.15$; Adjusted $R^2 = 0.12$; N = 296.

Predictor	β-Coefficient (95% CI)	SE	Standardized β-Coefficient (95% CI)	SE	p-value	R^2
OCD	7.2 (3.2, 11.3)	2.1	0.26 (0.12, 0.41)	0.08	0.001†	0.057
ADHD	2.2 (−2.5, 6.9)	2.4	0.08 (−0.08, 0.24)	0.08	0.35	0.040
ACE Score	2.3 (0.5, 4.1)	0.9	0.24 (0.05, 0.43)	0.10	0.02†	0.028
aPRS	−2.0 (−4.6, 0.6)	1.3	−0.15 (−0.33, 0.04)	0.10	0.13	0.005
ACE Score x aPRS	1.1 (0.1, 2.2)	0.6	0.16 (0.01, 0.30)	0.08	0.04†	0.012
ADHD x aPRS	1.5 (−1.9, 4.8)	1.7	0.06 (−0.08, 0.21)	0.08	0.39	<0.001
OCD x aPRS	−1.6 (−4.9, 1.7)	1.7	−0.09 (−0.27, 0.09)	0.09	0.34	0.002
ADHD x ACE Score	0.2 (−2.1, 2.5)	1.2	0.02 (−0.17, 0.21)	0.10	0.85	<0.001
OCD x ACE Score	−1.0 (−3.3, 1.3)	1.2	−0.10 (−0.32, 0.12)	0.11	0.39	0.002

between ACE exposures and both comorbid OCD and ADHD in our sample. In univariable analyses, both OCD and ADHD were significantly associated with ACE Score. This association was also evident by the reduction in variance explained by ACE Score when OCD and ADHD were included in subsequent multivariable models. Furthermore, there was a significant OCD × ACE interaction in the fully-saturated GxE model for tic severity, where each ACE Score unit exposure was associated with a 3.1 point increase in tic severity for subjects without OCD, but only a 1.5 point increase per ACE for subjects with OCD. However, this diminished effect of ACEs on tic severity in the presence of OCD was mostly offset by a 6.8 point baseline increase in tic severity due to the main effect of OCD in the GxE model. Previous studies of ACEs in individuals with OCD did not identify a relationship between ACEs and either OCD severity or chronicity, though ACE Scores correlated with the number of psychiatric comorbidities in OCD patients (Visser et al., 2014).

While comorbid ADHD was a strong predictor of tic severity and impairment in univariable analyses, it was not significant in the final multivariable models, despite strong prior evidence associating ADHD with higher tic severity and impairment in individuals with TS (Hirschtritt et al., 2015; Storch et al., 2007). However, there was minimal power to detect an ADHD-specific effect, as only 21 subjects in the study had ADHD without OCD. Future work in larger samples with adequate power to examine separate groups of TS subjects with and without OCD and/or ADHD will be needed to address this question further.

Mental illness in the household was the most commonly reported ACE, and, along with emotional abuse, represent the two ACEs most strongly associated with worst-ever impairment. In addition, these two ACEs were also the only categories of childhood adversity that were more prevalent in this sample than in previous population-based studies (Dube et al., 2001; Felitti et al., 1998). Of note, since OCD and ADHD have been demonstrated previously to have overlapping genetic risk in TS families (Brander et al., 2021; Hirschtritt et al., 2015), mental illness in the household may actually represent a genetic, rather than environmental, effect on tic impairment.

We have previously demonstrated that aggregated TS polygenic risk (aPRS) is correlated with higher tic severity among individuals with a positive family history of TS (Yu et al., 2019). However, we did not observe this association in the current sub-sample of the larger genetic study. This discrepancy is most likely due to the smaller sample size with available ACE data. Exploratory GxE analyses here, although not conclusive, do suggest that childhood adversity and TS polygenic risk may interact to influence lifetime tic impairment. However, the GxE analyses of tic severity did not meet a nominal significance threshold. Future studies of TS and related conditions would greatly benefit from assessing childhood adversity in large-scale genetic studies to allow more robust analyses of gene-by-environment interactions.

Of note, the positive relationship between TS aPRS and tic impairment was only present among subjects exposed to childhood adversity.

In contrast, among men with no ACE exposures, there was a negative association between aPRS and tic impairment. Such "cross-over" interactions between exposure to childhood trauma and polygenic risk scores have been observed previously for major depression (Mullins et al., 2016). However, the effect of the observed aPRS*ACE interaction on tic impairment was most prominent in subjects with high TS polygenic risk (aPRS above the sample mean), while this effect was minimal in men with low aPRS. These results are consistent with a model where the negative impact of ACEs on worst-ever tic impairment is greatest for subjects with high TS genetic risk which might reflect a higher disease burden. Future well-powered studies will be needed to dissect this complex relationship further.

Since the current study is cross-sectional and retrospective, it is not possible to infer causality from these findings. Specifically, without prospective data collection, we cannot distinguish whether ACE exposures cause higher tic severity or impairment, whether other unmeasured factors might increase risk for both childhood adversity and tic severity/impairment, or whether higher tic severity/impairment itself might increase risk for exposure to adversity. Since physical and psychological stressors have been demonstrated to cause worsening of tic severity more than a year later (Lin et al., 2007), ACE exposures could lead to long-term worsening of tic severity and impairment through a stress-diathesis model. This relationship has been demonstrated previously in studies of the effects of ACEs on ADHD (Brown et al., 2017). While the relationship between worst-ever YGTSS Severity and Impairment remained after controlling for OCD and ADHD, we were not able to control for the many additional internalizing and externalizing psychiatric disorders that we and others have demonstrated previously to co-occur in TS patients and their families (Hirschtritt et al., 2015). Higher tic severity has been associated with increased family dysfunction, which can increase the risk of parental separation/divorce (Vermilion et al., 2020).

Lastly, the presence of unmeasured co-occurring externalizing disorders could both increase lifetime tic severity and place individuals at higher risk of ACE exposures. In this scenario, higher genetic risk for TS – which also could increase genetic risk for OCD and ADHD due to overlapping, shared polygenic risk – would be complicated by an 'evocative gene-environment correlation' in which those at higher risk for externalizing disorders might have characteristics that also place them at higher risk of exposure to risky situations (Dick, 2011). A recent article by Mataix-Cols and colleagues demonstrated that individuals with tic disorders were at higher risk of violent assault, consistent with this scenario (Mataix-Cols et al., 2022). Furthermore, recent work using well-powered twin and/or sibling designs have demonstrated that some putative 'environmental' risk factors for disease may also have significant genetic effects (Hart et al., 2021; Mataix-Cols et al., 2022). For example, mental illness in the household and other types of family dysfunction could reflect the expression of shared TS genetic risk in other family members, given the established genetic relationships between TS, OCD and ADHD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). In this context, prospective studies including serial assessments of YGTSS Scores and ACE exposure frequency and intensity using genetically-sensitive designs, such as use of discordant twin or sibling controls or parental genetic data to calculate PRS, will be necessary to dissect the complex relationship between childhood adversity and tic severity/impairment.

The strengths of this study include the use of validated phenotypic assessments of TS, OCD, and ADHD in a large number of TS patients as well as the use of a quantitative aggregated measure of genome-wide TS genetic risk rather than a focus on individual candidate genes. However, multiple limitations must be noted. First, assessments were based on retrospective self-reports, and thus recall bias could have influenced the reporting of both adverse events and lifetime tic severity or impairment. Second, unmeasured affective disorders may also have influenced retrospective recall. Third, no treatment histories were available, which may have added additional variability in worst-ever severity in some subjects. Fourth, twenty-two subjects who opted out of answering some or all parts of the ACE Questionnaire were removed from the study, which may have resulted in an under-estimate of the prevalence of ACEs in the sample. Fifth, since current measurement of TS PRS only explains a small proportion of TS genetic risk, the study was underpowered to detect a significant gene-environment correlation which could confound the GxE analysis (Yu et al., 2019). Lastly, the GxE analyses could only be conducted in subjects of European ancestry, since currently there are no large-scale TS GWAS studies of individuals of non-European ancestry with TS with which to generate polygenic risk scores. Furthermore, since the current study was initially designed to examine potential relationships between androgens and tic severity, only male subjects were recruited. Therefore, a larger and more diverse sample with respect to race, ethnicity and gender is also needed to ensure that any future findings may be applied equitably for all individuals with TS.

5. Conclusion

Our findings indicate that childhood adversity is associated with higher lifetime tic severity and functional impairment in individuals with TS and are consistent with previous work demonstrating that childhood adversity plays a significant role in the expression and severity of neuropsychiatric disorders. However, in the absence of prospective, longitudinal data, well-powered polygenic risk score data and genetically-sensitive designs, it is not possible to disentangle the potentially bidirectional graded relationship between ACE exposures and higher tic severity and/or impairment. Replication of these findings should help to enhance our understanding of potentially modifiable non-genetic factors associated with TS disease severity and may shed light on social factors that may need to be addressed in order to reduce lifetime disease burden.

Author contributions

Kelly Yang: Conceptualization, Methodology, Data curation, Software, Formal Analysis, Visualization, Writing - Original draft preparation. **Angela Essa:** Conceptualization, Methodology, Data curation, Software, Formal Analysis, Visualization, Writing - Original draft preparation. **Daisy T. Noriega:** Methodology, Data curation, Software, Formal Analysis, Visualization, Writing – Revision draft preparation. **Lisa Osiecki:** Methodology, Data curation, Investigation, Software, Validation, Writing - Reviewing and Editing. **Caitlin A. Gauvin:** Methodology, Data Curation, Investigation, Writing - Reviewing and Editing. **Dongmei Yu:** Methodology, Formal Analysis, Software, Validation, Writing - Reviewing and Editing. **Cornelia Illmann:** Investigation, Supervision, Project Administration, Writing - Reviewing and Editing. **Marco Bortolato:** Conceptualization, Methodology, Funding Acquisition, Writing - Reviewing and Editing. **Erin C. Dunn:** Conceptualization, Methodology, Supervision, Writing - Reviewing and Editing. **Carol A. Mathews:** Conceptualization, Methodology, Funding Acquisition, Supervision, Project Administration, Writing – Original Draft and Revision, Writing - Reviewing and Editing. **Jeremiah M. Scharf:** Conceptualization, Methodology, Funding Acquisition, Supervision, Project Administration, Writing – Original Draft and Revision, Writing - Reviewing and Editing.

Declaration of competing interest

Drs. Mathews, Scharf and Bortolato have received travel and grant support from the Tourette Association of America (TAA). Drs. Mathews and Scharf are members of the TAA Scientific Advisory Board. Drs. Illmann, Dunn, Gauvin and Ms. Yang, Essa, Noriega and Osiecki report no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.08.024.

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Supplementary Methods

Definition of individual Adverse Childhood Experiences (ACE)

The ACE Study questionnaire was designed as a retrospective self-report to assess participants about eight categories of adverse childhood experiences (ACEs) in their first 18 years of life (Felitti et al., 1998; Dube et al., 2001). Participants could answer each question about individual ACE exposures with one of four responses: never, once or twice, sometimes, often, or very often. All thresholds to define the presence or absence of each ACE exposure were derived from the validated algorithm described in the original Dube et al, 2001 study. **Emotional abuse** was defined by answering "often" or "very often" to either of two questions in this category: (1) "How often did a parent, stepparent, or adult living in your home swear at you, insult you, or put you down?" and (2) How often did a parent, stepparent, or adult living in your home act in a way that made you afraid that you might be physically hurt?". **Physical abuse** was determined by a 2-part question: "Sometimes parents or other adults hurt children. How often did a parent, stepparent, or adult living in your home (1) push, grab, slap, or throw something at you or (2) hit you so hard that you had marks or were injured?". Those who responded "often" or "very often" to the first part or "sometimes," often, or "very often" to the second part qualified as experiencing physical abuse in childhood. **Sexual abuse** was determined if a participant responded "yes" to any of 4 questions regarding situations of sexual touch or sexual intercourse between the participant and a relative, family friend, or stranger. **Domestic violence** was defined by responses of "sometimes," "often," or "very often" to situations involving physical violence toward their mother and any response other than "never" to questions relating to the length and threats of abuse. **Household substance abuse** was determined by an affirmative response to questions indicating childhood exposure to substance abuse in the household. **Mental illness in the household** was defined by an affirmative response to anyone in the household

being mentally ill or depressed. **Parental separation or divorce** was determined by an affirmative response to parents ever being separated or divorced. **Incarceration** was defined by an affirmative response to childhood exposure to a household member who was incarcerated. The number of ACEs were subsequently summed to generate an individual ACE Score per subject with a range from 0 to 8.

Calculation of Tourette syndrome ancestry-adjusted Polygenic Risk Scores (aPRS)

Normalized, genome-wide ancestry-adjusted polygenic risk scores (aPRS) were derived from the previously published TS genome-wide association study (GWAS) of 4,819 TS cases and 9,488 controls (Purcell et al., 2009; Yu et al., 2019). PRS per subject was calculated from GWAS data using a cross-validation method (**Supplementary Methods)** (Yu et al., 2019). All data, including the subjects in the current study, were divided evenly into 8 subsets that were matched on the values of the first principal component. Individual sample PRSs within each of the 8 subsets (target samples) were calculated as the sum of all (GWAS $p \leq 1$) risk alleles of genome-wide, LD-independent SNPs ($r^2 < 0.2$), weighted by the SNP effect sizes derived from the meta-analysis of the other 7 subsets (the discovery sample). Although the PRS of each subset is expected to be drawn from the same distribution due to the conditional randomization described above, to ensure that derived PRSs from each subset remained robust to random fluctuations, all PRS were further adjusted by population stratification and subset effect. The final adjusted PRS (aPRS) values for all TS cases were then normalized to aid in interpretation.

Supplementary Results

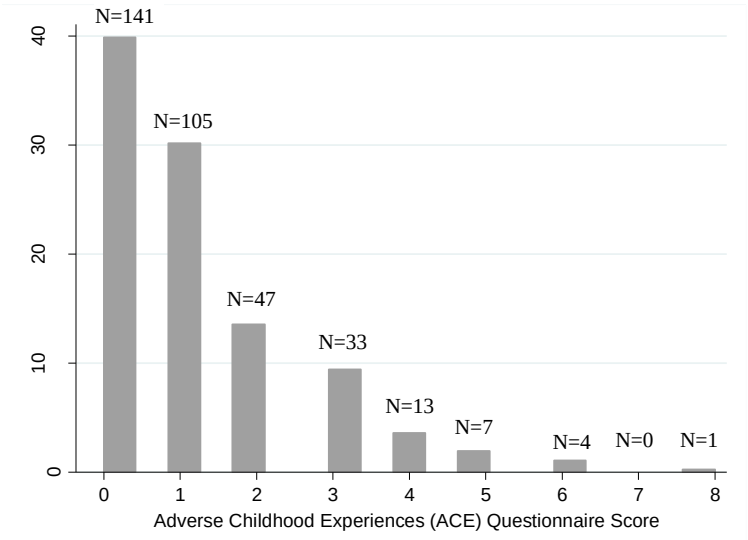

Figure S1. Distribution (percent) of Adverse Childhood Experiences (ACE) by summary scores (ACE Score). ACE Scores range from 0-8 and represent the number of 8 adversity categories experienced per subject. Numbers above each bar indicate the number of study subjects with each ACE Score level.

Adverse Childhood Experience	Frequency in sample N (%)	Frequency in males in Dube et al., 2001 N (%)	Chi2 statistic	p-value
Emotional abuse	66 (17.8)	602 (7.6)	50.8	<0.001
Physical abuse	32 (8.7)	2382 (29.9)	77.2	<0.001
Sexual abuse	45 (12.2)	1276 (16.0)	3.8	0.05
Domestic violence	18 (4.9)	920 (11.5)	15.3	<0.001
Substance abuse	69 (18.7)	1896 (23.8)	5.1	0.02
Mental illness in household	128 (35)	1058 (13.3)	13.0	<0.001
Parental separation/divorce	71 (19.2)	1738 (21.8)	1.4	0.2
Family member in prison	6 (1.6)	324 (4.1)	5.6	0.02
At least one ACE	210 (59.8)	4926 (61.8)	0.6	0.5

Table S1. Frequency and percent of individuals in the study sample who reported experiencing each of the 8 individual categories of childhood adversity in this sample (left) compared to previously published estimates (Dube et al., 2001). ACE, Adverse Childhood Experiences.

	Tic Severity				Impairment			
Univariable Predictor	**β-Coefficient (95% CI)**	**SE**	**p-value**	**N**	**β-Coefficient (95% CI)**	**SE**	**p-value**	**N**
Age of tic onset	-0.3 (-0.6-0.05)	0.2	0.1*	331	-0.3 (-0.7-0.2)	0.2	0.3	347
Race/ethnicity other than White and Non-Hispanic	3.8 (0.3-7.3)	1.8	0.03*	332	1.2 (-4.3-6.7)	2.8	0.7	348
OCD	6.9 (5.1-8.6)	0.9	<0.001*	332	8.1 (5.3-10.8)	1.4	<0.001*	348
ADHD	4.0 (2.1-6.0)	1.0	<0.001*	327	5.4 (2.5-8.4)	1.5	<0.001*	343
ACE Score	1.4 (0.8-2.1)	0.3	<0.001*	332	2.3 (1.3-3.3)	0.5	<0.001*	348
aPRS	-0.2 (-1.2-0.8)	0.5	0.7	285	-1.0 (-2.6-0.5)	0.8	0.2	301

Table S2. Univariable regression results for worst-ever YGTSS Total Tic Severity (left) and Impairment (right) scores. *Met pre-defined criteria for inclusion in the final multi-variable models ($p \leq 0.1$). ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. aPRS, ancestry-adjusted Tourette syndrome Polygenic Risk Scores.

	Tic Severity				Impairment			
Predictor	**β-Coefficient (95% CI)**	**SE**	**p-value**	**R^2**	**β-Coefficient (95% CI)**	**SE**	**p-value**	**R^2**
White and Non-Hispanic	ref				ref			
All other groups	2.0 (-1.2-5.2)	1.6	0.21	0.014	-1.1 (-6.3-4.0)	2.6	0.67	0.001
OCD	6.0 (4.1-7.8)	1.0	<0.001	0.115	7.0 (4.1-9.9)	1.5	<0.001	0.058
ADHD	1.0 (-0.9-3.0)	1.0	0.30	0.044	1.8 (-1.2-4.9)	1.6	0.24	0.019
ACE Score	1.1 (0.5-1.7)	0.3	0.001	0.030	1.9 (0.9-2.9)	0.5	<0.001	0.061
Age of Tic Onset	-0.09 (-0.4-0.2)	0.2	0.55	0.001	NA			

Table S3. Primary multivariable regression models for worst-ever YGTSS Total Tic Severity Score (left) and worst-ever YGTSS Impairment Score (right) including all variables significantly associated with Tic Severity and/or Impairment in the univariable analyses. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. NA, Not Applicable (Age of Tic Onset was not significant in the univariable analyses of Tic Impairment). The prespecified significance threshold for each covariate in the multivariable models was p<0.05. Model statistics (Tic Severity): $F_{5, 320}$=16.35, P<0.001; Overall model R^2=0.20; Adjusted R^2=0.19; N=326. Model statistics (Impairment): $F_{4, 338}$=13.74, P<0.001; Overall model R^2=0.14; Adjusted R^2=0.13; N=343.

	Tic Severity			Impairment		
Predictor	**β-Coefficient (95% CI)**	**SE**	**p-value**	**β-Coefficient (95% CI)**	**SE**	**p-value**
Emotional Abuse	3.5 (1.0-6.1)	1.3	0.007	9.2 (5.2-13.1)	2.0	<0.001
Physical Abuse	4.9 (1.4-8.3)	1.8	0.006	10.6 (5.4-15.8)	2.6	<0.001
Sexual Abuse	4.7 (1.8-7.6)	1.5	0.002	7.9 (3.3-12.5)	2.3	0.001
Domestic Violence	7.9 (3.4-12.4)	2.3	0.001	10.4 (3.6-17.2)	3.4	0.003
Substance Abuse	3.2 (0.6-5.7)	1.3	0.01	4.6 (0.7-8.5)	2.0	0.02
Mental Illness	3.1 (1.0-5.3)	1.1	0.005	6.9 (3.7-10.2)	1.7	<0.001
Divorce	4.0 (1.4-6.6)	1.3	0.003	6.3 (2.3-10.2)	2.0	0.002
Incarceration	11.3 (4.2-18.4)	3.6	0.002	16.1 (4.9-27.5)	5.7	0.006
ACE Score	1.5 (0.8-2.1)	0.3	<0.001	2.4 (1.4-3.4)	0.5	<0.001

Table S4. Linear regression assessing the relationship between individual ACE categories or ACE Score and worst-ever Total Tic Severity score (left panel) and Impairment score (right panel), compared to individuals who experienced no adversity as a reference. Each ACE category was adjusted for covariates that were significantly associated with ACE Score in the univariable analyses excluding OCD and ADHD. ACE, Adverse Childhood Experiences. The prespecified significance threshold for each covariate in the multivariable models was p<0.05. Model statistics (ACE Score, Tic Severity): $F_{3, 327}$=7.94, P<0.001; Overall model R^2=0.078; Adjusted R^2=0.07; N=331. Model statistics (ACE Score, Impairment): $F_{3, 343}$=7.94, P<0.001; Overall model R^2=0.065; Adjusted R^2=0.057; N=347.

Tic Severity	Excluding OCD & ADHD			Including OCD & ADHD		
Predictor	**β-Coefficient (95% CI)**	**SE**	**p-value**	**β-Coefficient (95% CI)**	**SE**	**p-value**
Race and ethnicity	3.8 (0.4-7.1)	1.7	0.03	2.1 (-1.0-5.3)	1.6	0.2
Age of tic onset	-0.3 (-0.6-0.04)	0.15	0.09	-0.1 (-0.4-0.2)	0.15	0.7
ADHD	-	-	-	0.7 (-0.3-1.6)	0.5	0.2
OCD	-	-	-	3.0 (2.1-3.9)	0.5	<0.001
Incarceration	8.0 (0.7-15.2)	3.7	0.03	5.8 (-1.1-12.6)	3.5	0.1
Domestic violence	6.2 (1.9-10.4)	2.2	0.005	5.7 (1.8-9.8)	2.0	0.005
Sexual Abuse	2.5 (-0.2-5.3)	1.4	0.07	-	-	-

Table S5. Stepwise backward elimination of all 8 ACE categories in a single multivariable model for lifetime, worst-ever YGTSS tic severity scores. Left, OCD and ADHD *excluded*; Right, OCD and ADHD *included*. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. Model Statistics (w/o OCD/ADHD): $F_{5, 316}$=5.03, P<0.001; Overall model R^2=0.07; Adj. R^2=0.06; N=322. Model Statistics (w/ OCD/ADHD): $F_{6, 310}$=13.26, P<0.001; Overall model R^2=0.20; Adj. R^2=0.19; N=317.

Tic Impairment	Excluding OCD & ADHD			Including OCD & ADHD		
Predictor	**β-Coefficient (95% CI)**	**SE**	**p-value**	**β-Coefficient (95% CI)**	**SE**	**p-value**
Race and ethnicity	0.5 (-4.8-5.8)	2.7	0.8	-1.4 (-6.5-3.7)	2.6	0.6
Age of tic onset	-0.03(-0.5-0.4)	0.2	0.9	0.2 (-0.3-0.6)	0.2	0.5
ADHD	-	-	-	0.9 (-0.7-2.4)	0.8	0.3
OCD	-	-	-	3.7 (2.2-5.1)	0.7	<0.001
Emotional Abuse	6.3 (2.6-9.9)	1.8	0.001	5.6 (2.1-9.1)	1.8	0.002
Mental Illness	4.0 (1.0-6.9)	1.5	0.008	3.3 (0.5-6.2)	1.5	0.02

Table S6. Stepwise backward elimination of all 8 ACE categories in a single multivariable model for lifetime, worst-ever YGTSS impairment scores. Left, OCD and ADHD *excluded*; Right, OCD and ADHD *included*. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. Model Statistics (w/o OCD/ADHD): $F_{4, 332}$=5.59, P<0.001; Overall model R^2=0.06; Adj. R^2=0.05; N=337. Model Statistics (w/ OCD/ADHD): $F_{6, 325}$=9.62, P<0.001; Overall model R^2=0.15; Adj. R^2=0.14; N=332.

	Tic Severity				Tic Impairment			
Predictor	**β-Coefficient (95% CI)**	**SE**	**p-value**	**R^2**	**β-Coefficient (95% CI)**	**SE**	**p-value**	**R^2**
ACE Score	2.3 (0.3-4.4)	1.0	0.03	0.048	2.1 (1.0-3.1)	0.5	<0.001	0.045
Age of Tic Onset	-0.1 (-0.6-0.3)	0.2	0.6	0.011	-	-	-	-
aPRS	-1.9 (-4.3-0.6)	1.2	0.1	0.002	-2.6 (-4.7-0.6)	1.0	0.01	0.006
ACE Score x aPRS	0.8 (0.1-1.6)	0.4	0.03	0.023	1.3 (0.2-2.4)	0.6	0.02	0.017
Age of Tic Onset x aPRS	0.1 (-0.2-0.3)	0.1	0.7	<0.001	-	-	-	-
ACE Score x Age of Tic Onset	-0.1 (-0.4-0.1)	0.1	0.3	0.004	-	-	-	-

Table S7. Fully saturated multivariable Gene-by-Environment (GxE) regression model for YGTSS worst-ever Total Tic Severity Score (left) and Impairment Score (right) including all Gene-by-Covariate and Environment-by-Covariate interaction terms excluding OCD and ADHD in the model. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. R^2, Effect size estimate for each predictor in the model. aPRS, ancestry-adjusted Tourette syndrome Polygenic Risk Scores. The prespecified significance threshold for each covariate in the multivariable models was p<0.05. Model statistics (Tic Severity): $F_{6, 277}$=448, P=0.002; Overall model R^2=0.09; Adjusted R^2=0.07; N=284. Model statistics (Impairment): $F_{3, 297}$=7.20, P<0.001; Overall model R^2=0.07; Adjusted R^2=0.06; N=301.

	Tic Severity			Tic Impairment		
Predictor	**β-Coefficient (95% CI)**	**SE**	**p-value**	**β-Coefficient (95% CI)**	**SE**	**p-value**
White and Non-Hispanic	ref					
All other groups	3.0 (-0.4-6.4)	1.7	0.08	-	-	-
OCD	6.0 (4.1-7.8)	1.0	<0.001	7.3 (4.4-10.2)	1.5	<0.001
ADHD	1.0 (-0.9-3.0)	1.0	0.30	1.7 (-1.4-4.8)	1.6	0.29
Age of Tic Onset	-0.09 (-0.4-0.2)	0.2	0.55	-	-	-
ACE Score	1.1 (0.5-1.7)	0.3	0.001	2.1 (1.1-3.1)	0.5	<0.001

Table S8. Multivariable regression model for worst-ever YGTSS Total Tic Severity (left) and Tic Impairment (right) including all variables significantly associated with Tic Severity and/or Impairment in the univariable analyses <u>after removing 19 subjects who reported experiencing age at worst tics before age at first ACE</u>. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. R^2, Effect size estimate for each predictor in the model. The prespecified significance threshold for each covariate in the multivariable models was p<0.05. Model statistics (Tic Severity): $F_{5, 308}$=17.19, P<0.001; Overall model R^2=0.22; Adjusted R^2=0.21; N=314. Model statistics (Impairment): $F_{3, 326}$=20.17, P<0.001; Overall model R^2=0.16; Adjusted R^2=0.15; N=330.

Predictor	β-Coefficient (95% CI)	SE	P-value
OCD	7.2 (4.6-9.9)	1.3	<0.001
ADHD	0.7 (-2.4-3.8)	1.6	0.6
ACE Score	3.1 (0.6-5.6)	1.3	0.02
Age of Tic Onset	0.1 (-0.4-0.5)	0.2	0.8
aPRS	-2.0 (-4.9-0.8)	1.4	0.2
ACE Score x aPRS	0.6 (-0.1-1.4)	0.4	0.1
ADHD x aPRS	0.1 (-2.1-2.2)	1.1	0.9
OCD x aPRS	0.7 (-1.5-2.8)	1.1	0.5
Age of Tic Onset x aPRS	0.1 (-0.2-0.4)	0.1	0.5
ADHD x ACE Score	0.4 (-1.1-1.9)	0.8	0.6
OCD x ACE Score	-1.5 (-3.0-0.01)	0.8	0.05
Age of Tic Onset x ACE Score	-0.2 (-0.5-0.1)	0.1	0.2

Table S9. Multivariable Gene-by-Environment (GxE) regression model for YGTSS worst-ever Total Tic Severity including an interaction term for ACE Score and adjusted TS Polygenic Risk Scores (aPRS) <u>after removing 19 subjects who reported experiencing age at worst tics before age at first ACE</u>. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. aPRS, ancestry-adjusted Tourette syndrome Polygenic Risk Scores. R^2, Effect size estimate for each predictor in the model. The prespecified significance threshold for each covariate in the multivariable models was p<0.05. Model statistics: $F_{12, 257}$=5.80, P<0.001; Overall model R^2=0.21; Adjusted R^2=0.176; N=270.

Predictor	β-Coefficient (95% CI)	SE	p-value
OCD	7.2 (3.1-11.3)	2.1	<0.001
ADHD	2.3 (-2.4-7.0)	2.4	0.3
ACE Score	2.1 (0.3-4.0)	0.9	0.02
aPRS	-2.0 (-4.6-0.6)	1.3	0.1
ACE Score x aPRS	0.9 (-0.2-2.0)	0.6	0.1
ADHD x aPRS	1.6 (-1.7-5.0)	1.7	0.3
OCD x aPRS	-1.6 (-4.9-1.7)	1.7	0.3
ADHD x ACE Score	0.2 (-2.1-2.5)	1.2	0.9
OCD x ACE Score	-0.5 (-2.8-1.8)	1.2	07

Table S10. Multivariable Gene-by-Environment (GxE) regression model for YGTSS worst-ever Tic Impairment including an interaction term for ACE Score and adjusted TS Polygenic Risk Scores (aPRS) <u>after removing 19 subjects who reported experiencing age at worst tics before age at first ACE</u>. ACE, Adverse Childhood Experiences. YGTSS, Yale Global Tic Severity Scale. aPRS, ancestry-adjusted Tourette syndrome Polygenic Risk Scores. R^2, Effect size estimate for each predictor in the model. The prespecified significance threshold for each covariate in the multivariable models was $p<0.05$. Model statistics: $F_{9, 276}=.0$, $P<0.001$; Overall model $R^2=0.17$; Adjusted $R^2=0.137$; N=286.