Clinical precursors of tics: an EMTICS study

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Background: Children with Tourette syndrome (TS) often have comorbid disorders, particularly attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). While subtle premorbid symptoms have been described in various psychiatric disorders, the presence of clinical precursors that may exist before the onset of tics is unknown. This longitudinal study aimed to find clinical precursors of tics by assessing a range of clinical characteristics prior to tic onset in comparison with children without onset of tics. Methods: A sample of 187 3- to 10-year-old first-degree unaffected relatives of children with TS were followed up to 7 years in the European Multicentre Tics in Children Study (EMTICS). We investigated whether clinical characteristics assessed at baseline predicted tic onset, comparing 126 children without tic onset to 61 children who developed tics. We used the least absolute shrinkage and selection operator (LASSO) method, a penalised logistic regression approach. We also explored sex differences and repeated our analyses in an age- and sex-matched subsample. Results: Children with tic onset were more frequently male (β = −0.36), had higher baseline severity of conduct problems (β = 0.23), autism spectrum disorder symptoms (ASD; β = 0.08), compulsions (β = 0.02) and emotional problems (β = 0.03) compared to children without tic onset. Conduct and ASD problems were male-specific predictors, whereas severity of compulsions and oppositional (β = 0.39) and emotional problems were female-specific predictors. Conclusion: This study supports the presence of clinical precursors prior to tic onset and highlights the need of sex-specific monitoring of children at risk of developing tics. This may aid in the earlier detection of tics, particularly in females. We moreover found that tics most often persisted one year after tic onset, in contrast to the common belief that tics are mostly transient. Keywords: Compulsions; conduct problems; clinical precursors; sex differences; tic onset.

Introduction

Chronic tic disorders, that is Tourette syndrome (TS) and persistent (chronic) motor or vocal tic disorder, are childhood-onset disorders characterised by the presence of multiple motor and/or vocal tics, lasting at least one year (American Psychiatric Association, 2000). Tic disorders are more common in males than in females (with a 3:1 ratio; Hirschtritt et al., 2015) with an average onset of 6 years of age (range 3–8.6; Leckman et al., 1998). An estimated 87.5% of individuals with TS have psychiatric comorbidity (Hirschtritt et al., 2015), most frequently attention-deficit/hyperactivity disorder (ADHD; 54%) and obsessive-compulsive disorder (OCD; 50%), but also disruptive behaviour disorders (oppositional defiant disorder [ODD] or conduct disorder [CD]; 30%), internalising disorders (anxiety and depression; 30%; Hirschtritt et al., 2015) and autism spectrum disorder (ASD; 4.5%–15%; Rizzo, Gulisano, Domini, Ferro, & Curatolo, 2017). Similar to tic disorders, ADHD, ODD, CD and ASD show a male preponderance and an onset in (early) childhood (Hirschtritt et al., 2015; Steinhausen & Jakobsen, 2019). In contrast, OCD and internalising disorders occur more frequently in females, especially in adolescents (Leckman et al., 1998; Steinhausen & Jakobsen, 2019). The potentially disabling tics and the high rates of psychiatric comorbidity can have a significant impact on the quality of life (Eapen, Snedden, Črnec, Pick, & Sachdev, 2016). Tic disorders are often under-recognised, with retrospectively estimated delays of 10 years between onset and diagnosis (Bäumer, Sajin, & Müchau, 2016), and reasons for first referral to mental healthcare are frequently due to other behavioural or emotional problems rather than tics (Khalifa & Von Knorring, 2005). As tic disorders and comorbid conditions share a common genetic background (Brainstorm Consortium et al., 2018), an early general liability to the presence of (milder levels of) behavioural and emotional problems seems plausible. A body of research has focussed on identifying (subtle) early-life clinical characteristics that precede the onset of psychiatric disorders (e.g. inattention as a precursor of ASD or neurological soft signs as a precursor of ADHD; Athanasiadou et al., 2020; Hafeman et al., 2017; Mörckie et al., 2019). However, it is not yet known whether early symptom characteristics precede the onset of tics. Insight into these factors may possibly aid in the timely detection of tics and early intervention. We therefore followed high-risk children aged 3–10 years for up to 7 years, who at study entry were...
unaffected first-degree relatives (siblings) of children with chronic tic disorders. We compared a variety of dimensional clinical symptom scales and a quality-of-life score assessed at baseline between children with and without subsequent onset of tics and explored possible sex differences. We expected the presence of premorbid symptoms prior to tic onset that differed between males and females in line with the sex-specific distribution of comorbid conditions.

Methods
Participants and procedures
As part of the ONSET cohort of the European Multicentre Tics in Children Study (EMTICS; Schrag et al., 2019), including 16 European clinical sites, we followed 259 3- to 10-year-old first-degree relatives (siblings) of children with a chronic tic disorder, who had no tics at baseline. Children were assessed every two months for possible tic onset for three years using the symptom list of the Yale Global Tic Severity Scale assessed by a semi-structured clinician interview (YGTTSS; Leckman et al., 1989). After the study ended, we re-evaluated the unaffected children for possible tic onset by a brief telephone interview in a similar way. The overall average participation in the study was 3.5 (range 0.6–9) years between February 2013 and May 2020. A total of 68 confirmed tic onsets occurred, confirmed by the study clinician (that is, in 26.3% of the siblings, of which 57.4% [n = 39] in males and 42.6% [n = 29] in females). To define the unaffected comparison group, we selected unaffected children who were at least 10 years old at the last regular study visit, to limit the possibility of tic onset in this group. Our final sample consisted of 187 children: n = 61 children with a tic onset and n = 126 children without a tic onset. Finally, during a brief 1-year follow-up telephone interview by the study clinician, we assessed the chronicity of tics in the children with a tic onset confirming a tic disorder diagnosis according to DSM-IV-TR. See Appendix S2 for a detailed description of the study participants and procedures, and Figures S1 and S2 for study flow charts. Study methods have been extensively described in Schrag et al. (2019).

Exclusion criteria for the ONSET cohort at study entry were presence of tics, OCD and trichotillomania, presence of a serious medical or neurological illness, treatment with antibiotics during the last month (given another EMTICS sub-study) and being unable to understand and comply with study procedures. Subjects were allowed to receive treatment for mental health problems. The children’s parents or legal guardians provided written informed consent in line with the local medical-ethical regulations. The study was approved by the local research ethics committees of the participating centres.

Clinical measures
At the baseline visit, parents were asked to complete questionnaires regarding their child’s current behavioural and emotional symptoms and quality of life. We used the Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; Scabilia et al., 1997; Storch et al., 2006) to assess past week severity of obsessions and compulsions using a semi-structured clinician interview at baseline. Further, we used the parent-rated Swanson Nolan and Pelham-IV rating scale (SNAP-IV; Bussing et al., 2008; Swanson et al., 2001) to assess past week inattention, hyperactivity/impulsivity and ODD severity; the parent-rated Autism Spectrum Screening Questionnaire (ASSQ; Ehlers, Gillberg, & Wing, 1999) to rate symptoms of ASD; and the Strengths and Difficulties Questionnaire (SDQ; Goodman, Ford, Restryst, Price, & Simmons, 2000) to assess conduct and emotional problems in the past two weeks. Health-related quality of life was measured by the parent-rated KINDL-R questionnaire over the past week (Ravens-Sieberer & Bullinger, 1998). See Appendix S3 for more information on the clinical measures.

Data analytic strategy
The percentage of missing data was <1% and imputed by means of the expectation-maximisation algorithm (Tabachnick & Fidell, 2001). Appendix S4 describes the statistical analyses of sample characteristics. We applied a logistic least absolute shrinkage and selection operator (LASSO; Tibshirani, 1996) using the glmnet-package (Friedman, Hastie, & Tibshirani, 2010) in R to determine predictors of tic onset. LASSO has good prediction accuracy, reduces overfitting and mitigates the issue of multicollinearity, especially when facing a small number of observations and a larger number of predictors. While LASSO is well-suited to select relevant predictors, the strengths of associations can be less well inferred. This method automatically assigns a different weight to the standardised predictors. As a result, all nonrelevant predictors are set to zero, and only the relevant (best fitting) predictors are selected. The selection of the penalty term is done by cross-validation, where the average mean cross-validated error is calculated through 10,000 iterations to get the best fitting penalty term. Of importance, no statistical significance is calculated with this analysis, only the relevance of a predictor to the outcome of interest. Statistical relevance of a predictor was defined as the presence of a nonzero beta coefficient and nonzero explained deviance (comparable to explained variance, but based on the –2 log-likelihood instead of the residuals of the model; explained deviance indicates model fit with a range of 0–1, with a higher score indicating better fit; Finch & Hernandez Finch, 2016). Of note, due to the shrinkage process of LASSO (i.e. only selecting the best fitting predictors and setting all other predictors to zero), the nonzero beta coefficients are estimates; hence, they should be interpreted with caution since LASSO creates an upward bias for nonzero coefficients. The explained deviance of the predictors was calculated through the leave-one-out method; the predictor of interest is left out of the total model causing a change in the explained deviance of the total model. The difference in the standardised explained deviance of the total model and the model without the predictor of interest is the contribution of this predictor to the model (Finch & Hernandez Finch, 2016), with a larger difference in explained deviance indicating a higher relevance as a predictor for tic onset.

As a first analysis, we performed a logistic LASSO regression with tic onset as an outcome measure in the whole sample (n = 187; of whom 61 had a tic onset) and the symptom scales and health-related quality of life as predictors of interest. We furthermore added age and sex (given significant univariate results) and site (using dummy variables) as covariates in all analyses. As a second analysis, we repeated the logistic LASSO regression separately for males (n = 86; of whom 36 had a tic onset) and females (n = 101; of whom 25 had a tic onset), respectively.

As a sensitivity analysis, we re-analysed the logistic LASSO regression in a matched group on age and sex (n = 122; n = 61 children with and without a tic onset), using propensity score matching in R (Randolph, Falbe, Kureethara Manuel, & Ballou, 2014). A second sensitivity analysis was performed using the ASSQ severity score without the three items that may resemble tic-like movements (a) ‘Expresses sounds involuntarily; clears throat, grunts, snarks, cries or screams’; (b) ‘Has involuntary face or body movements’; (c) ‘Has clumsy, ill-coordinated, ungracefully, awkward movements or gestures’, to remove the possible influence of these tic-like items on the ASSQ as a possible predictor for tic onset.

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Results

Group characteristics

Children (n = 61) were on average 7.9 years of age (range 3.5–13 years) at tic onset, and it took on average 1.1 years (range 0.1–5.4 years) from the start of the study until tics occurred. Table S1 shows the distribution of age of tic onset, with most tic onsets occurring between 4 and 8 years of age. See Table 1 for the group characteristics and univariate group differences in baseline measures in children with and without onset of tics (see Table S2 for group differences divided by sex). There were more boys, and children were younger in the tic onset group compared to the non-tic onset group. Ethnicity, education of the child, and parental education level did not differ between groups. Children in the tic onset group had higher baseline hyperactivity-impulsivity, ODD, CD, and ASD symptom scores compared to those in the non-tic onset group. Of note, all clinical measures significantly increased in severity between the baseline visit and tic onset, while the health-related quality-of-life score decreased.

Correlations between symptom scales

See Table S3, for the Pearson’s product-moment correlation coefficients (r) between symptom scales for the total sample and separately for the tic onset group and the non-tic onset group, and for males and females. Overall, correlations between the symptom scales were largely similar for the tic onset/non-tic onset and for males/females groups. However, a large correlation (r = .73, p < .01) between obsessions and compulsions was observed in the tic onset group, whereas a small correlation (r = .23, p < .01) was found in the non-tic onset group. Additionally, there were small-to-medium-sized significant correlations between compulsions and most clinical characteristics in males (r = .22 – r = .40, p < .05), but not in females (r = −.10 – r = .22, p > .05).

Chronicity of tics after 1-year follow-up

A total of 44 (72%) from 61 children with a tic onset (detected during the regular study term) took part in a 1-year follow-up assessment. We confirmed the continuation of tics after tic onset during at least several weeks in all but one case (n = 43, 97.7%). In 66% (n = 29), the tics were chronic lasting at least 12 months (TS: n = 17, 38.6%; chronic motor tic disorder: n = 12, 27.3%), and 32% (n = 14) fulfilled criteria for tic disorders lasting less than 12 months in accordance with DSM-IV-TR, namely transient tic disorder (i.e. lasting at least 4 weeks but less than 12 months; n = 9, 20.5%) and tic disorder—not otherwise specified (i.e. lasting less than 4 weeks, n = 5, 11.4%).

Predictors of tic onset in the total sample

See Table 2 for the beta coefficients and explained deviances of the first analysis in the total sample, using a logistic LASSO regression to investigate predictors of tic onset. Several factors were relevant (i.e. the beta coefficient and explained deviance were nonzero) as predictors for tic onset: being male, a younger age and a higher severity of compulsions, ASD symptoms and emotional and conduct problems. Note that, compared to the univariate analyses, hyperactivity-impulsivity was no longer relevant, possibly due to conduct problems in the LASSO model (as the correlation between hyperactivity-impulsivity symptoms and conduct problems was r = .76, p < .01).

Predictors of tic onset in males and females

See Table 3 for the beta coefficients and explained deviances in a logistic LASSO regression divided by sex. Precursors associated with tic onset in males were a younger age and a higher severity of ASD symptoms and conduct problems. Precursors associated with tic onset in females were a younger age, and a higher severity of compulsions, and ODD and emotional problems. Note that ODD emerged as a new symptom domain in females compared to the LASSO analysis not stratified by sex, perhaps due to the absence of conduct problems as a predictor in females. Obsessions, ADHD symptom severity and health-related quality of life were not relevant predictors of tic onset in any of the LASSO analyses.

Sensitivity analyses

See Table S4 for the logistic LASSO regression in a matched group on age and sex. Both conduct problems and compulsions remained relevant predictors of tics. Note that due to matching, the sample size was reduced leaving less power to detect relevant results.

In the second sensitivity analysis in the total sample, the beta for ASD symptoms after removing the three questions from the ASSQ resembling tic-like movements remained relevant (β = 0.08, explained deviance 0.17%). In the sex-specific analysis, the beta for ASD symptoms increased from β = 0.01 to β = 0.07, and the explained deviance from 0.03% to 0.31%. The other predictors in the model remained the same. This indicates the relevance of ASD symptoms reflecting social difficulties and autistic traits for tic onset, especially in males.

Discussion

This is the first study to prospectively investigate clinical precursors of tics in high-risk children aged 3-10 years. Tic onset occurred at an average age of
Table 1: Group characteristics in, and univariate group differences between children with and without a tic onset in baseline measures

|                          | Total sample (n = 187) | Tic onset baseline (n = 61) | No tic onset baseline (n = 126) | Test statistic (tic onset vs no tic onset) | Δ tic onset – baseline | Δ last visit (no tic onset) – baseline |
|--------------------------|------------------------|-----------------------------|---------------------------------|---------------------------------------------|-----------------------|--------------------------------------|
| Male sex, n (%)          | 86 (46.0)              | 36 (59.0)                   | 50 (39.7)                       | $\chi^2 = 6.19^a$                         | -                     | -                                    |
| Age years at baseline, M (SD), range | 7.43 (1.89)          | 6.71 (1.85)                 | 7.74 (1.83)                     | $U = 2529.50^b$                         | 0.92 (0.70)           | 2.27 (1.44)                          |
| M (SD), range            | 3.21–10.93             | 3.21–10.39                  | 4.12–10.93                      |                                            |                       |                                      |
| Age years at tic onset, M (SD), range | -                | 7.93 (2.00)                 | -                               |                                            | -                     | -                                    |
| M (SD), range            | -                      | 3.52–13.00                  | -                               |                                            |                       |                                      |
| Caucasian ethnicity, n (%) | 149 (79.7)            | 49 (80.3)                   | 100 (79.4)                      | $\chi^2 = 0.02^a$                        | -                     | -                                    |
| Regular education, n (%) | 167 (89.3)             | 49 (80.3)                   | 118 (93.7)                      | $\chi^2 = 0.41^a$                        | -                     | -                                    |
| Parental education level, M (SD), range | 4.17 (1.07)          | 4.21 (1.00)                 | 4.15 (1.11)                     | $T(182) = -0.35^c$                      | -                     | -                                    |
| M (SD), range            | (1.50–6.00)            | (1.50–6.00)                 | (1.50–6.00)                     |                                            |                       |                                      |
| OCD symptom severity     |                        |                             |                                 |                                            |                       |                                      |
| Obsessions, M (SD)       | 0.63 (2.34)            | 0.52 (2.29)                 | 0.67 (2.34)                     | $T(185) = 0.41^c$                        | 0.78 (3.12)           | 0.12 (0.80)                          |
| Compulsions, M (SD)      | 0.59 (2.34)            | 0.92 (2.29)                 | 0.44 (1.94)                     | $T(198) = -1.34^c$                       | 0.12 (4.10)           | 0.66 (2.51)                          |
| ADHD symptom severity    |                        |                             |                                 |                                            |                       |                                      |
| Inattention, M (SD)      | 5.28 (6.30)            | 5.73 (6.79)                 | 5.07 (6.07)                     | $T(198) = -0.66^c$                       | 1.85 (4.91)           | -0.39 (4.06)                         |
| Hyperactivity-impulsivity, M (SD) | 5.03 (6.11)          | 6.48 (8.67)                 | 4.33 (5.61)                     | $T(198) = -2.28^c$                       | 1.49 (4.00)           | -0.36 (3.49)                         |
| ODD symptom severity     | 4.07 (5.00)            | 5.19 (5.72)                 | 3.52 (4.53)                     | $T(198) = -2.18^c$                       | 1.49 (3.12)           | 0.62 (3.21)                          |
| ASD symptom severity1, M (SD) | 3.60 (6.25)          | 5.24 (8.97)                 | 2.81 (4.19)                     | $T(198) = -2.53^c$                       | -                     | -                                    |
| SDQ symptom severity     |                        |                             |                                 |                                            |                       |                                      |
| Emotional problems, M (SD) | 1.82 (2.09)            | 2.18 (2.29)                 | 1.64 (1.97)                     | $T(198) = -1.67^c$                       | 0.52 (2.09)           | 0.02 (1.96)                          |
| Conduct problems, M (SD) | 1.37 (1.56)            | 1.89 (1.63)                 | 1.13 (1.46)                     | $T(198) = -3.20^c$                       | 0.24 (1.39)           | -0.17 (1.45)                         |
| HR-QoL, M (SD)           | 79.07 (9.35)           | 77.54 (9.42)                | 79.69 (9.25)                    | $T(198) = 1.48^c$                        | -0.86 (9.68)          | -0.77 (9.70)                         |
| OCD1, n (%)              | 5 (2.7)                | 2 (3.3)                     | 3 (2.4)                         | $\chi^2 = 4.10^a$                        | -                     |                                      |
| ADHD1, n (%)             | 21 (11.2)              | 7 (11.5)                    | 14 (11.1)                       | $\chi^2 = 0.01^a$                        | -                     | -                                    |

Ethnicity measured as Caucasian or other; Regular education measured as regular education primary school or special education primary school; Parental education level measured as the average highest education level of both parents, with 1 = under 7 years of schooling to 6 = post-graduate/professional degree; OCD (obsessive-compulsive disorder) severity assessed by the Children’s Yale-Brown Obsessive Compulsive Scale (Scahill et al., 1997); ADHD (attention-deficit/hyperactivity disorder and ODD (oppositional defiant disorder) symptom severity by the parent-rated Swanson Nolan and Pelham-IV rating scale (SNAP-IV [Swanson et al., 2001]); ASD (autism spectrum disorder) symptom severity by the Autism Spectrum Screening Questionnaire (Ehlers et al., 1999); Severity of emotional problems and conduct problems by the Strengths and Difficulties Questionnaire (Goodman et al., 2000); HR-QoL (Health-Related Quality of Life) by the KINDL-R (Ravens-Sieberer & Bullinger, 1998). A diagnosis of comorbid OCD and ADHD was assigned by a trained study clinician according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (American Psychiatric Association, 2000). Between-group differences were tested by $^a$ a Mann-Whitney U test, and $^b$ an independent t-test; $^*p < .05$, $^{**}p < .001$; $\Delta$ = delta, indicating change; $^1$ Assessed only at baseline, $^2$ n = 49 participants with a complete tic onset visit during the study; $^3$ n = 57 participants with a complete final non-tic onset visit during the study.
ADHD symptom severity 0.36 0.74
Age −0.14 3.21
OCD symptom severity
Obsessions 0 0
Compulsions 0.02 0.11
ADHD symptom severity
Inattentive 0 0
Hyperactivity-impulsivity 0 0
ODD symptom severity 0 0
ASD symptom severity 0.08 0.12
SDQ symptom severity
Emotional problems 0.03 0.07
Conduct problems 0.23 0.93
HR-QoL 0 0
Total model 13.31

See for information Tables 1 and 2. LASSO; logistic least absolute shrinkage and selection operator (Tibshirani, 1996)

Statistically relevant predictors were determined by the presence of nonzero betas and nonzero explained deviance. Due to the shrinkage process of LASSO (i.e., only selecting the best fitting predictors and setting all other predictors to zero), the beta coefficients are estimations and must be interpreted with caution. The explained deviance shows the contribution in percentage (%) of the predictor to the model, with a higher explained deviance indicating a higher relevance of the predictor to tic onset. Of note, the explained deviations of the individual variables do not add up to the explained deviance in the total model due to the interrelationship of variables (i.e., leaving out one variable can lead to other variables taking over explained deviance).

Table 2 Estimated coefficients and explained deviance of predictors of tic onset using a logistic LASSO regression [n = 187, of which 61 had tic onset]

| Predictor                        | β     | Explained deviance (%) |
|----------------------------------|-------|------------------------|
| Sex                              | −0.36 | 0.74                   |
| Age                              | −0.14 | 3.21                   |
| OCD symptom severity             |       |                        |
| Obsessions                       | 0     | 0                      |
| Compulsions                      | 0.02  | 0.11                   |
| ADHD symptom severity            |       |                        |
| Inattentive                      | 0     | 0                      |
| Hyperactivity-impulsivity        | 0     | 0                      |
| ODD symptom severity             | 0     | 0                      |
| ASD symptom severity             | 0.08  | 0.12                   |
| SDQ symptom severity             |       |                        |
| Emotional problems               | 0.03  | 0.07                   |
| Conduct problems                 | 0.23  | 0.93                   |
| HR-QoL                           | 0     | 0                      |
| Total model                      | 13.31 |                        |

See for more information Table 1. LASSO; logistic least absolute shrinkage and selection operator (Tibshirani, 1996)

Table 3 Estimated coefficients and explained deviance of predictors of tic onset using a logistic LASSO regression divided by sex

| Predictor                        | Explan. deviance (%) | Explan. deviance (%) |
|----------------------------------|----------------------|----------------------|
| Males (n = 86, of which 36 with tic onset) |                       |                      |
| Age                              | −0.31                | 2.62                 |
| OCD symptom severity             |                      |                      |
| Obsessions                       | 0                    | 0                    |
| Compulsions                      | 0.39                 | 2.65                 |
| ADHD symptom severity            |                      |                      |
| Inattentive                      | 0                    | 0                    |
| Hyperactivity-impulsivity        | 0                    | 0                    |
| ODD symptom severity             | 0.39                 | 1.13                 |
| ASD symptom severity             | 0.01                 | 0.03                 |
| SDQ symptom severity             | 0.11                 | 0.39                 |
| Emotional problems               | 0.20                 | 1.49                 |
| Conduct problems                 | 0                    | 0                    |
| HR-QoL                           | 0                    | 0                    |
| Total model                      | 17.10                | 22.56                |

See for information Tables 1 and 2.

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degree relatives. It should be noted that the SDQ conduct problems scale partly includes ODD symptoms; yet, we did not find an association of the SNAP-IV ODD scale with tic onset in males. More large-scale studies are needed to further elucidate the relationship between externalising behaviours and tic disorders.

In males, tics were also preceded by ASD symptoms reflecting social difficulties and autistic traits such as repetitiveness or restricted interests (Posserud et al., 2008). Symptoms of autism are often already noticeable in early childhood (2–3 years of age; Steinhausen & Jakobsen, 2019), generally before the occurrence of tics (range 3–8.6 years of age; Leckman et al., 1998) with a male predominance (Steinhausen & Jakobsen, 2019). The association of ASD symptoms with tic onset may thus reflect the known co-occurrence of ASD in children with TS (e.g. 21%; Rizzo et al., 2017). Still, in contrast to ADHD and OCD, a recent genome-wide association study meta-analysis has shown that ASD has a low magnitude of genetic correlation with TS, suggesting that ASD and TS are more distinct than the other psychiatric disorders (Brainstorm Consortium et al., 2018). Yet other studies support the involvement of abnormalities in cortico-striatal circuits in both ASD and TS (McBride & Parker, 2015; Rizzo et al., 2017). Importantly, although certain repetitive stereotypic behaviours (e.g. hand/body movements) may be observed in both ASD and TS (Huisman-van Dijk, Schoot, Rijkeboer, Mathews, & Cath, 2016; Rizzo et al., 2017), ASD symptoms became an even stronger predictor of tic onset in our study after removing items that may resemble tic-like behaviours (e.g. ‘has involuntary face or body movements’ and ‘expresses sounds involuntarily’), confirming that indeed other ASD symptoms (such as social communication impairments and preoccupation with routines) precede tic onset, especially in males.

Precursors of tic onset in females were compulsions, emotional problems and ODD behaviours. Both OCD and emotional problems (anxiety/depression) show a higher occurrence in females than males, both in samples with TS and in the general population, increasing with age (Hirschtritt et al., 2015; Steinhausen & Jakobsen, 2019). In children with TS, being female was a strong predictor of emotional disorders (including anxiety, phobia and depression) in early adulthood (Groth, Skov, Lange, & Debes, 2019). Yet the onset of OCD and mood disorders is typically in the early adolescent years (from age 11–14 years; Steinhausen & Jakobsen, 2019) in females and thus after the usual age of onset of tics (Leckman et al., 1998). However, subthreshold OCD symptoms and anxiety disorders have also been reported in children as early as age 5–6 years (Fineberg et al., 2013; Hirschtritt et al., 2015), and OCD symptoms may be experienced up to 5 years before meeting criteria for an OCD diagnosis (Coles, Johnson, & Schubert, 2011). Consistent with our prospective finding, early-onset OCD (†10 years of age) has been associated with a higher risk of tic disorders (Chabane et al., 2005; Janowitz et al., 2009). Although early-onset OCD has often been linked to male sex (Steinhausen & Jakobsen, 2019), Hirschtritt et al., (2015) reported an age of onset of comorbid OCD as early as seven years in both boys and girls with TS. In line with our study, females with TS were more likely than males to display compulsive tics at tic onset (Santangelo et al., 1994). The close interrelationship between OCD and TS is also reflected in recent studies suggesting a shared genetic architecture (Brainstorm Consortium et al., 2018; Yu et al., 2015), and in shared or similar clinical characteristics such as repetitive behaviours (e.g. counting, touching), often not without ambiguity in distinguishing between (compulsive) tics, compulsions or ASD-related movements (Huisman-van Dijk et al., 2016; Rizzo et al., 2017). Of note, despite OCD being underrepresented in our study (as an OCD diagnosis was an exclusion criterion; Schrag et al., 2019), compulsions still emerged as a consistent predictor for tic onset in our study. Yet, the lack of association of compulsions with tic onset in males in our study may perhaps be due to the considerable correlation of compulsions with the other symptom domains found only in males. Finally, we may not have observed obsessions as a significant predictor of tics due to the age of our sample, in line with previous observations that compulsions are generally reported earlier than symptoms of obsessions (Coles et al., 2011; Fineberg et al., 2013).

ODD problems as a female predictor of tic onset were unexpected given that externalising disorders (ADHD, ODD and CD) are typically male-predominant, and frequently co-occurring (Hirschtritt et al., 2015; INSERM Collective Expertise Centre, 2015; Steinhausen & Jakobsen, 2019). Perhaps ODD problems emerged as a predictor in female participants, given the absence of conduct problems as a predictive factor of tic onset in females. Consistent with this, females with ODD generally present with higher comorbidity of symptoms in the internalising domain (anxiety and depression), whereas in males ODD has been more associated with symptoms in the externalising domain (CD and ADHD; Trepat & Ezpeleta, 2011). More recently, an affective dimension of ODD (irritability/negative affect) has been distinguished from a behavioural dimension (defiant behaviour/headstrong) suggestive of distinct aetiologies (Leadbeater & Homel, 2015). Indeed, a recent study in TS indicated that these ODD dimensions in childhood are developmentally linked to respectively internalising (as well as to OCD; Thériault et al., 2014) and externalising mental health symptoms in adulthood (Thériault et al., 2018). Overall, our sex-specific findings in females seem to reflect symptoms in the affective-anxiety
domain (note that anxiety and harm avoidance also largely underlie compulsions), consistent with their higher prevalence in females. These symptoms may be closely watched in females with a familial risk to develop tics.

Important strengths of this study are the large sample and prospective design enabling us to investigate clinical precursors of tic onset in children at heightened risk of developing tics. Also, the use of LASSO regression overcomes issues with multicollinearity and minimises overfitting, yet the method is most suited to indicate the relevance of associations rather than their strengths. Weaknesses of this study are an underestimation of the presence of OCD in our sample; nevertheless, compulsions still emerged as a predictor for tic onset in our study. Moreover, the assessment of past week symptom severity at baseline rather than longer time windows may also have caused an underestimation of effects. In addition, we made comparisons with unaffected first-degree relatives, who may have higher rates of psychiatric problems than the general population, thus potentially masking differences in clinical characteristics preceding tics, in comparison to the general population. Also, we cannot rule out that some of the unaffected children may still develop tics after the age of 10, even though the typical age of onset of tics is well below that age; still, the recurrence risk rate of tic onset of our sample is in line with the literature (Heiman et al., 2020), thus not suggesting many missing tic onsets. Further, we may have failed to include young children in our high-risk sample, perhaps having resulted in a higher average age of tic onset than in other studies (Leckman et al., 1998). Lastly, the time difference between baseline and tic onset varied between children; we chose characteristics at baseline to capture the earliest possible precursors. Future studies may focus on longitudinal analyses assessing multiple time points that lead up to tic onset. Moreover, future research may include younger children than in our cohort and explore genetic loading (polygenic risk) across symptom domains between cases with tics and unaffected siblings as well as nonfamiliar controls. Other factors may be considered, including family history, contextual variables that may be shared between family members (e.g. family and parental functioning) and other environmental risk factors (e.g. prenatal adversities, early life stress) potentially affecting premorbid symptomatology.

Conclusion
Our study points to a distinct symptom presentation in children prior to the onset of tics. Our results clearly suggest a sex-specific profile, with conduct problems and ASD symptoms preceding tic onset in males, and compulsions, and emotional and ODD problems as precursors in females. A variety of premorbid subtle symptoms may exist as precursors to tics, highlighting the need of regular monitoring of high-risk children from preschool age onwards, taking sex differences into account. Increased awareness of health professionals and parents may benefit the early detection of tics setting off treatment strategies preventing negative outcomes often associated with this highly stigmatising condition compromising quality of life. Girls may particularly benefit as they may be particularly prone to late diagnosis of tics, due to their different symptom presentation than in boys who typically show problematic behaviour at an earlier age than girls.

Supporting information
Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. EMTICS group authorship.
Appendix S2. Full description of study sample, procedures and quality assessment.
Appendix S3. Further description of clinical measures.
Appendix S4. Description of the statistical analyses of the sample characteristics.
Appendix S5. Further funding support and acknowledgements.
Table S1. Distribution of age of tic onset.
Table S2. Group characteristics for males and females.
Table S3. Correlations between clinical symptom scales.
Table S4. Logistic LASSO regression in a matched sample on age and sex.
Figure S1. EMTICS ONSET cohort study procedures flow chart.
Figure S2. Study flow chart: final study n=187 participants.

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Key points

- Whether subtle clinical precursors may exist before the onset of tics is currently unknown.
- This prospective study aimed to find subtle clinical precursors of tics by assessing a range of symptoms prior to tic onset in comparison with children without tic onset.
- Our results indicate a distinct symptom presentation prior to the development of tics.
- Findings are sex-specific, with conduct problems and autism spectrum symptoms as precursors of tics in males and with compulsions and emotional and oppositional-defiant problems in females.
- Our results highlight the need of regular monitoring of high-risk children from preschool age onwards, taking sex differences into account.

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