Tourette syndrome in a longitudinal perspective

Clinical course of tics and comorbidities, coexisting psychopathologies, phenotypes and predictors

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This review has been accepted as a thesis together with three previously published papers by University of Copenhagen 28th February 2017 and defended on 11th May 2017

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Dan Med J 2018;65(4):B5465

The thesis is based on the following papers:

1. Groth C, Debes NM, Rask CU, Lange T, Skov L. Course of Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study. J Am Acad Child Adolesc Psychiatry 2017; 56: 304–312.

2. Groth C, Debes NM, Skov L. Phenotype development in adolescence with Tourette syndrome: a large clinical longitudinal study. J Child Neurol 2017 Nov;32(13):1047-1057

3. Groth C, Debes NM, Lange T, Skov L. Predictors for the clinical course of Tourette syndrome: a longitudinal study. Manuscript submitted.

INTRODUCTION

The Marquise de Dampierre was the first patient reported with motor and vocal tic symptoms in a case described in 1825 by Jean Marc Itard at the Salpetriere Hospital in Paris. In 1885, Georges Albert Edouard Brutus Gilles de la Tourette described nine patients in "Étude sur une affection nerveuse caractérisée par de l'incoordination motrice accompagnée d'écolalie et de coprolalie"(1) as having motor incoordination accompanied by echolalia and coprolalia, but distinct from hysteria and chorea. His teacher Jean-Martin Charcot later named the syndrome 'Gilles de la Tourette.'

Tourette syndrome (TS), which was previously regarded as rare, is now a well-known disorder with a prevalence of approximately 0.8% (range 0.3–5.7) in children and adolescents, and predominantly affects boys (ratio 3–4:1) (2–4). TS is a hereditary, chronic neurodevelopmental disorder characterised by multiple motor and vocal tics and by frequent comorbidities and coexisting psychopathologies (3,5–8). It is diagnosed using clinical criteria defined by the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5).

Definition*: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.*

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease or post-viral encephalitis).

This study has used the previous DSM-IV-Text Revision (DSM-IV-TR) criteria, which differs only in criteria B and requires that there has never been a tic-free period of more than 3 consecutive months. Similarly, the International Classification of Diseases (ICD) 10 criteria can be used to diagnose a "Combined vocal and multiple motor tic disorder [de la Tourette]" without the criteria C and D.

Motor tics can be simple as eye blinking, eye, nose or mouth-movements, grimacing or quick and sudden movements of the upper or lower extremities. Complex motor tics may be more prolonged and goal-directed, and include jumping, rotating or copropraxia. Similarly, simple vocal tics may be rapid and sudden, and include coughing, sniffing, grunting or throat clearing whereas complex vocal tics include echolalia, palilalia, speech blocking and coprolalia (9,10).
Onset of tics commonly first appears between the ages of 4 and 6 years, with simple motor tics developing into more complex tics and vocal tics, and peak in severity between the ages of 10 and 12 years. Tics typically follow a waxing and waning course and often

decline in severity during adolescence (5,6,11). The fluctuating severity and intensity of tics affects the patient's quality of life (12–14). The clinical course of tic severity has only been examined longitudinally in a few small clinical studies (15,16) and clinical guidance for patients has been based primarily on a retrospective study by Leckman *et al*. that illustrates expected tic severity from childhood and throughout adolescence, based on 36 participants (16) (Fig. 1).

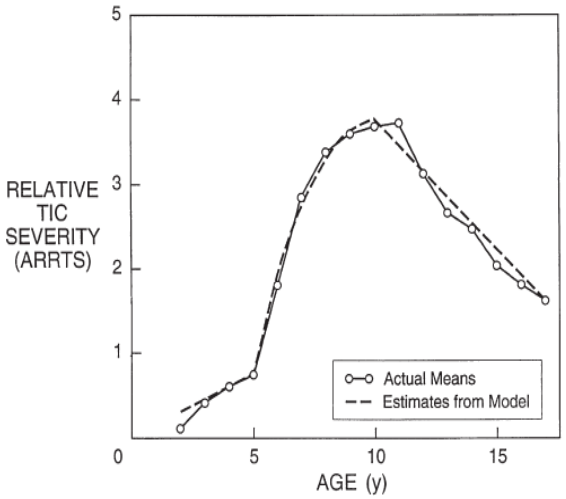

Figure 1. Clinical course of tic severity in childhood. Plot of average tic severity in a cohort of 36 children aged 2 to 18 years. Parents have retrospectively rated their children's tic severity on a six-point ordinal scale; absent [0], least severe, mild, moderate, severe and most severe [6]. Annual rating of relative tic severity (ARRTS). Reprinted with permission from Elsevier. Bloch and Leckman, 2009 (6).

Most TS studies are cross sectional and illustrate only a given time point, or retrospectively report lifetime symptoms with the risk of recall bias and often not including patients in partial or full tic remission. The longitudinal study design enables an established cohort to be followed, providing a unique opportunity to elucidate the clinical course of TS and its comorbidities. In addition, the development of phenotypes and predictors of tic severity and comorbidities can be studied, providing an evidential basis for clinicians to guide patients on the expected clinical course, address preventive efforts and optimise resource allocation.

COMORBIDITIES

TS is characterised by frequent comorbidities and coexisting psychopathologies that have a negative impact on quality of life (3,12,14,17,18). The most frequent and well-characterised comorbidities are Obsessive Compulsive Disorder (OCD) and Attention Deficit Hyperactivity Disorder (ADHD) (3,6,7), although Autism Spectrum Disorder (ASD) is also common (8,19). Coexisting psychopathologies including emotional disorders, disruptive behavioural disorders and personality disorders are also frequent (3,5,7,8). In addition, co-occurring disorders that include migraines and elimination disorders may also be present (3,7). Accordingly, prevalence of pure TS without comorbidities or coexistent psychopathologies has been reported in only 8–14% of clinical and community setting studies (5,7,8,19,20) supporting the contention that TS is not a unitary condition (3,21) but a complex disorder consisting of frequent comorbidities and based on a complex aetiology derived from both environmental and genetic factors (7,22).

Obsessive Compulsive Disorder

OCD is characterised by the presence of excessive recurrent and intrusive thoughts (obsessions) and repetitive behaviours or mental acts (compulsions), which are time consuming, cause significant anxiety and distress, and interfere with the child's daily life (23,24). Comorbid OCD has a huge impact on social life and relationships and can be more debilitating than the tics (6,12,14,17).

The prevalence of TS-associated OCD is approximately 36–50% with a predominance of females (3,6–8). Onset of comorbid OCD is reported to be in the period of worst-ever tics (10–12 years)(6), but can also be earlier (7) or appear de novo in early adulthood (6,25). Tic-related OCD symptoms appear to differ from non-tic-related OCD symptoms with the former showing more symmetry obsessions, and counting, repeating, ordering, and arranging compulsions (6). In addition, tic-related OCD is more likely to remit in adulthood than non-tic-related OCD and it has been suggested that the developmental trajectory improving tics in adolescence may also ameliorate comorbid OCD symptoms in these children (6,26). However, two follow-up studies found increases in TS-associated OCD severity with age at respectively age 16 (21) and 19 years (15) at follow-up.

Attention Deficit Hyperactivity Disorder

ADHD is characterised by persistent patterns of inattention, hyperactivity and impulsivity interfering with functioning to a degree that is maladaptive and inconsistent with developmental level of the child (24,27). Quality of life and global psychosocial functioning are significantly affected by ADHD symptoms (3,6,14). Although not all clinical studies find a clear association between TS and ADHD (20), the co-occurrence of these conditions is well established in clinical studies with ADHD prevalent in 50–60% of children with TS, and predominantly affecting boys (3,5,7,27). Comorbid ADHD is often associated with greater social, behavioural and academic problems, increases in maladapted behaviour and decreases in executive functioning (3,6). Behavioural, mood and anxiety disorders, together with cognitive dysfunction have been linked with, and may be secondary to, comorbid ADHD (3,7,27). The clinical courses of ADHD and TS appear to be independent, and ADHD symptoms typically precede tic-onset at approximately 2–6 years of age (6,7,28) and with a greater likelihood of tic than ADHD remission in adulthood (29). In childhood, hyperactivity and impulsivity is often dominant. Later in life inattentive difficulties, which can be less perceivable, may persist into adulthood (30,31). The developmental trajectory of TS-associated ADHD requires further study.

Autism spectrum disorders

ASD is characterised by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behaviour across multiple contexts (24). ASD, which includes autism and Asperger's, is diagnosed in 6–16% of individuals with TS (8,19,32). However, up to 40% of those with TS experience major problems with social interactions that include lack of friends and difficulties with empathy (19). To diagnose tics in ASD it is essential to differentiate between tics and stereotypies (32,33).

COEXISTING PSYCHOPATHOLOGIES AND OTHER CO-OCCURRING DISORDERS

Coexisting psychopathologies are common in the TS population (3,5,7) and often have a later onset than tics (Fig. 2). Coexisting

psychopathologies include anxiety disorders (36.1%), mood disorders (29.8%), disruptive behavioural disorders (29.7%), psychotic disorders (0.8%), eating disorders (2.0%), substance abuse (6.2%)(7), personality disorders, intellectual disability and learning disabilities (3,5,8). Other co-occurring disorders include sleeping difficulties, stuttering, elimination disorders and migraines (3,5,8). However few clinical studies have investigated these coexisting psychopathologies and co-occurring disorders despite they all have a considerable impact on the quality of life of the child or adolescent (14).

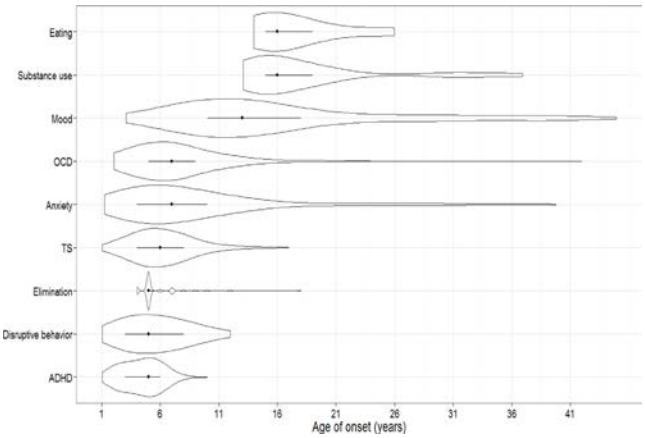

Figure 2. Ages-for onset of coexisting psychopathologies and other co-occurring disorders in individuals with Tourette syndrome. Points and bars are median ages-of-onset and interquartile ranges, respectively. The width of each plot is proportional to the number of individuals with a given age-of-onset.
Eating disorders: anorexia and bulimia nervosa; substance use: alcohol and other substance use or dependence, excluding tobacco use; mood: major-depressive disorder, dysthymia and bipolar disorder; Obsessive compulsive disorder (OCD): clinical and subclinical OCD; anxiety: generalised anxiety disorder, panic disorder, agoraphobia without panic, post-traumatic stress disorder, separation anxiety disorder, social phobia and specific phobias; elimination: enuresis and encopresis; disruptive behaviour: oppositional defiant and conduct disorders, Attention deficit hyperactivity disorder (ADHD). Reprinted with permission from JAMA. Hirschtritt el al 2015 (7).

AETIOLOGY

The multifactorial aetiology of TS involves immunological, environmental and genetic factors but is not completely defined. Family studies have shown that TS is a familial disorder and the associaton of OCD, ADHD and ASD indicates overlapping genetic relationships. Neuroimaging studies suggest abnormalities in the cortico-striatal-thalamic cortical circuitry, and several neurotransmitters may be associated with pathogenesis and tic persistence in many TS cases (6,34) and with comorbid OCD and ADHD (21). Environmental factors, especially in the pre- and perinatal period, that include maternal smoking, alcohol, severe psychosocial maternal stress, delivery complications and low Apgar scores (25) have all been associated with TS. An additional possibility is that infections during the tic-onset period, particularly streptococcal infections (see paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection - PANDAS) (35), initiate an autoimmune reaction involved in TS pathogenesis.

Genetics and neurotransmitters

Recent studies have suggested a complex and multifactorial inheritance pattern that includes interactions between polygenic and environmental factors, see for review (34). Twin studies have also demonstrated a relationship between TS and OCD (34), and OCD is much more frequent among relatives suggesting a shared basis for aetiology (3,7). The genetic relationship between TS and ADHD is more complex with only some studies supporting a shared genetic aetiology (3,7,20). It is also possible that the genetic relationship between OCD and ADHD can partially explain the relationship between TS and ADHD (20,34,36). Family studies also support a biological relationship between TS and ASD (32). Genetic and neuroimaging results support the involvement of neurotransmitters regulating messages in the cortico-striato-thalamic-cortical circuits, and these include dopamine, glutamate, gamma-amionobutyric acid (GABA) and serotonin (34,37). Abnormalities of dopamine modulating the cortico-basal ganglia pathways may play important roles in consolidation and performance of tics (25). Moreover, these interacting signalling pathways and neurotransmitters are also involved in the comorbidities OCD and ADHD, increasing the complexity of pathophysiology (37). Overall, signalling in the cortico-striatal-thalamic-cortical circuits is characterised by imbalances in excitatory and inhibitory signalling, but the complex interactions involved are currently undefined.

Accordingly, a polygenic inherited genetic vulnerability to TS exists, which is influenced by interactions between immunological, environmental and neuroanatomical factors and expressed as tics, and comorbidities and a broad spectrum of TS phenotypes. These phenotypic presentations can vary between individuals and change dynamically over time (7) as a result of their natural clinical course (15,30,31), pharmacological interventions or external factors. They provide important information for clinicians on how to address preventive efforts and optimise resource allocation.

QUALITY OF LIFE

Childhood and adolescence are vulnerable periods and several studies have reported significant distress and the negative impact that tic-related impairment has on the quality of life of children and young people with TS (3,12,14,17,18), and this also applies to their parents (38). The individual's self-esteem, their social relationships, and their ability to perform in academic environments can be affected by tics and comorbidities (9). TS without comorbidities has been associated with poorer perceived quality of life, but often the comorbidities contribute more to this perception than the tics themselves (12,14). Cavanna *et al*. investigated predictors during childhood of future health-related quality of life and found that higher tic severity, the presence of a premonitory urge and family history of TS explained 32% of the variance for the Gilles de la Tourette Syndrome Quality of Life Scale (GTS-QOL) (40).

INTRODUCTION TO THE STUDY

Leckman *et al*. illustrated the clinical course of tic severity in a retrospective study of 36 children and adolescents aged from 2 to 18 years old in 1998, and created a basis for clinical guidance on the expected course of tics (Fig. 1) (16). An age of onset of approximately 6 years old (range 4–8 years) was confirmed in two large studies by Freeman *et al*. (5) and Hirschtritt *et al*. (7). In a prospective follow-up study of 46 young adults aged between 16 and 23 years old, Bloch *et al*. confirmed the peak of worst-ever period of tics being at an age of approximately 10.6 years [standard deviation (SD), ± 2.6 years] and that tics often declined in severity during adolescence (15). However, relatively few clinical studies have investigated the development of tic severity and

comorbidities during adolescence. Larger longitudinal studies are needed to provide significant evidence for the expected clinical course of tics and comorbidities, enabling clinicians to guide children with TS, and their parents and provide sufficient preventive support and knowledge. In addition, many adolescents in partial remission or with subthreshold symptoms may still experience difficulties that require clinical support and guidance, why it is important to elucidate this area.

Adolescence is a particularly vulnerable period and several studies have reported the significant negative impact and distress that tic-related effects on quality of life can have in young people with TS, especially with regard to their social lives and relationships. These impacts are more pronounced in individuals with severe tics or comorbidities (12,18,21). To our knowledge, there have been no studies investigating the development of tic-related impairments and how they are affected by age-related tic decline, even though clarity in this area would provide a better understanding of adolescents with TS.

Several studies have tried to characterise TS phenotypes using cluster and exploratory factor analyses in cross-sectional studies (3,20,22,41,42).

Rizzo *et al*. (21) followed the expression and modification of TS phenotypes in childhood with a retrospective longitudinal study. A positive long-term clinical course for individuals with *pure TS* was indicated, whereas the prognosis was more severe for those who also had comorbidities (21). However, to the best of our knowledge, there are no prospective clinical studies investigating the development of phenotypes during adolescence. Such studies could also play an important role in identifying genes that are linked with susceptibility to TS, and in aetiological and clinical research (43,44).

The developmental trajectories of TS phenotype expression changes with age and the precise nature of impairments and their impact on quality of life differs in the TS population (12,14). Presentation of tic can vary from few to severe (3,9,25). Prognostic issues related to the expected clinical course are very difficult to predict for each individual child. Nevertheless, solid predictors for the clinical course of TS can improve preventive measures, early intervention and monitoring of tics and comorbidities. However, only a few small longitudinal studies have investigated potential predictors of future health-related quality of life (40), severity of tics, comorbidities and coexisting psychopathologies (45–48). Similarly, few cross-sectional studies have examined the predictive associations between TS and comorbidities (7,49). Altogether, some clinical factors and family history (40) have the potential to predict aspects of the clinical course of TS but no clear trends have been established.

Peterson *et al*. (20) conducted a prospective longitudinal study of tics and comorbidities in a large epidemiological sample to look for associations and factors that predicted the course of Tics Disorder (TD). Tics, OCD and ADHD predicted future coexisting psychopathologies, especially those related to the emotions. In addition, tics, OCD and ADHD in childhood also predicted future tics, OCD and ADHD; however, the relationships were not completely consistent. Intelligence quotient (IQ) scores have also shown some potential for predicting future TS comorbid OCD (15,20). Lin *et al*. (46) used the impact of psychosocial stress to predict future symptoms of tics, OCD and depression in a longitudinal study. These inconsistencies highlight the need for further studies that may identify predictive factors and for confirmatory studies to be carried out in a TS population so that the findings can be applied in a clinical setting.

In summary, a knowledge gap of the development of tic severity and comorbidity as well as the development of TS phenotypes still exists. This prospective longitudinal study was conducted to clarify these issues, to highlight tic-related impairments and to identify factors that predict the clinical course of TS.

At baseline, this cohort presented with a high prevalence of OCD (39.8%), ADHD (37.1%), rage attacks (34.8%), sleep disturbance (17%), depressive symptoms (26.5%), stuttering (14.7%) and seasonal affective disorder symptoms (39.2%), and only 10.2% of the cohort had no comorbid symptoms (50). In this study, we elucidate coexisting psychopathologies and improve diagnostic evaluation using new research instruments to produce a broader spectrum of validated DSM-IV diagnoses.

OBJECTIVE OF THE STUDY

The aim of this longitudinal study was to characterise the prospective clinical course of TS from childhood to early adulthood. To describe and explore the age-related severity of tics and comorbidities, tic-related impairment over time, the development of different phenotypes, the broad spectrum of coexisting psychopathologies and to identify factors that predict the clinical course of TS.

Specific study objectives:

We hypothesised:

- an age-related decline in tics followed by a decrease in tic-related impairment albeit comorbidity might influence the subjective perception of tic-specific impairment
- that OCD symptoms persist with age
- a decline in TS-associated ADHD with age but persistent subclinical ADHD symptoms
- that with age the expression of TS phenotypes develops toward TS-only phenotype albeit a substantial number of patients still experience threshold symptoms of OCD or ADHD
- that factors as early onset of tics or comorbidities, family history of TS, OCD and/or ADHD, severity of tics and comorbidities, vocal tics, low IQ, and psychosocial and educational problems predict a more severe clinical course
- that a substantial prevalence of emotional, behavioural and neurodevelopmental TS-associated comorbidities and coexistent psychopathologies is present during adolescence and early adulthood (in cross-sectional view).

METHODS

This prospective follow-up study was conducted at the Danish National Tourette Clinic in two phases: during the periods 2005–07 (T1) and 2011–13 (T2). All children from the Tourette Clinic in Copenhagen meeting DSM-IV-TR (51) TS criteria on 1 September 2005 were invited to participate (n = 376). In total, 314 patients (83.5%) were included at T1 and examined by N. M. Debes M.D. Ph.D. No selection bias affecting the clinical generalisability was found (50). At T2, we included all participants from T1 and 227 patients (72%) were re-examined by C. Groth M.D. There were no exclusion criteria at T1 or T2.

Informed written consent was obtained from both parents and adolescents above the age of 15 years at T1 and at T2. The study was approved by The Scientific-Ethical Committees (protocol H-2-2010-058) and the Danish Data Protection Agency (protocol HEH-2014-002).

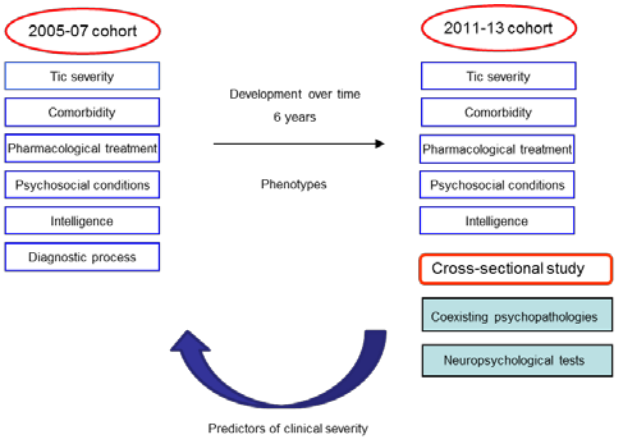

Figure 3. Overview of the baseline (T1) and follow-up (T2) study design

All participants completed a comprehensive, standardised examination procedure to assess tics, comorbidities and coexisting psychopathologies at both T1 and T2. This included assessment for OCD, ADHD, intermittent explosive disorder (IED), sleep disturbances and IQ. It also included a structured interview to clarify medical history, pharmacological treatments and psychosocial conditions including educational consequences related to TS, see Table 1. For further information regarding T1, see Debes *et al*., 2008 (50).

Characteristics	**T1** (2005 07)	**T2** (2011–13)
Inclusion criteria	TS diagnosis - 1 Sep. 2005	All participants from T1
Exclusion criteria	None	None
Severity of tics	YGTSS	YGTSS
OCD	CY-BOCS	CY-BOCS/Y-BOCS
ADHD	DSM-IV criteria	ADHD-RS/ASRS-RS DSM-IV criteria
IED	Modified DSM-IV criteria	Modified DSM-IV criteria
Sleep disturbance	Selected items from CBCL	Selected items from CBCL
Psychopathology	CBCL and structured interview	DAWBA
Neuropsychological test	WISC/WAIS III	WISC/WAIS III
Medication, SES, psychosocial conditions and education	Structured interview	Structured interview

Table 1. Survey of the baseline (T1) and follow-up (T2) studies. Measurements were used according to age in examinations. Yale Global Tic Severity Scale (YGTSS); Yale-Brown Obsessive Compulsive Scale for children and adults (CY-BOCS/Y-BOCS); Obsessive Compulsive Disorder (OCD); Attention Deficit Hyperactivity Disorder rating scale (ADHD-RS); Adult Self Report Scale (ASRS); Diagnostic and Statistical Manual IV (DSM-IV); Intermittent Explosive Disorder (IED); Child Behavior Checklist (CBCL); Development and Well-Being Assessment (DAWBA); Socioeconomic status (SES); Wechsler intelligence tests for children and adults, version III (WISC/WAIS).

CLINICAL INTERVIEW AT T1

At T1 a structured clinical interview was performed by N. M. Debes including questions on the diagnostic process, symptoms and age of onset (28). Psychosocial conditions including teasing, loneliness, social restraints and education were also clarified (52). In addition, most participants (n = 266) were tested using the Wechsler Intelligence Scale for Children (WISC III) (53) or the Wechsler Adult Intelligence Scale (WAIS III) (54,55).
For psychopathology, the Child Behavior Checklist (CBCL) was used at T1 to assess symptoms of depression and specific questions from the structured clinical interview were used to assess symptoms of seasonal affective disorder and stuttering.

DIFFERENCES BETWEEN T1 AND T2

At T2, we used the Development and Well-Being Assessment (DAWBA) including the Strengths and Difficulties Questionnaire (SDQ) instead of the CBCL. In addition, we assessed for ADHD using the ADHD-RS or Adult Self Report Scale (ASRS) according to age. These were not available at T1. This change of instruments was introduced to improve the diagnostic evaluation and to generate validated DSM-IV diagnoses at T2. For the neuropsychological testing, we reduced the test to seven subscales representative of all the cognitive areas tested by the WICS and WAIS to reduce the examination time for participants. This test correlated well with the full tests. These results will be published separately.

CLINICAL INTERVIEW AT T2

The participants were all contacted by phone and letter before examination at T2. At home they completed self-, parent- and teacher-reports covering ADHD symptoms, sleep disturbance, IED and a diagnostic evaluation for psychopathologies. C. Groth performed the structured clinical interview. All self- and parent-rated questionnaires were reviewed with participants and their parents present and any issues were addressed. Most participants were also tested using a neuropsychological test battery.

MEASURES

Tics

The severity of tics was rated using the Yale Global Tic Severity Scale (YGTSS), which is considered a reliable and valid instrument for assessing tic severity and based on DSM criteria (10,39). The participants' motor and vocal tics, both simple and complex, during the previous week were rated on a scale of 0 to 5 in five dimensions: number, frequency, intensity, complexity and interference. Impairments related to a tics impact on the individual's self-perception and self-esteem, their social, peer and family relationships, or their ability to perform in academic or occupational environments were rated separately on a six-step ordinal scale (0–50). Five severity index scores were provided: total motor tic score, total vocal tic score, total tic score (total motor + vocal score), overall impairment score, and global severity scores (total tic score + overall impairment score). If the neuropsychological testing was performed more than six months after the clinical interview at T2, tics were reassessed resulting in an additional tic-score time point (T2+). To clarify the distribution of tic severity the YGTSS Total scores were divided into six groups corresponding to: absence of tics (score = 0), minimal tics (score = 1–9), mild tics (score = 10–19), moderate tics (score = 20–39) and severe tics (score ≥ 40) as defined by Leckman *et al.* (16).

OCD

OCD symptoms were assessed using the semi-structured interview Yale-Brown Obsessive Compulsive Scale for adults (Y-BOCS) in patients over 18 years of age, or for children (CY-BOCS) in patients under 18 years. This is regarded as the gold standard for obsessive compulsive symptom severity assessment and has strong psychometric properties (56–62). The interview provides a rating of obsessive compulsive symptom severity based on five dimensions: time occupied by-, interference from-, resistance to-, distress from-, and control over both obsessions (0–20) and compulsions (0–20) with a total score ranging from 0 to 40. The diagnostic criteria for OCD are defined in the DSM-IV.

No diagnostic cut-off score is provided by the CY-BOCS/Y-BOCS, but Block and Leckman (63) defined a cut-off score of 10 points as corresponding to OCD symptoms of clinical significance. We used this cut-off score and evaluated symptoms corresponding to DSM-IV criteria for OCD. OCD severity was separated in four categories: subclinical OCD (8–9), mild OCD (10–18), moderate OCD (19–29) and severe OCD (≥ 30) as defined by Bloch *et al*. (63). Participants receiving selective serotonin reuptake inhibitor (SSRI) medication for OCD symptoms but scoring less than 10 on the scale were considered positively affected by the medication and included in the OCD group.

ADHD

Symptoms of ADHD were assessed using the ADHD-RS (64,65) distributed to the parents of participants younger than 18 years and the ASRS (66–68), a version with questions targeted to adults, was completed by participants ≥ 18 years old. The 18 DSM-IV diagnostic criteria were used to evaluate whether participants fulfilled criteria for *combined type* (requiring 12 diagnostic criteria), *predominately inattentive type* (requiring 6 inattentive criteria) or *hyperactive-impulsive type* (requiring 6 hyperactive-impulsive criteria). Participants with subthreshold symptoms and impairment were specified being *in partial remission*. The Danish national norm scores (65,69) corrected for age and sex were used to compare our adolescents within the age range of 11 to 18 years with their Danish peers and illustrate the severity of ADHD diagnoses or subclinical symptoms of inattention, hyperactivity-impulsivity and conduct. Norm scores are not available for ASRS representing those ≥ 18 years old.

Participants receiving treatment containing methylphenidate or atomoxetine for ADHD symptoms but who did not fulfil the diagnostic criteria were considered positively affected by the medication and included in the ADHD group.

Intermittent explosive disorder (IED)

Symptoms of IED were assessed using a modified version of the DSM-IV diagnostic criteria as described by Budman *et al*. (70) and Debes *et al*. (50). Symptoms included having episodes of failure to resist aggressive impulses and acting severely in a manner out of proportion to precipitating psychosocial stressors. A frequency threshold of two episodes per week over a period of one month was used (50).

Sleep disturbance

Sleep disturbance was assessed using questions from the CBCL as applied by Kostanecke-Endress *et al*. (71) and Debes *et al*. (50). Sleep disturbance assessments included both the quality and quantity of sleep with dyssomnia and parasomnia scored using seven items (score 0–14). The CBCL provides no validated cut-off for sleep disturbance so we used a clinically based cut-off score of more than 6 to indicate significant sleep disturbance.

Other diagnoses

During the clinical interviews, participants were asked about currently diagnosed comorbidities in addition to OCD, ADHD, IED and sleep disturbance. Diagnoses were confirmed using participants' medical files and diagnoses were recorded.

DAWBA and SDQ

We independently evaluated coexisting psychopathologies at T2 using the DAWBA (72–74) including the Strengths and Difficulties Questionnaire (SDQ) (75–77). The DAWBA and SDQ are validated standardised diagnostic interviews based on self-, parent- and teacher-rated reports and using the DSM-IV criteria. The DAWBA covers a broad spectrum of emotional, behavioural and hyperactivity disorders. Diagnoses were categorised as follows to improve reliability:

emotional disorders*: anxiety, post-traumatic stress disorder, and depression;* ***hyperactivity****: ADHD-combined, predominately inattentive or hyperactive-impulsive type;* ***behaviour****: oppositional defiant disorder, conduct disorders, IED, and other behavioural disorders;* ***developmental disorders****: autism, Asperger's, and other developmental disorders;* ***eating disorders****: anorexia nervosa, bulimia nervosa, and other eating disorders;* ***psychosis****: psychosis and schizophrenia;* ***other diagnoses****: personality disorders and substance abuse disorder.*

Two raters (C. Groth and C. U. Rask), who were blinded to other information, assessed the diagnoses and inter-rater reliability was assessed on 24 randomly selected participants.

Socioeconomic status (SES)

SES was assessed using a scale from the Danish National Centre for Social Research (78) for all participants according to their parent's education and occupation. The highest score from the two parents was chosen to represent family status (range 1–5, with one representing the best education and occupation) (52).

Neuropsychological examination

All participants were tested using a neuropsychological test battery by a psychologist, Kristine Swierkosz Kristjansen, and three psychology master's students, Ane Lemche, Miriam Utzon and Katrine Neisig. All participants under the age of 16 were subjected to subtests using the WISC III (53) and for those over 16 years, subtests of the WAIS III were used (54).

Genetics

For each participant a family tree with symptoms and diagnoses that included possible tics and comorbidities was recorded. Family history of OCD, ADHD and tics was recorded based on parent- and self-reports of confirmed medical diagnoses in each family(79–81).

PHENOTYPE GROUPS

All participants were divided into the following phenotype groups at baseline and follow-up: *TS-only, TS + ADHD, TS + OCD,* and *TS + ADHD + OCD*. At follow-up, groupings included participants with subthreshold symptoms and in partial remission: *full tic remission*, *OCD subclinical*, *ADHD partial remission,* and *ADHD predominately inattentive and hyperactive/impulsive type*.

In the phenotype groupings, *TS-only* is defined as TS without an OCD or ADHD diagnosis. When examining overall comorbidity and coexisting psychopathologies we use the term *pure TS* defined as TS without any comorbidity or coexisting psychopathologies. These terms are not consistently and uniformly used in the literature and can cause confusion.

PREDICTORS

For the predictive analyses we selected outcomes which have a significant impact in early adulthood in TS. We used four binary outcomes of clinical significance in early adulthood: high/low tic score, diagnoses of OCD, ADHD or emotional disorders. The diagnoses were defined as absent or present. High tic score was corresponding to moderate-severe tics (20-50) and low score to absent-mild (0-19) in the YGTSS (63,82). Participants with ASD or IQ<70 combined with a developmental disorder were excluded. Based on the recent literature and our clinical experience, we selected following clinical factors in childhood to predict the clinical course of TS: age and symptoms at onset, vocal tics, IQ, severity and family history of tic, OCD and ADHD, psychosocial and educational conditions.

STATISTICS

Most analyses were conducted using SPSS statistical software (ver. 22.0; SPSS Inc., Chicago, IL, USA). The characteristics of follow-up participants and nonparticipants were compared using *t*-tests for the continuous data. Nominal and ordinal data were compared using Fisher's exact test. For descriptive statistics, means, SDs, percentages and quantiles were used as appropriate. The inter-rater reliability of the DAWBA was assessed on 24 randomly selected participants and a weighted kappa coefficient was calculated.

To visualise the clinical course of tics, TS-associated OCD, ADHD and sleep disturbance, we pooled all scores from T1 and T2 and plotted all observations graphically. In order to model age trends we included all measurements taken from each individual. To accommodate the inherent dependence of a single individual providing multiple observations we employed a mixed effects model with a random effect for each person. Assuming missing at random, this model can accommodate missing outcome data. The repeated measurements included the YGTSS, CY-BOCS/Y-BOCS, ADHD-criteria, and sleep disturbance scores. The linear age effect was evaluated by initially including non-linear terms (square roots and squares of age variables) and subsequently testing whether these non-linear terms could be removed from the model. To visualise age-related severity of tics and OCD, the respective scores were divided in age-groups for the pooled T1 and T2 data: 5–10 years, 11–15 years, 16–20 years and 21–26 years.
The ADHD rating scale (ADHD-RS) was analysed using the Danish national norm scores (65,69) to assess symptom severity. The ADHD norm was calculated using a formula provided by Bilenberg (T_score = 50 + (score – mean) / SD x 10).

The development of phenotype groups from baseline to follow-up was described using percentages. Additionally, the cohort was divided into three age groups (5–10, 11–15 and 16–20 years) at T1, to evaluate the effect of age. These age-groups corresponded to age of onset, worst ever period and period of decline in tics (6).

Tic severity (based on the YGTSS) was subdivided into *improved tic score* (decrease of > 5 points), *stable tic score* (change ≥ 5 ≤), and *worse tic score* (increase of > 5 points) all based on our clinical experience of changes in total tics (83). Likewise, tic-related impairment (based on the YGTSS) was subdivided into *improved score*, *stable score* and *worse score* according to one-step changes on the six-step ordinal scale of the YGTSS. In addition, we correlated tic-related impairment (Spearman's correlation, 2-tailed) with the following subgroups: sex; age; vocal, motor and total tic score; IQ score; a diagnosis in the autism spectrum; and severity of comorbid OCD and ADHD. To obtain patterns of individual variation, characteristics of individuals with a high impairment score (≥ 40 on the YGTSS) were collected in a subgroup and described.

In all analyses, we have not differentiated between participants receiving medication currently or historically or medication free participants. We have described the percentage of those currently receiving medication as part of their treatment in all relevant subgroups.

The predictive data were analysed using R software (ver. 3.3.1; The R Foundation, 2016). For all four outcomes we used a 3 step procedure to assess the potential for predicting the outcomes. Step 1; each predictive variable was used individually in logistic regression of the binary outcome. Step 2; significant predictors from step 1 were included in a second multiple logistic regression analysis simultaneously. Step 3; a relative operating characteristic (ROC) curve was produced to differentiate between the overall effect with all significant predictive variables from step 1 and the highly significant predictors found at step 2.

RESULTS

At baseline, 314 children and adolescents with TS with a mean age of 12.4 years (SD = 2.8, range 5.3–19.8 years) were examined. At both baseline and follow-up, females constituted 18% and Caucasians 98% of the cohort. Follow-up was performed 4 to 8 years later (median = 5.6, quartiles 5.4–6.8), giving a mean age of 18.5 years (SD = 2.8, range 11.1–25.9 years). A total of 227 (72.3%) participants were re-examined: 212 were examined in the clinic and 15 were interviewed by telephone because of difficulty in attending the clinic. Reasons for non-participation included: inability to locate subjects (n = 17), not willing to re-participate (n = 46), positive but unable to participate (n = 16), and unable to complete a clinical interview due to severe comorbidities recorded by the parents (n = 8).
Demographic measurements did not differ significantly between the participating and nonparticipating individuals with regard to age, sex, SES, tic- and OCD severity, presence of OCD or ADHD, and IQ, see Table 2.

CLINICAL COURSE OF TS

The clinical course of tics, OCD, ADHD, IED and sleep disturbance was based on pooled data from T1 and T2 (and additionally from T2+ for tics) to optimally illustrate relationships between age and symptom severity. All observations were plotted on scatterplots to visualise the wide variation (Fig. 4). The clinical course did not differ significantly between the sexes (p > 0.05) in any of the analyses, see Table 6.

Characteristics	ParticipantsT2 (data from T1)	Non-participants T2 (data from T1)	P-Value	ParticipantsT2 (data from T2)
Sample size (n)	227	87	--	227
Age (mean years +/– SD)	12.5 +/–2.7	12.3 +/–2.9	0.69	18.5 +/–2.8
Males (n)	185 (81.5%)	72 (82.8%)	0.87	185 (81.5%)
IQ (mean +/– SD)	90.0 +/–18.4	85.3 +/–16.1	0.07	95.2 +/–15.8
SES (mean +/– SD)	2.5 +/–1.0	2.7 +/–1.0	0.10	2.6 +/–1.1
ADHD (n)	93 (41.2%)	42 (48.3%)	0.31	68 (30.4%)
OCD (n)	89 (39.2%)	33 (37.9%)	0.90	60 (26.4%)
OCD (mean CY-BOCS score +/– SD)	8.4 +/–8.0	8.2 +/–7.9	0.82	6.1 +/–7.2
Tics (mean global YGTSS score +/– SD)	24.5 +/–18.2	25.6 +/–17.6	0.68	18.1 +/–16.0

Table 2. Characteristics of participants and non-participants at T2 compared with data from baseline (T1) and follow-up (T2). There were no significant differences ($p < 0.05$) between participants or non-participants at T2 and data from T1, in any of the demographic variables examined. Characteristics for participating individuals at T2 are shown to characterise the cohort. Fisher's exact test was used for: sex, SES (socioeconomic status), ADHD (Attention Deficit Hyperactivity Disorder), and OCD (Obsessive Compulsive Disorder). t-tests were used for: age, tic severity, OCD severity and IQ (Intelligence quotient).

Tics

A total of 518 tic-assessments were made at T1, T2 and T2+ using the YGTSS. The severity of tics between the ages of 6 and 26 years is categorised in Table 3. In addition, participants over 16 years of age were categorised to illustrate age-related changes in severity. The clinical course of tics showed an age-related decline in mean total tics-score of 0.80 points annually on the YGTSS (Fig. 4A and Table 6). This reflected declines in both motor (0.45) and vocal tics (0.35). Age at onset of tics did not significantly affect their clinical course (Table 6). Medication was used for tics in 94 (18.1%) of the total tic-assessments (T1, T2 and T2+).

OCD

At T1 and T2, a total of 541 OCD assessments were scored using the CY-BOCS (n = 411) and Y-BOCS (n = 130). The OCD severity scores, within the age range of 5 and 26 years are categorised in Table 4. Of this number, 182 (33.6%) assessments fulfilled the DSM-IV criteria for OCD. Of those 89 participants meeting OCD criteria at T1 who were re-examined at T2, 36 (40.4%) still fulfilled the OCD criteria.

The clinical course of OCD showed a small yearly mean decline of 0.24 for combined obsessions and compulsions on the CY-BOCS/Y-BOCS (Fig. 1B and Table 6). Compulsions showed a significant but modest decline (mean = 0.17), and obsessions showed a small and non-significant decline (mean = 0.06). SSRIs were used to treat OCD in 6.1% (n = 33) of all assessments (T1 + T2).

ADHD

A total of 496 ADHD assessments from T1 and T2 were recorded and 189 (38.1%) of these fulfilled DSM-IV criteria for combined ADHD. Of the 90 participants meeting ADHD criteria at T1 who were re-examined at T2, 48 (53.3%) still met the criteria for ADHD, 22 (24.4%) were in partial remission and 20 (22.2%) were in full remission.

The clinical course of ADHD demonstrated a highly significant age-related, yearly decline in mean total symptoms of 0.42 DSM-IV criteria (Fig. 4C and Table 6). This reflected declines in both inattention (mean = 0.21) and hyperactivity-impulsivity (mean = 0.21). Methylphenidate and atomoxetine were used to treat ADHD in 143 (28.8%) of the total ADHD assessments.

The Danish national norm scores, corrected for age and sex (norm = 50), were used to analyse the ADHD-RS (11 to 18 years) assessments from T2 (n = 83). The results demonstrated highly significant increases in T-scores for inattention (mean = 59.16, CI: 56.0–62.3; Fig. 4D), hyperactivity-impulsivity (mean = 58.24, CI: 54.6–61.9), and conduct (mean = 58.01, CI: 54.4–61.6). The severity of inattention, hyperactivity-impulsivity and conduct within the age range of 11 to 18 years is shown together with the number of ADHD combined type, predominantly inattentive type and predominantly hyperactive-impulsive type of ADHD in Table 5. Medication was used to treat ADHD in 20 (24.1%) of these participants (T2, n = 83).

	5–10 years	11–15 years	16–20 years	21–26 years	All assessments
Tic score	*n = 63*	*n =218*	*n = 182*	*n = 55*	*n = 518*
Absence (0)	*4 (6.3%)*	*31 (14.2%)*	*32 (17.6%)*	*10 (18.2%)*	*77 (14.9%)*
Minimal (1–9)	*3 (4.8%)*	*14 (6.4%)*	*39 (21.4%)*	*14 (25.5%)*	*57 (11.0%)*
Mild (10–19)	*19 (30.2%)*	*70 (32.1%)*	*70 (38.5%)*	*18 (32.7%)*	*134 (25.9%)*
Moderate (20–39)	*37 (58.7%)*	*99 (45.4%)*	*39 (21.4%)*	*13 (23.6%)*	*244 (47.1%)*

Table 3. The severity of total tic scores (T1, T2 and T2+) divided into age subgroups and including all assessments. The Total tic scores from the Yale Global Tic Severity Scale Score were categorised according to Leckman (16)

Table 4. The severity of OCD (T1 and T2) divided into age subgroups and including all assessments. The scores from the Yale-Brown Obsessive Compulsive Scale for children (< 18 years) and adults (≥ 18 years) were categorised according to Bloch et al. *(63)*. One patient on SSRI treatment could not be categorised.

	5–10 years	11–15 years	16–20 years	21–26 years	All assessments
OCD score	*n = 95*	*n = 233*	*n = 173*	*n = 40*	*n = 541*
Normal (0–7)	*45 (47.4%)*	*147 (63.1%)*	*113 (65.3%)*	*27 (67.5%)*	*333 (61.6%)*
Subclinical (8–9)	*5 (5.3%)*	*17 (7.3%)*	*8 (4.6%)*	*1 (2.5%)*	*30 (5.5%)*
Mild (10–18)	*29 (30.5%)*	*45 (19.3%)*	*30 (17.3%)*	*10 (25.0%)*	*114 (21.1%)*
Moderate (19–29)	*13 (13.7%)*	*24 (10.3%)*	*22 (12.7%)*	*2 (5.0%)*	*61 (11.3%)*
Severe (≥ 30)	*3 (3.2%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*3 (0.6%)*

	11–15 years T-score (%)	16–17 years T-score (%)	All assessments T-score (%)
Inattention T-score	*n = 40*	*n = 43*	*n = 83*
Low score ≤ 60	*24 (60.0%)*	*25 (58.1%)*	*49 (59.0%)*
Middle score 61–69	*8 (20.0%)*	*9 (20.1%)*	*17 (20.5%)*
High score ≥ 70	*8 (20.0%)*	*9 (20.1%)*	*17 (20.5%)*
Mean score	*58.6*	*59.7*	*59.2*
Range	*39–104*	*39–96*	*39–104*
Hyperactivity-impulsivity T-score			
Low score ≤ 60	*26 (60.0%)*	*30 (69.8%)*	*56 (67.5%)*
Middle score 61–69	*4 (10.0%)*	*5 (11.6%)*	*9 (10.8%)*
High score ≥ 70	*10 (25.0%)*	*8 (18.6%)*	*18 (21.7%)*
Mean score	*58.8*	*57.8*	*58.2*
Range	*40–107*	*41–114*	*40–114*
Conduct T-score			
Low score ≤ 60	*26 (60.0%)*	*30 (69.8%)*	*56 (67.5%)*
Middle score 61–69	*4 (10.0%)*	*5 (11.6%)*	*9 (10.8%)*
High score ≥ 70	*10 (25.0%)*	*8 (18.6%)*	*18 (21.7%)*
Mean score	*58.5*	*57.5*	*58.0*
Range	*41–110*	*42–100*	*41–110*
Diagnoses			
Combined type	*Numbers (%):*		
Inattentive type	*9 (22.5%)*	*11 (25.6%)*	*20 (24.1%)*
Hyperactive-impulsive	*0 (0%)*	*3 (7.0%)*	*3 (3.6%)*
type	*1 (2.5%)*	*0 (0%)*	*1 (1.2%)*
Total	*10 (25.0%)*	*14 (32.5%)*	*24 (28.9%)*

Table 5. The severity of ADHD in subgroups at T2 (n = 83) assessed using the ADHD-RS and divided into two age groups. The scores from the ADHD-RS are corrected for age and sex with the Danish National Norm scores *(65,69)* given the T-scores. A low T-score is ≤ 60 (±1 SD) and is defined as within the normal range, a medium score is 61–69 and is subclinical, and a high score ≥ 70(±2 SD) and is above the normal range. Diagnoses of ADHD combined type, predominantly inattentive type and predominantly hyperactive-impulsive type, based on DSM-IV criteria are shown for the different age groups. *Attention Deficit Hyperactivity Disorder rating scale (ADHD-RS)*

For the T2 age group over 18 years old and assessed using the ASRS, no norm data were available and consequently it was not possible to analyse symptom severity. However, the following diagnoses based on DSM-IV criteria were made on this subgroup: ADHD combined type (n = 33, 33.0%), predominantly inattentive type (n = 1, 1.0%) and predominantly hyperactive-impulsive type (n = 2, 2.0%).

IED

From a total of 540 assessments at T1 and T2, 69 (12.8%) fulfilled the modified version of the DSM-IV diagnostic criteria for IED.

Historical symptoms were reported in 139 (25.7%) and sub-threshold symptoms in 83 (15.4%) assessments. At T1 50.8% had IED, at T2 this number was decreased with age to 10.6%

Sleep disturbance

From a total of 392 sleep assessments at T1 and T2, 38 (9.7%) scored above the cut-off definition for sleep disturbance. The median symptom score was 3 (quantiles 1–5). Symptoms were significantly age-related with an increase of 0.07 points per year. The course of symptoms is illustrated in Figure 4E and listed in Table 6.

Measurement	Yearly decline (CI)	Age	Sex	Age at tic-onset
YGTSS				
Total tics (0–50)	0.80 (0.58–1.01)	P < 0.001*	P = 0.897	P = 0.279
Motor tics (0–25)	0.45 (0.33–0.57)	P < 0.001*	P = 0.379	P = 0.466
Vocal tics (0–25)	0.35 (0.22–0.48)	P < 0.001*	P = 0.252	P = 0.275
CY-BOCS/Y-BOCS				
Total score (0–40)	0.24 (0.09–0.39)	P = 0.001*	P = 0.325	
Compulsions (0–20)	0.17 (0.09–0.26)	P < 0.001*	P = 0.628	
Obsessions (0–20)	0.06 (0.15 to + 0.03)	P = 0.178	P = 0.211	
ADHD-criteria				
Total score (0–18)	0.42 (0.32–0.52)	P < 0.001*	P = 0.173	
Inattention (0–9)	0.21 (0.13–0.26)	P < 0.001*	P = 0.163	
Hyperactivity-impulsivity (0–9)	0.21 (0.17–0.27)	P < 0.001*	P = 0.288	
Sleep disturbance (0–14)	+0.07 (+0.01 to +0.13)	P = 0.016*	P = 0.149	

*Table 6. Results of the clinical course of tics, OCD, attention deficit hyperactivity disorder (ADHD and sleep disturbance. Significant results (P < 0.05) are marked with *.* Yale Global Tic Severity Scale Score (YGTSS); Yale-Brown Obsessive Compulsive Scale for children and adults (CY-BOCS/Y-BOCS).

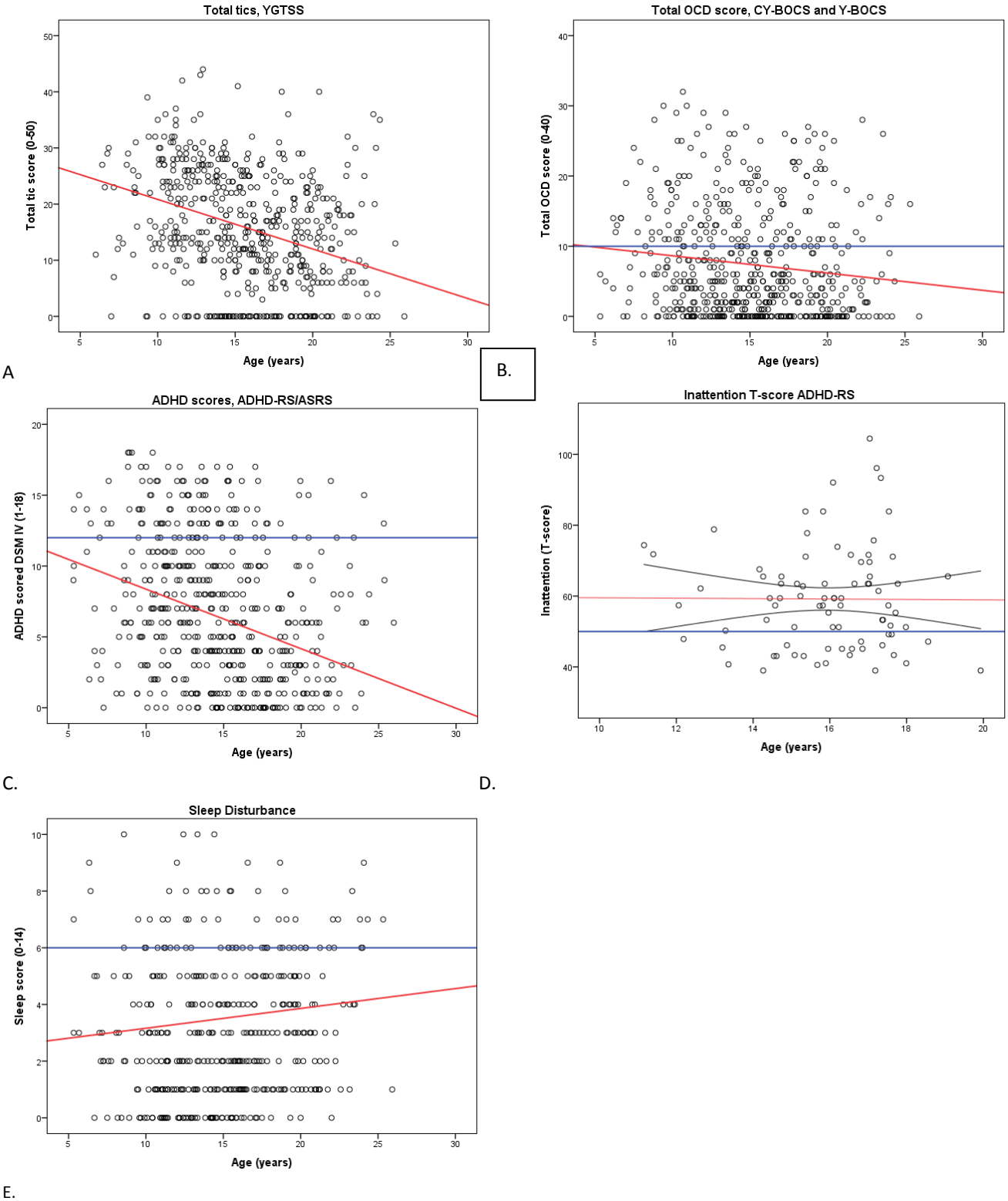

Figure 4. Clinical course of tics, OCD, ADHD and sleep disturbance in the age range 5–26 years. The red lines indicate mean age-related scores. The blue lines indicate the defined diagnostic cut-offs. A. Total tic score on the Yale Global Tic Severity Scale (YGTSS) (Range 0–44, yearly decline = 0.80). B. Total Obsessive Compulsive Disorder (OCD score on the Yale-Brown Obsessive Compulsive Scale for adults (Y-BOCS and CY-BOCS (Range 0–32, yearly decline = 0.24). C. Attention Deficit Hyperactivity Disorder (ADHD diagnostic criteria from the DSM-IV (Range 0–18,yearly decline = 0.42). D. ADHD according to the Danish norm scores (blue line). The ADHD Rating Scale mean inattention score was significantly higher (59.16, CI 56.0–62.3). E. Sleep disturbance (Range 0–10, yearly increase = 0.07, quantiles 1–5).

TIC-RELATED IMPAIRMENT

To examine the association between tic severity and tic-related impairment we used the *total tic score* and the *impairment score* form the YGTSS. A total of 204 YGTSS scores were collected at T1 and T2. The mean *total tic score* decreased significantly ($p < 0.001$) by 6.4 points between T1 and T2. Conversely, the mean *impairment score* increased slightly but not significantly ($p = 0.54$) by 0.54 points at T2. Furthermore, only 17.2% of participants reported an improved *impairment score*, with 54.4% reporting a stable score and 28.4% reporting a poorer *impairment score* at T2 compared with T1.

Table 7 shows the changes in both mean total tic scores and mean impairment scores for the relevant subgroups. The subgroup reporting an improved YGTSS total tic score of more than 5 points also reported a significant mean improvement in impairment score of 3.64 but 19.6% of this subgroup reported worse tic-related impairment. The subgroup reporting with worsening YGTSS total tic score of more than 5 points also reported a significant mean increase in impairment score of 7.43 and 40% of this subgroup reported worse tic-related impairment. In addition, worse tic-related impairment at T2 was reported by the girl-group (37.5%), the group with vocal tics (37.7%), the autism spectrum subgroup (42.9%) and the subgroup with both ADHD and OCD diagnoses (65.2%). Overall, total tic score decreased in all groups (except the group selected to have an increased tic score) but these decreases were not reflected in decreases in impairment scores.

To identify associations between the development of tic-related impairment and relevant factors we correlated impairment scores at T2 with sex; age; parents' SES; vocal, motor and total tic score; IQ score; autism spectrum diagnoses; OCD severity and ADHD severity (Table 8).

Characteristics		Number	Tic- change (T1–T2)	Impairment change (T1–T2)	Impairment development T1 to T2		
Groups	Subgroups	*N = x*	*Tic score change mean*	*Impairment change mean*	*Worse ≤ 10 points %*	*Stable 0 points %*	*Improved ≥ 10 points %*
Sex:	All	*N = 204*	*6.4 ***	*–0.54*	*28.4*	*54.4*	*17.2*
	Girls	*N = 40*	*4.0 **	*–1.25*	***37.5***	*45.0*	*17.5*
	Boys	*N = 164*	*7.0 ***	*0.37*	*26.2*	*56.7*	*17.1*
Age:	< 18 years, T2	*N = 92*	*8.5 ***	*0.65*	***30.4***	*47.8*	*21.7*
	≥ 18 years, T2	*N = 112*	*4.7 ***	*–1.52*	*26.8*	*59.8*	*13.4*
Tic score:	Improved tic-score (5 points)	*N = 107*	*15.1 ***	*3.64 **	*19.6*	*53.3*	*27.1*
	Stable tic-score	*N = 62*	*0.8 **	*–3.87 ***	***37.1***	*56.5*	*6.4*
	Worse tic-score (–5 points)	*N = 35*	*–10.5 ***	*–7.43 **	***40.0***	*54.3*	*5.7*
Vocal tics:	Vocal tics, T1	*N = 120*	*12.3 ***	*2.08*	*26.7*	*47.5*	*25.8*
	Vocal tics, T2	*N = 106*	*2.1 **	*–2.55*	***37.7***	*45.3*	*17.0*
Autism:	Autism spectrum, T2	*N = 14*	*8.8 ***	*–3.57*	***42.9***	*50.0*	*7.1*
IQ < 70:	IQ < 70, T2	*N = 12*	*9.1 **	*–2.50*	***33.3***	*58.3*	*8.3*
Phenotypes T1:	TS Only	*N = 83*	*5.5 ***	*–1.69*	***30.1***	*59.1*	*10.8*
	TS + ADHD	*N = 38*	*8.3 ***	*1.08*	*21.6*	*62.2*	*16.2*
	TS + OCD	*N = 36*	*3.3*	*–0.83*	***30.6***	*50.0*	*19.4*
	TS + ADHD + OCD	*N = 47*	*9.0 ***	*0.43*	*29.8*	*42.6*	*27.6*
Phenotypes T2:	TS Only	*N = 111*	*8.1 ***	*0.90*	*20.7*	*65.8*	*13.5*
	TS + ADHD	*N = 37*	*5.1 **	*1.62*	*24.3*	*45.9*	*29.8*
	TS + OCD	*N = 30*	*2.9*	*–4.67 **	***36.7***	*56.7*	*6.7*
	TS + ADHD + OCD	*N = 24*	*4.0*	*–7.39 **	***65.2***	*13.0*	*21.8*

Table 7. Development of tic-related impairment scored on the YGTSS from T1 to T2. Change in total tic score is presented as a mean score for the groups, with a positive score indicating an improvement with fewer tics at T2 and a negative score indicating an exacerbation in tic score at T2. Similarly, the change in impairment score is presented as a mean for the groups. Worse impairment scores of more than 30% in the subgroups are marked in bold. Significance level *P < 0.05, **P ≤ 0.00. Yale Global Tic Severity Scale Score (YGTSS); Obsessive Compulsive Disorder (OCD); Attention Deficit Hyperactivity Disorder (ADHD); Intelligence quotient (IQ).

Correlations to impairment score	Spearman's correlations R	P-value
Sex	0.168	0.012*
Age	–0.022	0.745
SES	0.095	0.154
Vocal tic	0.327	0.001**
Motor tic	0.536	0.001**
Total tic	0.493	0.001**
IQ Score	0.031	0.682
Autism diagnosis	0.046	0.494
OCD severity	0.329	0.001**
ADHD severity*	0.282	0.001**

Table 8. Tic-related impairment scores (YGTSS) at follow-up (n = 226) correlated with sex, age, SES, tic severity, IQ and comorbidities. Significant correlations P ≤ 0.05 are marked with * and P ≤ 0.001 with **. Yale Global Tic Severity Scale Score (YGTSS)

Sex and impairment scores were significantly correlated, with girls having higher impairment scores than boys. OCD and ADHD severity and vocal, motor and total tic score were highly significantly positively correlated to the impairment score. Of the 16 participants with a tic-related impairment score ≥ 40 at T1 or T2, 87.5% had comorbidities and 62.5% had more than one diagnosis, but no participant had an impairment score of more than 40 at both T1 and T2.

Development of phenotypes

A total of 224 participants had sufficient clinical data to set phenotype at T1 and T2. Their development in expression of TS phenotypes between T1 and T2 and their subclinical symptoms at T2 are shown in Figure 5. Slightly more than half of the cohort (53%) altered their phenotype and were classified in a different group. A clear tendency toward the TS-only group was seen with 56 (42%) participants moving from the baseline comorbidity groups into the TS-only group, and there was a corresponding decrease in OCD and ADHD comorbidity. Conversely, 25 (27%) participants from the T1 TS-only group developed comorbidities. However, in total, the TS-only group increased by 31 (15%) participants at T2.

Subclinical and subthreshold symptoms at T2 were recorded for 34 (26%) participants fulfilling the diagnostic criteria for OCD and/or ADHD at T1. Subclinical OCD symptoms were recorded for four participants and partial ADHD remission was observed in 30 individuals, of whom four fulfilled the criteria for a hyperactive-impulsive type, and one for inattentive type ADHD. Furthermore, four participants who had no ADHD comorbidity at T1 fulfilled the criteria for inattentive ADHD at T2. No participants fulfilled the criteria for hyperactive-impulsive ADHD. Complete remission from tics (total absence of tics) was recorded for 38 (17%) participants at T2.

The developmental trajectories of the phenotypes in the different age groups are shown in Figure 6. For the youngest participants (aged 5–10 years) the group-composition at T1 varied with fewer individuals in the TS-only group (22.5%, n = 9), but more in the TS + ADHD + OCD (30%, n = 12) and TS + OCD (25%, n = 10) groups compared with the whole cohort. At T2 this composition changed with an increase in the TS-only group (60%, n = 24) and fewer individuals in the TS + ADHD + OCD group (5%, n = 2) compared with the whole cohort, which had 55% (n = 124) of individuals in the TS-only group and 13% (n = 28) in the TS + ADHD + OCD group. In the medium age range group (11–15 years), the TS-only group was 7% larger at T1, but this levelled off at T2. In the oldest group (age 16–20 years) fewer participants developed toward the TS-only group at T2, and more remained in the TS + ADHD + OCD group (23%, n = 9) compared with the whole cohort (13%, n = 28). The prevalence of an OCD diagnosis (39.4% at T1) decreased at T2 (26.8%). The prevalence of ADHD at T1 was 41.2%, and this also decreased at T2 (30.4%).

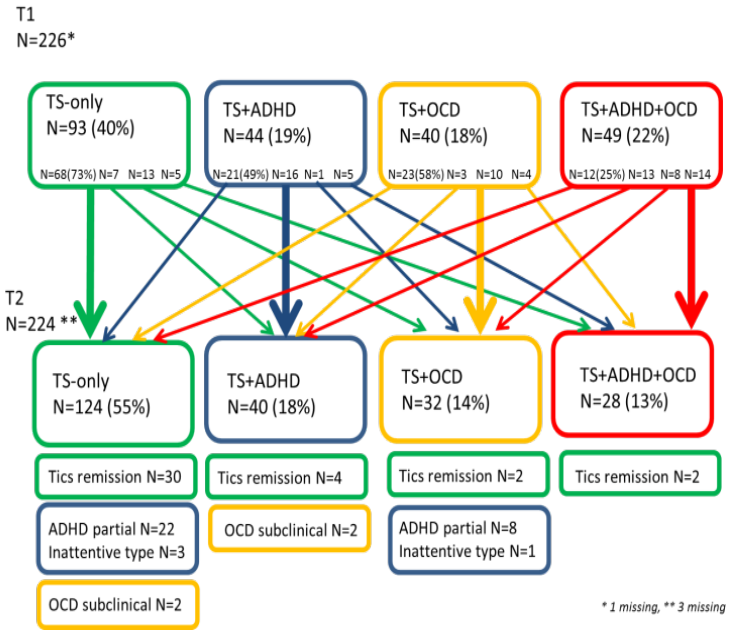

Figure 5. The development of phenotypes from T1 to T2. At T2, the groups were subdivided illustrating subclinical symptoms and full tic remission (tic score on the YGTSS = 0), partial ADHD, inattentive type ADHD and subclinical OCD (OCD-score 8–9 on Y-BOCS). No participants at T2 fulfilled the criteria for predominantly hyperactive/impulsive ADHD. Yale Global Tic Severity Scale Score (YGTSS); Obsessive Compulsive Disorder (OCD); Attention Deficit Hyperactivity Disorder (ADHD)

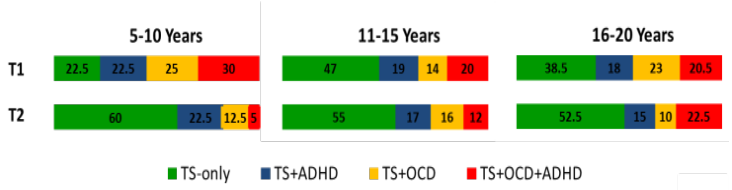

Figure 6. The development of phenotypes from T1 to T2 in different age groups. The subgroups were separated according to age at T1. Numbers shown are percentages. Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD)

Predictors

In the predictive analyses a total of 213 participants were included. Thirteen were excluded because of ASD. No participants were excluded because they had an IQ < 70 combined with a developmental disorder.

Analysis of predictors of tics

In total, 44 participants had a high tic score (score ≥ 20) and 169 participants had a low tic score (score = 0–19) on the YGTSS at T2.

At step 1, we identified five significant predictive variables: total tic score, ADHD score, teasing, presence of vocal tics and family history of TS + OCD + ADHD. These predictive variables were included in a second multiple logistic regression analysis to examine whether they reflected truly independent predictors in step 2.

The predictive variables total tic score ($p = 0.01$), family history of TS + OCD + ADHD ($p = 0.03$) and teasing ($p = 0.04$) remained significant and can be considered valid predictors. The full predictive power of the three predictors and the predictor total tic score were tested in a ROC curve in step 3 to differentiate between the overall effect with all three significant predictors and the highly significant predictor. Using all three predictors improved the model only moderately providing some additional predictive power.

For every one point increase in the YGTSS score rated in childhood, individuals had an increased odds ratio of 1.09 for moderate to severe tics in early adulthood. For every 10 point increase on the YGTSS in childhood, the odds of a *high tic score* in early adulthood increased by a factor of 2.42. Additionally, having a family history of TS + OCD + ADHD, or being teased in childhood, increased the odds of having moderate to severe tics in early adulthood by a factor of 3.10 and 2.25, respectively.

In summary, *total tic score, family history of TS + OCD + ADHD* and *teasing* in childhood were found to be predictors of *high tic scores* at T2.

Analysis of predictors of OCD

For the analyses of predictors of OCD in early adulthood, we had 57 participants with OCD present and 156 participants with OCD absent.

At step 1, we identified 3 significant predictive variables: OCD score, ADHD score and social restraints. These predictive variables were included in the second multiple logistic regression analysis.

The predictive variable OCD score remained significant and was the best predictor. The full predictive power of the three predictors from step 1 and the strong predictor OCD score were tested in the ROC curve in step 3. Using all three predictors did not add predictive power to the model.

Every additional point on the CY-BOCS rated in childhood increased the odds of having an OCD diagnosis in early adulthood by a factor of 1.08. For every 10 point increase on the CY-BOCS in childhood, the odds of having OCD in early adulthood increased by a factor of 2.09.

In summary, OCD score in childhood is the best predictor for the presence of OCD in early adulthood.

Analysis of predictors of ADHD

For the analyses of predictors of ADHD present in early adulthood we had 62 participants with ADHD present and 151 participants with ADHD absent at T2.

At step 1, we identified nine significant predictive variables: ADHD score, OCD score, total tic score, family history of TS, family history of ADHD without TS, special education, teasing, social restraints and age at T2. These nine predictive variables were included in the second multiple logistic regression analysis.

The predictive variables ADHD score and special education remained highly significant ($p < 0.01$) and Family history of ADHD without TS was significant ($p < 0.05$), so these can be considered valid predictors. The full predictive power of the nine predictors and the highly significant predictors ADHD score and special education were tested in the ROC curve in step 3. Using all nine predictors compared with using the two highly significant predictors did not add predictive power to the model.

However, a lack of statistical power and non-significant results can result from including more than the maximum number of predictive variables in relation to the sample size.

Every one point increase in DSM-IV ADHD criteria rated in childhood increased the odds of having an ADHD diagnosis in early adulthood by a factor of 1.13. For every five criterion increase in DSM-IV ADHD criteria in childhood, the odds of having ADHD in early adulthood increased by a factor of 1.88. In addition, receiving special education in childhood increased the odds of future ADHD by a factor 3.13 and having a family history of ADHD increased the odds by a factor 2.58.

In summary, *ADHD score* and *special education* in childhood were the strongest predictors for the presence of ADHD in early adulthood.

Analysis of predictors of Emotional Disorders

For the analyses of predictors of emotional disorders present in early adulthood, we had 32 participants with emotional disorders present and 104 participants with emotional disorders absent from the DAWBA subgroup at T2.

At step 1, we identified four significant predictive variables: ADHD score, OCD score, teasing and sex. These predictive variables were included in the second multiple logistic regression analysis.

The predictive variables sex ($p < 0.01$) and ADHD score ($p < 0.05$) remained significant and can be considered valid predictors. The full predictive power of the four predictors from step 1 and the predictors sex and ADHD score were tested in the ROC curve in step 3. Using all four predictors did not add predictive power to the model compared with using the two significant predictors.

Every one point increase in DSM-IV ADHD criteria rated in childhood increased the odds of having emotional disorders in early adulthood by a factor of 1.11. For every five point increase in DSM-IV ADHD criteria in childhood, the odds of having ADHD in early adulthood increased by a factor of 1.66. Additionally, being female increased the odds of having emotional disorders in early adulthood by a factor of 3.94.

In summary, being female and ADHD score in childhood were the strongest predictors of emotional disorders in early adulthood

All significant predictors are presented in Table 9.

COMORBIDITIES, COEXISTING PSYCHOPATHOLOGIES AND OTHER CO-OCCURRING DISORDERS

	OR	Standard Error	P-value
Predictors of *high tic score T2*			
Total tic severity score T1	1.09	0.0351	0.0118
Teasing T1	2.25	0.4019	0.0435
Family history of TS + OCD + ADHD	3.11	0.5255	0.0311
Predictors of *OCD present* at T2			
OCD severity score T1	1.08	0.0204	0.0003
Predictors of *ADHD present* at T2			
ADHD severity score T1	1.13	0.0472	0.0076
Special education T1	3.13	0.4273	0.0076
Family history of ADHD without TS	2.58	0.4757	0.0467
Predictors of *Emotional disorders present* T2			
Sex (female)	3.94	0.5138	0.0076
ADHD severity score T1	1.11	0.0491	0.0392

Table 9. Predictors of the outcomes of TS severity defined as high/low tic score, OCD, ADHD or emotional disorders present at T2. Severity scores of Total tics, OCD and ADHD are continuous scores, and every additional point indicates an increase in the OR of the outcome. All results are significant ($p < 0.05$). Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD); Time 1 (T1); Time 2 (T2); Tourette syndrome (TS).

Additional diagnoses from the T2 clinical interview

In total, 33 participants (14.5%, T2) reported currently diagnosed comorbidities of which 15 (6.6%) reported ASD, eight (3.5%) reported depression and six (2.6%) reported anxiety. Seventeen participants (7.5%) described other diagnoses that included personality disorders (n = 4, 1.8%), schizophrenic disorders (n = 4, 1.8%) and psychosis (n = 2, 0.9%). Several participants had more than one diagnosis.

DAWBA

A diagnostic evaluation for psychiatric coexisting psychopathologies was performed at T2 on 146 (65.2%) participants aged 11 to 26 years, using the DAWBA. Demographic measurements differed significantly only for age: DAWBA participants were younger (mean = 18.2 years) than non-participants (mean = 19.0 years).The inter-rater reliability was very high with a weighted kappa coefficient of 0.89 for emotional disorders and 0.83 for neurodevelopmental disorders. A total of 84 sure diagnoses in 53 participants and 31 unsure diagnoses in 15 participants were recorded. Unsure diagnoses were only used if confirmed in the clinical examination. Several participants had more than one diagnoses and consequently 64 participants (43.8%) had comorbidities.

Comorbidities, coexisting psychopathologies and other co-occurring disorders

Diagnoses collected from the subgroup participating in the DAWBA (n = 146) and T2 clinical examinations were collected (Table 10). A total of 185 diagnoses were distributed among 92 participants. In total, 54 (37.0%) participants had no comorbidities, 44 (30.1%) had one, and 48 (32.9%) had two or more.
Hyperactivity was the most common diagnosis (34.2%), followed by OCD (24.7%), emotional disorders (24.0%) and developmental disorders (12.3%). In total, 63.0% of the cohort had comorbidities

and/or coexistent psychopathologies sufficiently severe to fulfil DSM-IV diagnoses, and the remaining 37.0% were considered *Pure TS*. T1 assessments of the same subgroup for OCD, ADHD, IED, sleep disturbance, stuttering, symptoms of depression, and seasonal affective disorder found *Pure TS* in only 9.7%.

DISCUSSION

CLINICAL COURSE

In this large prospective study, we examined the clinical course of tics and comorbidities to gather evidence for the expected clinical course of TS in adolescents so that clinicians can provide guidance to their patients, implement preventive measures and allocate resources more effectively.
As hypothesised, we found a significant age-related decline in tics and ADHD symptoms. However, OCD severity during adolescence did not persist as predicted, and also showed a significant age-related decline. Conversely, sleep disturbance increased significantly with age, and age-related declines in tic severity were not reflected in improvements in tic-related impairment.

Tics

Changes in tic severity were highly significantly related to age, with an annual decline in mean total tic score of 0.8 points on the YGTSS, between the ages of 6 and 26 years. This included a decline in both motor and vocal tics, although there was some variability. We demonstrated that tic severity declined with age and in the oldest age group (21–26 years), 18.2% was in full remission with tics being absent.
The declining tic-severity during adolescence observed in this study has also been demonstrated in two smaller follow-up studies. In a study by Leckman *et al*. that included 36 participants with a mean age of 18 years, 47.2% of participants were tic-free and 11.1% were in the moderate–severe category at follow-up (16). In addition, a study by Bloch *et al*. that included 46 adolescents with a mean age of 19 years demonstrated that 33% of the study participants were tic-free and 22% were in the moderate–severe category at follow-up (63). In our population of 237 participants over the age of 16 (mean = 19 years), 18% were tic-free, 60% had minimal or mild tics, and 22% were in the moderate–severe category. Our study had the same prevalence of moderate–severe-tic

Diagnoses	Clinical assessment T2	DAWBA	Total
	participants (%)	*participants (%)*	*participants (%)*
OCD	***35*** (24.1%)	**10** (6.8%)	**36** (24.7%)
Emotional	**9** (6.2%)	**35** (24.0%)	**35** (24.0%)
Hyperactivity	**50** (34.2%)	**24** (16.4%)	**50** (34.2%)
Behaviour	**14** (9.6%)	**3** (2.1%)	**16** (11.0%)
Developmental disorders	**10** (6.8%)	**12** (8.2%)	**18** (12.3%)
Intellectual disability IQ < 70	**8** (5.6%)	-	**8** (5.6%)
Eating disorders	-	**3** (2.1%)	**3** (2.1%)
Sleep disturbance	**15** (11.4%)1	-	**15** (11.4%)1
Psychosis	**2** (1.4%)	**1** (0.7%)	**2** (1.4%)
Other diagnoses	**2** (1.4%)	**1** (0.7%)	**2** (1.4%)
Comorbidity and coexistent Psychopathologies	**81** (55.9%)	**64** (43.8%)	**92** (63.0%)

Table 10. Comorbidities, coexistent psychopathologies and other co-occurring diagnoses in participants from the subgroup (n = 146) participating in the Development and Well-Being Assessment (DAWBA). Participants with diagnoses from the clinical examination are presented in the first column, diagnoses from the DAWBA in the second column and the total number of participants with a diagnosis from the clinical examination or DAWBA in this subgroup is shown in column 3. 1 = Fewer participants for sleep disturbances (n = 132). Emotional: anxiety, post-traumatic stress disorder and depression. Hyperactivity: ADHD - combined, predominately inattentive or hyperactive-impulsive type. Behaviour: oppositional defiant disorder, conduct disorders, intermittent explosive disorder and other behavioural disorders. Developmental disorders: autism, Asperger's and other developmental disorders. Intellectual disabilities: Intelligence Quotient (IQ < 70. Eating disorders: anorexia nervosa, bulimia nervosa and other eating disorders. Sleep disturbance. Psychosis: psychosis and schizophrenia. Other diagnoses: personality disorders and substance abuse disorder.

cases as Bloch *et al*. (63) although we observed fewer participants in the tic-free category compared with both the Bloch *et al*. (63) and Leckman *et al*. (16) studies. Most of our participants had minimal or mild tics (60%).

A comparison of our age-related results with those of Leckman *et al*. (16) demonstrates an equivalent tic decline during adolescence. However, the longitudinal result scores cannot be compared directly on scores because Leckman *et al*. used a retrospective annual rating of relative tic severity, whereas we used YGTSS scores prospectively.

Adding our age at tic onset observations (n = 283) to the persisting observations would produce a graph of mean age-related tic severity score similar to that created by Leckman *et al*. (16).

All clinical and semi-structured interviews were performed and analysed using the same procedure so that the results could be compared, although inter-rater testing between T1 and T2 was not included. Tic severity was assessed using the YGTSS recording self-reported tic, which is considered the gold standard (39,82). However, the reliability and accuracy of self-reported tic assessments have been questioned. Pappert *et al*. (84) videotaped adults who self-reported being tic-free and 50% of them displayed objective evidence of tics, despite significantly improved tic scores. Accordingly, caution should be exercised when interpreting the results of all studies that include self-reported 'tic-free' participants. We took precautions to minimise this potential for bias and participants were observed during the clinical interview and following neuropsychological tests. If parents were present, they were asked for their observations and any discrepancies between reported and observed tics were resolved by consensus.

Our data confirmed existing observations on the clinical course of tics with approximately 20% of participants in the moderate–severe tic category at follow-up. We found fewer participants in the tic-free group but more in the minimal–mild category. We also showed that there is a great deal of variation among individual cases and made significant evidence of the expected clinical course.

Tic-related impairment

Previous studies have reported the significant negative impact and distress caused by tic-related impairment on quality of life, particularly concerning the individual's social life and relationships, and difficulties were more pronounced in individuals with severe tics or comorbidities (12,18,21). We expected that tic-related impairment would reflect the age-related decline in tics and also decrease, even if comorbidities might influence the subjective perception of tic-specific impairment. However, our findings showed a more complex pattern, which might reflect that the impairment score is based on the individual's self-perception and self-esteem, their social, peer and family relationships, and their ability to perform in academic or occupational environments. Therefore, tic-related impairment may be influenced by many factors during adolescence, as described below. Our results demonstrated a slight, non-significant increase in mean tic-related impairment score of 0.54 points on the YGTSS at follow-up, with almost 30% of participants reporting greater impairment despite a significant decline in tics in the same group (mean = 6.4 points on the YGTSS) . Factors that were highly significantly correlated with impairment score at follow-up included female sex, OCD and ADHD severity, and vocal, motor and total tic score. The correlation between tic severity and tic-related impairment was consistent with earlier findings (12,18,85), although the suggestion by Storch et al. that vocal tics are more strongly correlated with the impairment index than the total motor tic score, was not confirmed (18). Interestingly however, analysis of the subgroup with vocal tics at follow-up, who had a small mean improvement in total tic score, demonstrated that 37.7% had poorer impairment scores. Therefore, vocal tics might have influenced tic-related impairment and as Storch et al. (18) suggested, "attention or disruption resulting from phonic tics may invite peer ridicule and reprimands" thereby increasing the perception of impairment related to the tics.

A correlation between impairment and comorbidities has also been suggested by Rizzo *et al*. (21), who described patients presenting with a variety of impairments correlated with the presence of comorbid conditions. We found that ADHD and OCD severity were highly significantly correlated with impairment scores. In addition, 65.2% of participants in the TS + ADHD + OCD group at follow-up reported greater tic-related impairment and significantly increased impairment scores, although their mean total tic score was slightly improved relative to T1. Impairment was also apparently influenced by autism and IQ < 70 in these subgroups, although the correlations were not significant. In addition, the subgroup with YGTSS impairment scores of more than 40 at both baseline and follow-up showed high co-occurrence of comorbidities. Tic-related impairment was correlated with sex, with more girls having impairments than boys, although tic severity and the presence of OCD and ADHD did not differ between the sexes at follow-up. Moreover, tic-related impairment was not correlated with age as could be expected if young adults are more sensitive to their tics. However, even if young adults are more sensitive to tic-related impairment, the age-related decline in tics might counteract this. Altogether we found an unexpected, small and non-significant increase of 0.54 in tic-related impairment score with almost 30% of participants reporting greater impairment despite a significant decline in tic severity. Tic-related impairment had a high correlation with the female sex, OCD and ADHD severity, and vocal, motor and total tic score.

OCD severity

The severity of combined compulsions and obsessions was highly significantly related to age (in the 5 to 26 year-old age range) with a modest yearly decline of 0.24 in mean total OCD score on the CY-BOCS/Y-BOCS, although symptoms may persist. This reflected a highly significant decline in compulsions (mean score = 0.17), whereas a smaller decline in obsessions (mean score = 0.06) was not significant. This confirms a pattern in the development of OCD symptoms, with compulsions being more dominant in childhood and obsessions becoming more prevalent in adolescence (86).
In contrast, a follow-up study of 46 patients (mean age = 19 years) by Bloch *et al*. found a TS-associated OCD increase of 6.7 points on the CY-BOCS (63). However Bloch *et al*. (63) only assessed patients with a minimum of mild worst-ever symptoms (CY-BOCS score ≥ 10), whereas we included all children with and without OCD symptoms. Moreover, when we selected our participants who scored > 10 (CY-BOCS/Y-BOCS) at both T1 and T2 they actually still scored less at T2 (1.9 points on average) than at T1, and only 13.9% of participants had increased severity. This discrepancy might be caused by different demographic characteristics in the cohorts. In contrast to Bloch *et al*. (63), we did not exclude patients with IQ score < 80. The mean IQ of the participants included in Bloch's study was 111, whereas the mean IQ in our study was 91. In agreement with Bloch *et al*. (63), we found that TS patients with co-morbid OCD at T1 had higher Full Scale Intelligence Quotient scores compared with other phenotype groups (55). Peterson *et al*. also reported an association between high IQ and OCD, although their study was an epidemiological sample and mean IQ scores were probably closer to the norm of 100 and therefore higher than in our clinical study sample (20). In addition, Peterson reported that young children with tics were more likely to have lower IQ scores (20). This association might explain the higher severity of OCD in Bloch's cohort where the patients had a higher mean IQ. This selection bias could contribute to the difference between our results and Bloch's, because Bloch's cohort would then correspond to a subgroup of our total cohort. In addition, only 20% of patients with ADHD participated in Bloch's follow-up study compared with a non-participating 33% at baseline (63). In our study, 41% of ADHD patients participated at follow-up compared with a non-participating 48% at baseline. This difference in selected participants together with the association between OCD and ADHD described previously (20,34) might help explain these complex interactions (36).

In summary, we found a small but highly significant age-related decline in OCD severity that is not consistent with previous reports. The inconsistencies might result from heterogeneity in our cohort, which had no exclusion criteria and would be less influenced by factors associated with IQ and OCD compared with other studies (20,63).

ADHD severity

ADHD symptoms defined by the DSM-IV criteria were highly significantly age-related, and symptoms of inattention, hyperactivity and impulsivity decreased annually in line with the clinical impression, although some executive difficulties persisted. More surprisingly, the mean scores for ADHD symptoms at T2 analysed against the Danish national norm scores revealed that symptoms of inattention, hyperactivity and conduct persisted. The method of measuring ADHD symptoms changed between T1 and T2 because better methods became available and we wanted to include measurements of symptoms severity. The Danish Norm scores (69) allowed us to compare TS-associated ADHD symptoms with the Danish population in general. Unfortunately however, Danish Norm scores were only available for the ADHD-RS and not for the equivalent adult version (the ASRS).
At follow-up, 18% of the TS-only group had ADHD in partial remission with persistent symptoms and impairment. In general, participants improved during adolescence and fulfilled fewer ADHD criteria, although many still had subthreshold symptoms and experienced difficulties in daily functions including planning, education and relating to their peers. These young people might require continued support. The same developmental trajectory is seen in ADHD without TS (31,87).

Prevalence

The prevalences of OCD (T1 = 39%, T2 = 26.8%) and ADHD (T1 = 41%, T2 = 30%) in our cohort are similar to previous reports suggesting a prevalence of 36–50% for OCD and 50–60% for ADHD (3,5–8) in clinical settings. Our results suggested a slightly lower prevalence of these comorbidities especially at T2, which might be because most studies report lifespan prevalences. We decided not to report lifetime prevalences and worst ever periods to avoid recall bias and relied only on validated diagnoses. In addition, we defined ADHD prevalence as ADHD combined.
Comparing our clinically based results with the epidemiological samples described by Scharf *et al*. (88) (OCD co-occurring with TS = 5–10%; ADHD co-occurring with TS = 4–9%) or Khalifa and Von Knorring (19) (OCD co-occurring with TS = 16% and ADHD co-occurring with TS = 60%) demonstrated that our sample had a markedly higher prevalence of the comorbidities OCD and ADHD, except for ADHD prevalence in the Khalifa and Von Knorrings cohort. We would expect a lower prevalence in epidemiological samples when compared with our sample from a tertiary clinic. An epidemiological sample will additionally include children and adolescents with mild tics and fewer comorbidities, whereas a

clinical cohort includes children with more severe symptoms requiring greater assistance and treatment.

Our study demonstrated a clear co-occurrence between tics and ADHD, both at T1 and T2. This might be a reflection of our clinically-based sample, which as Peterson *et al*. (20) suggested demonstrates that "the presence of tics and ADHD results from a complex sharing across development of numerous psychopathological risk factors".

Understanding how ADHD remission is defined, as discussed by Faraone and Biederman (30,31), is important because natural developmental changes make it more difficult for children to meet ADHD diagnostic criteria as they get older. Hyperactivity is often dominant in childhood, but this can be replaced by inattentive difficulties in adolescence (29), and these may be less perceivable. We have tried to limit the possibility of assessment bias here by using the ASRS (66), which is targeted at young adults. However, the diagnostic criteria are still based on a childhood-specific disorder (51). This issue could be reflected in our follow-up observation that 18% of the TS-only group had ADHD in partial remission, including subgroup diagnoses of predominantly inattentive type and hyperactive-impulsive type. Using a different definition of persistence (e.g., the DSM-IV's definition of ADHD in partial remission instead of the criteria for combined ADHD) could provide a much higher rate of persistence.

Summary clinical course

In summary, we found a decline in tics and comorbid OCD and ADHD severity during adolescence, although persistent symptoms manifest as subthreshold diagnoses or partial remissions were still present. Interestingly, the decline in tic severity did not result in a corresponding decline in tic-related impairment. The prevalence of OCD and ADHD in our cohort at T1 was consistent with existing literature. This declined at T2, probably due to the natural age-related course of ADHD and OCD, with changes in symptoms and selected remission criteria. We have provided solid evidence that clinicians can use to advise patients on the expected clinical course of tics and comorbidities.

PHENOTYPE DEVELOPMENT

The development of TS phenotype expression was expected to develop in the direction of fewer comorbidities in parallel with the age-related changes that included declining severity of tics, OCD and ADHD. As hypothesised, many individuals moved to the TS-only group (42%). Conversely, 27% of TS-only participants at baseline had developed comorbidities at follow-up, but the TS-only group had still increased by 15%. This trend was most pronounced in the youngest age group, which had substantially fewer comorbidities at T2 compared with T1. In the oldest subgroup, we noted a tendency for individuals in the OCD or ADHD baseline comorbidity groups to remain in the same group. This pattern illustrated a wide variety in the severity of TS-associated comorbidities and showed how comorbidities were able to persist, although the overall severity of both OCD and ADHD significantly declined.

Only one previous follow-up clinical study has examined the developmental trajectory of TS phenotype expression. Rizzo *et al*. carried out a retrospective clinical study that included 100 children aged 3–8 years at onset (mean = 5.3 years), who were followed-up after 10 years (21). The cohort was separated at baseline into *pure TS* (38%), *TS + ADHD* (18% combined type), *TS + OCD* (0%) and *TS + ADHD + OCD* (14%). At follow-up, the distribution was: *pure TS* (53%), *TS + ADHD* (0%), *TS + OCD* (44%) and *TS + ADHD + OCD* (3%), with 76% changing phenotypes. The prevalence of *pure TS* observed in the study by Rizzo and co-workers was consistent with our *TS-only* population (T1 = 40%, T2 = 55%). However, their observed *TS + OCD* group at baseline (0%) differed significantly from ours (18%), and this difference was even greater when we used our most-comparable age subgroup (5–10 years, mean = 9 years, baseline *TS + OCD* = 25%). The younger referral age used in the Rizzo *et al*. study and the difficulties associated with assessing OCD in pre-school children (89) could account for this difference. Hirschtritt *et al*. (7) described how the age-at-onset of OCD could range from 2 to 11 years old, peaking at 7–8 years of age, and Leckman (25) reported that TS-associated OCD had a pre-pubertal age of onset. These reports by Hirschtritt *et al*. (7) and Leckman (25) are consistent with our finding OCD occurring in the 8–10 year-old age group. At follow-up, the Rizzo *et al*. *TS + OCD* group increased to 44% whereas ours decreased to 13% in the most-comparable subgroup (5–10 years) (21). Although both studies used the CY-BOCS and DSM-IV criteria, the methodology for selecting participants with OCD using the CY-BOCS could have differed. Because no validated cut-off was available in the CY-BOCS, we used a cut-off score adopted by Bloch *et al*. (15), but methodologically this was insufficient for an OCD diagnosis and so it was supplemented by a diagnostic evaluation of all participants with scores that were greater than the cut-off value. As discussed above, an association between IQ and OCD has been demonstrated and the Rizzo *et al*. study excluded patients with mental retardation, which could partly explain the higher prevalence of TS + OCD at follow-up.

The baseline prevalence of *TS + ADHD* (18%) in the study by Rizzo´s study coincides with our findings (19%). However, while our group remained stable at follow-up, all of those in the Rizzo *et al*. *TS + ADHD* group expressed a different phenotype (21).

The study by Rizzo *et al*. concluded that those who presented comorbid condition at onset had a more severe prognosis (21). However, our results suggested a more positive trend with a decline in the *TS + ADHD + OCD* group (T1 = 22%, T2 = 13%). In the youngest subgroup (5–10 years), the decline in the *TS + ADHD + OCD* group was even more marked (T1 = 30%, T2 = 5%). Conversely, the *TS + ADHD + OCD* group changed little (T1 = 21%, T2 = 23%) in the young adult group (16–20 years) and there was least general improvement in comorbidities in the TS + ADHD + OCD group. The differences between our observations and those of Rizzo *et al*. may be due to differences in the age range or mean age together with differences in the method of data analysis (i.e., prospective versus retrospective analysis). Our *TS-only* group prevalence at T2 is consistent with that of Rizzo *et al*. (53%), based on OCD and ADHD diagnoses (21).

Although the prevalence of comorbidities at T2 was lower than at T1, many individuals still had subthreshold symptoms and required monitoring. Furthermore, we must bear in mind that only OCD and ADHD phenotypes were analysed and other coexisting psychopathologies and co-occurring disorders were not considered.

Summary phenotype development

In summary, the developmental trajectory of the TS phenotype expression changed toward fewer comorbidities and the TS-only phenotype. The TS-only group increased by 15%. A total of 42% of those with comorbidities at T1 moved into the TS-only group at T2. Conversely, 27% of the TS-only group at T1 developed comorbidities at T2. For the youngest group this trend was most pronounced as they had more comorbidities at T1 and fewer com-

pared with the overall result at T2. In the oldest subgroup, a tendency for those with OCD or ADHD to remain in the same comorbidity group at follow-up was observed. In general, the TS phenotype development is dynamic with 53% of individuals changing the phenotype expressed during this time period. Elucidating the development of TS phenotypes can be useful in clinical settings, not only for patient guidance but also for future genetic, aetiological and clinical research.

PREDICTORS

We explored clinical childhood predictors for the clinical course of TS in early adulthood. Based on recent follow-up and cross sectional studies exploring predictors, we hypothesised that tic severity, OCD, ADHD and emotional disorders could be predicted by different baseline clinical characteristics. We expected factors including early onset of tics or comorbidities, presence of vocal tics, positive family history of tics, OCD and/or ADHD, severity of tics, OCD and ADHD, IQ and psychosocial or educational problems to be able to predict a more severe clinical course of TS.
We identified strong predictors for all predicted outcomes. As expected, we found that the strongest predictors of high tic score, OCD and ADHD in early adulthood were the respective symptom severities in childhood. For example, a high tic score in childhood predicted a high tic score in early adulthood, the OCD score on the CY-BOCS in childhood could predict the presence of OCD in early adulthood, etc. In addition, sex, family history and some psychosocial factors including, teasing and special education also predicted future diagnoses of tics, ADHD and emotional disorders.

Few clinical follow-up studies have examined predictors of future tics and comorbidities (15,45,46), but one large epidemiological prospective longitudinal study of tics and comorbidities examining associations and predictors was performed by Peterson *et al*. (20). This suggested an aetiological continuity between TS and chronic tics or tic disorders with a similar pattern of symptoms and comorbidities, although the chronicity of TS possible contributes to a higher rate of comorbidity (20). Taking this into account, the results from Peterson's study are similar to ours. As in our study, Peterson *et al*. found that tics, OCD and ADHD could predict future symptoms, although not consistently at all time points. However, Peterson used four examination time points: childhood, early and late adolescence and early adulthood. In general, comparisons between existing and new studies predicting outcomes of the clinical course of TS are difficult because of different study objectives, methods and TS populations with regard to age and symptom severity (e.g., tics and comorbidities) (15,45,46).

A longitudinal study by Lin *et al*. (46) examined the impact of psychosocial stress in predicting future tics, OCD and depression and found that psychosocial stress could predict OCD severity and depressive symptoms and was a modest predictor of tic severity. This was in line with our results of teasing in childhood predicting future tic severity and special education predicting future ADHD diagnoses. These psychosocial factors and childhood stress can have a variety of causes but we suggest that a combination of major social interaction difficulties, lacking friends and problems with empathy might be important. As described in the background section, Khalifa *et al*. (19) reported that as many as 40% of children with TS have these social interaction problems.

Predictors for tics

Our study identified three significant predictors of moderate to severe total tic score in early adulthood. The tic score in childhood was the strongest predictor of high tic score in early adulthood. For every 10-point increase in the YGTSS score in childhood the odds of having moderate to severe tics in early adulthood was increased 2.4-fold. In addition, having a family history of TS + OCD + ADHD or being teased in childhood increased the odds of having a high tic score in early adulthood by a factor of 3.10 and 2.25, respectively. These results are consistent with those of Bloch *et al*. (63) whose prospective follow-up study, discussed earlier in the clinical course section, identified an association between tic severity in childhood and early adulthood. Bloch *et al*. found that for every 10-point increase in the YGTSS in childhood the odds of having moderate to severe tics in early adulthood was increased 2.8-fold (63). A study by Goetz *et al*. (45) did not find an association with childhood tic severity but did find that mild tics during early and late adolescence predicted mild tics in adulthood. In general, the current literature supports the contention that tic severity in childhood correlates with future tic severity.

Predictors for OCD

The one strong predictor of an OCD diagnosis in early adulthood identified by our study was OCD severity in childhood. For every 10-point increase in childhood CY-BOCS score, the odds of having an OCD diagnosis in early adulthood increased 2.09-fold. Our results contrast with those of Bloch *et al*. (63) who found no association between childhood and future OCD severity. Furthermore, Bloch *et al*. (63) and Peterson *et al*. (20) found an association between higher IQ in childhood and increased future OCD severity, discussed in the clinical course section, but our study did not find an association between IQ and future OCD severity. Moreover, Peterson *et al*. (20) demonstrated that tics and ADHD in early adolescence predicted more severe OCD in early adulthood. Our analysis also showed that ADHD symptoms had a significant effect on future OCD, although not as an independent predictor.

Predictors for ADHD

The strongest predictor of ADHD in early adulthood was ADHD severity in childhood. For every five-point increase of ADHD DSM-IV criteria in childhood the odds of having ADHD in early adulthood increased 1.88-fold. Additionally, having special education in childhood or a family history of ADHD increased the odds by a factor of 3.13 and 2.58, respectively. Peterson *et al*. (20) were able to demonstrate that anxiety, depression and disruptive behaviour predicted future ADHD symptoms. However, we did not find any psychosocial predictors of future ADHD.

Predictors for emotional disorders

The strongest predictor for having emotional disorders in early adulthood was being a female. This increased the odds of having emotional disorders by a factor 3.94. In addition, for every five-point increase of ADHD DSM-IV criteria in childhood the odds of having an emotional disorder in early adulthood increased 1.66-fold.
Peterson *et al*. (20) demonstrated that tics, OCD and ADHD could predict future emotional disorders including anxiety, depression and phobias. We confirmed ADHD as a predictor but not tics or OCD. As described in the background section, behavioural, mood

and anxiety disorders and cognitive dysfunction are closely associated with, and possibly secondary to comorbid ADHD (3,7,20,27). This is consistent with ADHD being a predictor of future emotional disorders.

TS exhibits a broad heterogeneity and can be expressed in many dynamic phenotypes. Our study has shown this variability and in the study by Peterson et al. (20), the dynamic presentation over time is illustrated by inconsistencies in the predictors important during childhood, adolescence and early adulthood. This emphasises the difficulties involved in finding strong predictors of the future clinical course of TS.

Limitations of predicted outcome

Some limitations should be considered when interpreting these findings, in addition to the more general methodological limitations mentioned in a separate section. We have a large cohort, but when analysing outcomes the samples become smaller and difficulties maintaining sufficient power arise (e.g., high tic score n = 44, limiting the number of predictive variables in the multiple logistic regression analysis to four). However, to analyse the outcomes ADHD and emotional disorders we included nine and four predictive variables, respectively. This exceeded the preferred number of predictive variables relative to sample size and increases the risk of generating non-significant results, which might be explained by a lack of statistical power.

Summary predictors

In summary, we have identified some strong predictors for the clinical outcomes of TS in early adulthood. In the clinic, prognostic issues can be difficult to address for a very complex disorder with a varying clinical course of both tics and comorbidities. However, strong predictors may assist in providing guidance as to the expected clinical course, targeting early interventions and monitoring the child.

A CROSS-SECTIONAL VIEW OF COMORBIDITIES, COEXISTING PSYCHOPATHOLOGIES AND CO-OCCURRING DISORDERS

The cross-sectional part of our study, which investigates comorbidities, coexistent psychopathologies and co-occurring disorders using the DAWBA on a subgroup of patients (n = 146), supports existing findings from both clinical (5,7,8) and community settings (2,20) that describe substantial coexisting psychopathologies including anxiety, mood, behavioural, and developmental disorders. Hereby we support the contention that TS is not a unitary condition (3,21) but a complex disorder consisting of frequent comorbidities based on a complex aetiology derived from both environmental and genetic factors. In a study on the Swedish school population (aged 7–15 years), Khalifa and Von Knorring found at least one additional psychiatric diagnosis in 92% of children with TS (2). In addition, a large international clinical study by Freeman *et al*. concluded that *Pure* TS occurred in only 11–12% of the TS population from childhood to adulthood (5). Hirschtritt *et al*. reported a lifetime prevalence of any psychiatric comorbidity in TS patients of 85.7%, and 57.7% of these patients had two or more psychiatric disorders (7). Furthermore, Robertson demonstrated that 90% of the TS population had comorbidities and coexisting emotional and behavioural psychopathologies (8). Results from the baseline analysis showed *Pure TS* in only 10.2% of our cohort (50).

The DAWBA subgroup consisted mainly of adolescents (mean age = 18.2 years), some of whom had persisting tics, and some were in partial or full tic remission. Comorbidities, coexisting psychopathologies and co-occurring disorders were present in 63.0% of the participants, with the majority having more than one additional diagnosis.

Robertson (8) and Hirschtritt (7), who both described lifetime prevalence, identified a greater proportion of emotional and behavioural disorders than we did. Like Robertson (8) we reported personality disorders. Hirschtritt *et al*. (7) reported a lifetime clinical prevalence of 2.0% for eating disorders and 0.8% for psychotic disorders, which is consistent with our observations of 2.1% and 1.4%, respectively. For comorbidities on the autistic spectrum, we found a prevalence of 12.3%, which is similar to Robertson's observation of 6–11% (8) and Khalifa and Von Knorring's report of 16% (19). Little attention has been paid to this comorbidity, although both a biological (32) and genetic (34) relationship has been established. In addition as much as 40% of the TS children experience major social interaction problems with lacking friends or problems with empathy (2). In 40–60% of participants at T1, we also observed psychosocial consequences (including social restraint, being teased and feeling lonely) and educational consequences (including special education, changing schools, comprehension difficulties at school, etc.) (52). Our study confirms the findings from previous studies and provides solid evidence for the frequent comorbidities and severe psychopathologies present in the TS population.

Pure TS

Pure TS was present in 9.7% of the DAWBA subgroup at baseline but in 37.0% of patients at follow-up. Because of the different methodological procedures (described in the methods section) these numbers are not directly comparable, but they do indicate a decline in the prevalence of comorbidities and coexisting psychopathologies.

The cross-sectional part of our study had a higher prevalence of *Pure TS* than previous clinical studies (5,7,8). This may be due to our assessment of only current comorbidities to avoid recall bias, and consequently we cannot draw conclusions regarding lifetime prevalence. In addition, we examined individuals in partial and full remission from tics and comorbidities. Therefore, our cohort is likely to be a more heterogeneous clinical TS population than those found in other clinical studies. Furthermore, our cohort consisted mainly of older adolescents and, as we demonstrated in the longitudinal part of the study, the clinical course tends toward a decrease in symptom severity with age and increasing numbers of patients in partial or full remission.

As discussed above, remission cut-offs can significantly influence final prevalence. We did not include participants with partial remission or subthreshold diagnoses in the comorbidity groups, so these patients were included in the *Pure TS* group increasing the prevalence of *Pure TS*. The increase we observed in the *Pure TS* group is consistent with that reported by Rizzo *et al.* (21). These investigators reported 38% *Pure TS* in children at the onset of their study and 53% ten years later, but they only considered OCD and ADHD as comorbidities, resulting in a higher prevalence of *Pure TS* that is comparable with our *TS-only* group. The study by Peterson *et al*. concluded that predicting the course of tics and comorbidities depends on age and current comorbidities (20).

Limitations of the DAWBA

The DAWBA is a validated standardised diagnostic interview and agreement between DAWBA and clinical diagnoses are fair to moderate, which is comparable with similar interviews (74). The

DAWBA had a limited participation rate of 65.2%. Discrepancies between participants and non-participants with regard to age and IQ were noted. Participants were 0.8 years younger (18.2 versus 19.0 years) and had a higher IQ score than non-participants (96.5 versus 92.3), although these differences were not significant. The severity of tics and comorbidities did not differ significantly between DAWBA participants and non-participants. The DAWBA relied on available information but the inter-rater testing indicated strong inter-rater reliability (weighted kappa coefficient = 0.83–0.89).
The DAWBA replaced selected CBCL questions at T2 to improve diagnostic evaluation and consequently the results and prevalence of *Pure TS* from the DAWBA cannot be compared directly with those at T1 and merely suggest a decline in prevalence. However, the DAWBA does provide validated DSM-IV diagnoses that are comparable with other international studies.

Discrepancies in diagnoses between validated instruments
Comparing the diagnostic results from the clinical examination supported by standardised instruments (i.e., the CY-BOCS and ADHD-RS) and the DAWBA, all based on DSM-IV criteria, demonstrated that diagnosis rates were affected by focusing strictly on a few diagnoses, versus evaluating a wide range of different diagnoses and using different assessment techniques. More diagnoses were made at the clinical examination based on semi-structured and standardised interviews and individually evaluated as fulfilling DSM-IV criteria, than using the DAWBA. One study reported an underestimation of ADHD when only parent and not teacher reports were assessed as part of the DAWBA interview (90). This issue may also be reflected in discrepancies between our DAWBA and clinical diagnoses, although self-selection bias might also play a role.
We believe the strength of the DAWBA is in its wide diagnostic evaluation providing an overview of coexisting psychopathologies, whereas clinical examinations with their individual observer contact can perform a more thorough exploration but also consume more time and resources. This might also affect how our results compare with those from previous studies that use different diagnostic instruments, and could be a factor in our higher prevalence of *Pure TS*.

Summary of comorbidities, coexisting psychopathologies and co-occurring disorders
In summary, we have provided evidence of significant comorbidities, coexisting psychopathologies and co-occurring disorders that require clinical attention as well as demonstrating that a substantial proportion of patients have subthreshold symptoms, which present continuing difficulties that affect their daily life.

GENERAL LIMITATIONS
When interpreting these findings several limitations should be considered.

Demographic characteristics and selection bias
Our tertiary clinic-based recruitment may have biased our sample toward participants with more severe TS-associated comorbidities, limiting the generalisability of our findings compared with those from other clinical TS populations (20,63). The demographic characteristics recorded at T2 did not differ significantly between study participants and non-participants. We observed a non-significant tendency toward lower mean IQ at T1 among the non-participants (IQ = 85.3) compared with participants (IQ = 90.0). However, IQ scores were not associated with more severe tics or comorbidities (55).
Overall the re-participation rate between T1 and T2 was 72% and attrition bias is a possibility, although the non-participating group was very heterogeneous in terms of tic and comorbid severity.
In this study, we tried to reduce recall bias by only using data from current observations with symptoms reported during the preceding four weeks. However, for the additional diagnoses, age at onset of tics and first symptoms we have relied on parental reports, confirmed by data from medical records.

Age range and subgroups
The large age range in our population (5–26 years) relative to the developmental trajectory of TS and the TS-associated comorbidities, presents some challenges for analysing and describing the cohort. We tried to accommodate this by pooling data from T1 and T2 and illustrating the age-related course of TS using a mixed effects model with a random effect for each person. In addition, we created subgroups within the cohort using age-groups that correlated with the expected course of tic severity (6). However, fewer participants were under 10 or older than 20 years of age, reducing the power in these subgroups compared with the strong power of the central group, where ages ranged from 10 to 20 years. In addition, we generated subgroups that corresponded to the most frequent comorbidities to describe phenotype development. The use of different groups might obscure patterns of individual variation. In the tic-related analyses, we tried to limit this bias by extracting individuals with high impairment scores and describing any characteristics of these individuals that had a negative prognosis.

Missing data
Missing data can be problematic in analyses. We assumed any missing data were 'missing at random,' an assumption which was accommodated by the mixed model. For the phenotype groupings, the clinical questions relating to ADHD onset, impairment, presence in different settings and pharmacological treatment were able to exclude or include diagnoses for most missing ADHD questionnaires.

Pharmacological treatment
We investigated the clinical course and development of phenotypes, and pharmacological treatments were recorded but not analysed. Participants receiving pharmacological treatment for OCD or ADHD, who had subthreshold or subclinical diagnoses were considered positively affected by the treatment and categorised as having the comorbidity. This strategy reflects the clinical course, but pharmacological treatment should be taken into account when interpreting the data. Patients receiving pharmacological treatment may have less severe symptoms during treatment but the long-term effects on the development and severity of the comorbidity are unknown (36). Furthermore, all participants received psychoeducation and some cognitive therapy in the clinic, which should also have a positive effect on symptom severity and is recommended by European guidelines (91). Therefore, this study is indicative of the clinical course of TS and not necessarily its natural course.

Strengths
This is the largest prospective clinical longitudinal study performed in a single clinic on a well-characterised cohort, examining

the clinical course of TS with a uniform procedure and validated instruments.

The study is firstly strengthened by including all individuals having a TS diagnosis at a set date, and following all individuals in full, partial or no remission of tics or comorbidities. Secondly, all comparisons and observed results were based on uniform and prospectively assessed examinations for tics, OCD, ADHD, IED and sleep disturbance at both baseline and follow-up, and supplemented by a diagnostic evaluation at T2. Finally, this study is comprehensive in terms of the size of our cohort and the re-participation rate.

CONCLUSIONS

In this thesis the clinical course of TS, the development of TS phenotypes expression, predictors, comorbidities and coexisting psychopathologies are described and analysed.

This study adds solid evidence to the existing literature by longitudinally and prospectively examining a large clinical cohort with uniform and validated measurements. Guidelines for this field have mainly been based on cross-sectional studies or previous longitudinal studies, which are relatively small in number and size (15,16). The results of this study confirm previous findings (15,16) and clinical experience by describing a general decline in the severity of tics and comorbidities during adolescence.

The severity of comorbidities declined significantly, although some OCD symptoms remained and ADHD norm analyses confirmed that subthreshold symptoms often persisted.

Our observations of a general decline in tics and comorbid OCD and ADHD severity were not reflected in a decline in tic-related impairment, as had been expected. However, tic-related impairment was influenced by a variety of parameters and very significantly correlated with the female sex, OCD and ADHD severity, and vocal and motor tic score.

We described the developmental trajectory of TS phenotypes as being dynamic and changing as part of the overall clinical course toward fewer comorbidities and a TS-only phenotype, although some age-dependent differences were apparent.

Furthermore, we identified predictors of the expected clinical course of tics and comorbidities. The strongest predictors were tic, OCD and ADHD severity in childhood, with each predicting the same diagnosis in early adulthood. In addition, a family history of TS-related diagnoses and psychosocial consequences influenced the future clinical course of TS. Predictors are important in providing guidance for newly TS-diagnosed children, implementing preventive measures, and informing monitoring and early intervention strategies.

We have provided solid evidence for clinicians advising patients on the expected clinical course of tics and comorbidities. Moreover, we have described the significant coexisting psychopathologies and demonstrated that many adolescents in partial remission, or with subclinical or threshold symptoms, still experience difficulties which require clinical support and guidance. Consequently, this information may assist them in completing their education, managing their social life, avoiding self-medication, and promoting a healthy transition into adulthood.

CLINICAL AND FUTURE PERSPECTIVES

This study was based on a clinical cohort and its results are directly applicable to a clinical population of children and adolescents with TS. The study findings have a great deal of potential for guiding new patients, implementing preventive measures, initianting monitoring and early intervention strategies, and allocating resources. Our new results will although require further confirmation. The decline in OCD symptom severity we observed in early adulthood is not consistent with other studies. The complex interaction between tic severity, comorbidities and tic-related impairment suggests that although tic severity declines with age, an equivalent decline in tic-related impairment is not necessarily evident. The tendency toward *TS-only* phenotype development, the considerable prevalence of severe coexisting psychopathologies, and the new predictors of the clinical course of tics and comorbidities should all be confirmed by future investigations.

Our descriptions of the development of TS phenotypes will inform future genetic, aetiological and clinical research and our findings will inspire studies that may confirm these results but also studies that will explore new areas of research.

Tic-related impairment was influenced by a variety of parameters during adolescence, and these could be investigated further together with the relationship between tic-related impairment and health-related quality of life. New disease-specific questionnaires for measuring health-related quality of life (e.g., the Gilles de la Tourette syndrome-Quality of Life Scale(92)) will make this easier in future studies.

This study examined the clinical course of TS without analysing the possible effect of pharmacological or behavioural treatment. Further studies could focus on the effect of pharmacological treatment on tic severity and comorbidities in both the short and long terms. Moreover, it would be interesting to examine and compare the clinical course of TS and comorbidities in a cohort provided with Behavioural Therapy as new guidelines recommend (36,91,93).

Our cohort was recruited through the National Danish Tourette clinic, a tertiary clinic located in the capital city but with patients from throughout country. However, it would be interesting to examine the entire Danish TS population and thereby expand the cohort, most likely including patients with less severe tics and comorbidities.

Additionally, following the cohort into adulthood could generate new insight into the developmental trajectory of TS and its comorbidities.¨

LIST OF ABBREVIATIONS

ADHD:	Attention Deficit Hyperactivity Disorder
ADHD-RS:	Attention Deficit Hyperactivity Disorder rating scale
ASD:	Autism Spectrum Disorder
ASRS:	Adult Self Report Scale
CBCL:	Child Behaviour Checklist
CY-BOCS:	Yale-Brown Obsessive Compulsive Scale for children
DAWBA:	Development and Well-Being Assessment
DSM-IV:	Diagnostic and Statistical Manual IV
DSM-IV-TR:	Diagnostic and Statistical Manual IV Text revision
GTS-QOL:	Gilles de la Tourette Syndrome Quality of Life Scale
IED:	Intermittent Explosive Disorder
IQ:	Intelligence quotient
OCB:	Obsessive Compulsive Behaviour
OCD:	Obsessive Compulsive Disorder
SDQ :	Strengths and Difficulties Questionnaire
SES:	Socioeconomic status
TD:	Tourette disorder
TS:	Tourette syndrome
Y-BOCS:	Yale-Brown Obsessive Compulsive Scale for adults
YGTSS:	Yale Global Tic Severity Scale Score
WAIS:	Wechsler intelligence tests for adults
WISC:	Wechsler intelligence tests for children

SUMMARY

Introduction: Tourette syndrome (TS) is a childhood onset neurodevelopmental disorder characterised by motor and vocal tics and frequent associated comorbidities. The developmental trajectory of tic shows tic-onset in the age of 4-6, peak in the age of 10-12 and decline during adolescence, although only few and small longitudinal studies form the basis of this evidence. Recent studies suggest that comorbid obsessive-compulsive disorder (OCD), attention deficit-hyperactivity disorder (ADHD) and coexisting psychopathologies tend to persist and become more dominant in adolescence. This large prospective follow-up study want to examine the clinical course of TS: tic and comorbidities during adolescence, the prevalence of coexisting psychopathologies, the tic-related impairment, development in phenotype expression and find predictors for the expected course of TS.

Method: This study is examining a large clinical cohort recruited at the Danish National Tourette Clinic during the period 2005-07 and 2011-13. At baseline, 314 participants aged 5-19 years were included and at follow-up 6 years later 227 participated, aged 11-26. All participants were uniformly clinically examined at basis and follow up with a clinical interview and validated measurements to assess comorbidities. The Yale Global Tic Severity Scale was used to asses tic severity and tic-related impairment. At follow-up a cross-sectional diagnostic evaluation was made with the Development and Well-Being Assessment to assess coexisting psychopathologies.

Results: A significant decline in tic and the most frequent comorbidities OCD and ADHD was found although some variation existed and some subclinical and partial remissions persisted. Tic-related impairment was not reflected in the tic-decline as expected but influenced by several parameters. The phenotype expression was found to be dynamic but overall changed toward TS without comorbidities. Several predictors were found to predict the clinical course of TS in adolescence and early adulthood. Childhood tics, OCD and ADHD severity were the strongest predictors for future symptoms of the respectively diagnoses. Comorbidities and coexisting psychopathologies were found in 63% at follow up, whereas 37% had *pure* TS.

Conclusion: The clinical course of TS during adolescence was confirmed, with solid evidence, with decline in tics, OCD and ADHD severity. We provide evidence of considerable coexisting psychopathologies requiring clinical support and partial remissions and subthreshold symptoms requiring monitoring and clinical guidance to assist the young adults in promoting a healthy transition into early adulthood. Furthermore we provide predictors for the clinical course of TS to be used in the preventive efforts, early intervention and allocation of resources improving quality of life for the children and their families.

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