Long-Term Outcomes of Obsessive-Compulsive Disorder in Children and Adolescents

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*"By the sea I relax, get inspired, and find peace.
But it was also by the sea and the big rolling waves that my long and
winding road to this dissertation started, on 26th December 2004."*

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To my family!

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ABSTRACT

Aim: The overall aim of this thesis is to investigate the long-term course and outcome of pediatric OCD following evidence-based treatment of pediatric OCD. Outcome is assessed with regard to severity of OCD symptoms (Studies I-III), psychosocial functioning (Studies I & II), and depressive symptoms (Study II). **Method:** Studies I and II include the same 109 participants (5-17 years), assessed and treated in Western Sweden, based on the clinical guidelines for OCD and individually adapted for each patient. Study III comprises 269 participants (7-17 years) from a multicenter study, in Sweden, Norway, and Denmark. Participants were treated with a first step of manualized cognitive-behavioral therapy (CBT). Non-responders were randomized to an extended treatment of either continued CBT or pharmaco-therapy with sertraline. Both study samples were repeatedly assessed during a three-year follow-up period, using the semi-structured *Children's Yale-Brown Obsessive-Compulsive Scale* (CY-BOCS) interview, and the self- and parent-rated questionnaires *Children's OCD Impact Scale* (Studies I-II) and *Children's Depressive Inventory* (Study II). **Results:** Studies I and II revealed a significant improvement of OCD symptoms from baseline to one-year follow-up, and improvements maintained and continued until the three-year follow-up. Participants' psychosocial functioning and depressive symptoms improved during the follow-up period as well. Further, findings from the Study III sample showed that participants' improvements from the one-year follow-up were maintained, and symptoms decreased further during the three-year follow-up period as well. Improvements were similar regardless of the treatment duration and type of extended treatment. **Conclusions:** The three studies indicate that the course of pediatric OCD is favorable, possibly due to treatment gains of evidence-based treatment, following expert consensus guidelines. Gains were sustained over a three-year period and symptoms decreased further during the follow-up period.

SAMMANFATTNING PÅ SVENSKA

Tvångssyndrom (eng. Obsessive-Compulsive Disorder - OCD) är ett allvarlig och förhållandevis vanligt psykiatriskt sjukdomstillstånd som ofta debuterar i barn- och ungdomsåren. OCD orsakar ett stort lidande för både barnen/ungdomarna och deras familjer. De barn och ungdomar som drabbas, hämmas i sin utveckling och får en försämrad psykosocial funktionsförmåga. Om barn och ungdomar med OCD inte behandlas kan det hos många bli ett kroniskt sjukdomsförlopp och hindra barnets/ungdomens normala utveckling. Dessutom finns det risk att utveckla andra psykiska störningar i vuxen ålder. Tidigt ställd diagnos och snabb start av behandling kan vara avgörande för att förhindra eventuellt livslångt lidande. Kognitiv beteendeterapi (KBT) är rekommenderat som förstahandsval av behandling medan läkemedelsbehandling med selektiva serotonin återupptags hämmare (SSRI) är andrahandsval. Det är väl etablerat att dessa behandlingar har god effekt med symtomförbättring på kort sikt, medan långtids förloppet är mindre känt.

Det övergripande syftet med denna studie är att undersöka långtidsutfallet hos barn och ungdomar med OCD, efter att de har behandlats med evidens-baserade metoder enligt kliniska riktlinjer. Utfallet av behandlingen bedöms med avseende på svårighetsgraden av OCD-symtomen (studier I-III), psykosocial funktionsförmåga (studier I & II) och depressiva symtom (studie II).

I studierna I och II, ingår samma 109 deltagare (5–17 år, 56% flickor) som är bedömda och behandlade i Västsverige, baserat på kliniska riktlinjer för OCD och med individuell anpassning för varje enskild patient. Studie III omfattar 269 deltagare (7–17 år, 51% flickor) från en multicenterstudie, ett samarbete mellan forskare och kliniker i Sverige, Norge och Danmark. Deltagarna behandlades i första steget med manualbaserad kognitiv beteendeterapi (KBT) i 14 veckor. De som inte haft tillräcklig nytta av behandlingen randomiserades till en utökad behandling i 16 veckor med antingen fortsatt KBT eller medicinering med sertralin. Båda studiegrupperna följdes upp med upprepade utvärderingar (fyra tillfällen) under en treårig uppföljningsperiod med hjälp av den semi-strukturerade intervjun *Children´s Yale-Brown Obsessive Compulsive Scale (sv. tvångssymptom skala* (CY-BOCS)) och själv-och föräldraskattnings frågeformulären *Child OCD Impact Scale* (Studier I-II) och självskattningsskalan *Children's Depressive Inventory* (Studie II).

Studierna I och II, visade en signifikant förbättring av OCD-symtomen från starten av behandling till ett-årsuppföljningen, och att förbättringen bibehölls och ökade ytterligare fram till tre-årsuppföljningen. Även deltagarnas psykosociala funktion och depressiva symtom förbättrades under uppföljningsperioden. Vidare visade resultaten från studie III att deltagarna som hade måttlig-svår OCD före behandlingen, hade förbättrats under behandlingen och fram till ett-årsuppföljningen. Förbättringen bibehölls under uppföljningsperioden och symtomen minskade ytterligare fram till 3-årsuppföljningen. Resultaten var likvärdiga oavsett behandlingstid och typ av utökad behandling. Avhandlingens resultat visar på vikten av att erbjuda KBT till unga personer med OCD, då KBT verkar vara den mest fördelaktiga och säkra behandlingen, på kort och lång sikt.

De tre studierna tyder på att långtids förloppet för barn och ungdomar med OCD är gynnsam, troligen på grund av evidensbaserad behandling i enlighet med de kliniska riktlinjerna. Deltagarna förbättrades under behandlingen och symtomen minskade ytterligare under den treåriga uppföljningsperioden.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   Holmgren Melin, K, Skärsäter, I, Mowatt Haugland, B.S, Ivarsson, T. Treatment and 12-month outcome of children and adolescents with obsessive–compulsive disorder: A naturalistic study. Journal of Obsessive-Compulsive and Related Disorders. 2015;6:1-6.

II.   Melin, K, Skarphedinsson, G, Skärsäter, I, Mowatt Haugland B.S, Ivarsson T. A solid majority remit following evidence-based OCD treatments: a 3-year naturalistic outcome study in pediatric OCD. European Child Adolescent & Psychiatry. 2018;27(10):1373-81

III. Melin K, Skarphedinsson G, Thomsen PH, Weidle B, Torp NC, Valderhaug R, Højgaard DRMA, Hybel KA, Nissen JB, Jensen S, Dahl K, Skärsäter I, Haugland BS, Ivarsson T. Treatment gains are sustainable in pediatric obsessive-compulsive disorder: Three-year follow-up from the NordLOTS. Manuscript. *Submitted* (J. Am. Acad. Child Adolesc. Psychiatry)

CONTENT

ABBREVIATIONS

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
ASSQ	Autism Spectrum Screening Questionnaire
BDD	Body dysmorphic disorder
CANS	Childhood acute neuropsychiatric symptoms
CAP	Child and Adolescent psychiatric
CBCL	Child Behavior Checklist
CGAS	Children's Global Assessment Scale
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
CGI-S	Clinical Global Impression-Severity
CBT	Cognitive Behavioral Therapy
CDI	Children's Depressive Inventory
CI	Confidence Interval
COIS	Children's OCD Impact Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders fourth edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders fifth edition
E/RP	Exposure and response prevention
ICD	International Classification of Diseased
IRB	Internal Review Board

ITT	Intention-to-treat
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia – Present State and Lifetime Version
LME	Linear Mixed-Effects models
NordLOTS	Nordic Long-term OCD Treatment Study
OCD	Obsessive-Compulsive Disorder
OCRD	Obsessive-Compulsive and Related Disorders
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with streptococcal infection
PANS	Pediatric Acute-onset Neuropsychiatric Syndrome
PDD-NOS	Pervasive Developmental Disorder – Not Otherwise Specified
QoL	Quality of Life
RCT	Randomized Controlled Trial
SGA	Second Generation of Antipsychotics
SSRI	Selective Serotonin Reuptake Inhibitors
SRPs	Sleep-Related Problems
SD	Standard Deviation
WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a persistent and highly disabling psychiatric disorder, which the World Health Organization (WHO) ranks as the tenth most disabling medical disorder in the world (1). Untreated, pediatric OCD can become chronic and disrupt the normal development of a young person, and there is an increased risk of developing multiple concurrent mental disorders into adulthood (2, 3). Consequently, early diagnosis and treatment is crucial for the prevention of possible lifelong impairment (4). Current first-line treatments for pediatric OCD are cognitive behavior therapy (CBT) and pharmacotherapy with selective serotonin re-uptake inhibitors (SSRI). It is well established that these treatments for pediatric OCD are associated with significant symptom improvement in the short term, based on controlled trials (5-9), although the long-term outcomes are less well known.

Earlier on, many pediatric OCD patients were neither diagnosed nor treated adequately. Thus, thirty years ago, the mental health services struggled with even recognizing these patients. Moreover, the use of evidence-based methods for these patients were erratic at best. Thus, as better treatments have become available (5, 9) and been implemented, it is important to examine whether the outcome has improved compared to earlier studies.

This thesis will focus on the long-term outcomes of pediatric OCD. Two different clinical cohorts, including 109 respectively 269 children and adolescents with OCD, are followed with assessments repeatedly across three years. While the results presented in this thesis are limited in several ways, as will be discussed, they can still provide important information and increase our knowledge about the long-term outcome for pediatric OCD. In particular, these two cohorts were provided with evidence-based treatment in accordance with clinical guidelines still followed.

Characteristics of OCD

Symptomology

Pediatric OCD is a heterogeneous condition, in that the specific constellation of obsessions and compulsions varies a lot between different persons. Further, the OCD symptoms can fluctuate over time, both in intensity and presentation. The core features of OCD are obsessions and compulsions, with the former characterized as unrealistic, intrusive and unwanted thoughts, urges, or images that are recurrent and persistent, and which elicit acts designed to neutralize them. Even if the obsessions are unrealistic, they cause marked feelings of anxiety, distress, and/or disgust for most of the affected individuals (10, 11). The most common obsessions in pediatric OCD are a fear of contamination (dirt or germs), fear of harming oneself or important people, or the urge to ensure exactness and symmetry (12). Compulsions are repetitive behaviors such as excessive washing, checking, ordering, repeating, asking reassurance questions, and/or performing mental rituals such as praying, repeating words silently, and counting. These compulsions are carried out in order to neutralize the anxiety or feeling of distress or disgust caused by the obsessions, as well as with the aim of preventing the dangers perceived to be inherent in these obsessions (10, 13, 14). The most common compulsions are excessive handwashing and a range of other cleaning rituals, as well as checking and repeating behaviors (12).

Furthermore, avoidance behaviors are common and sometimes the most frequent and prominent phenomenon present in patients. They occur when a person avoids different things, places, people, or situations where obsessions might be elicited or evoked. The rationale behind avoidance behaviors is that if obsessions can be lessened to the extent that they are no longer present or at least less overwhelming, there is no need for compulsive behaviors and anxiety is lowered, which in turn strongly reinforces avoidance. Avoidance is important as OCD symptoms are maintained by the avoidance behavior and it is often an obstacle to working with the symptoms (15-17). In a large (n=317) clinical sample of pediatric OCD patients, a high degree of avoidance appears to be associated with more severe OCD at baseline and less probability of reaching remission (17).

In OCD with childhood onset, it is common that the children do not talk about their symptoms, try to hide them, and keep them secret. The children often feel shame and guilt due to their OCD-symptoms. They may also be frightened by some of the more bizarre or aggressive obsessions, and dare not talk about

them for fear of triggering them. Consequently, for parents and other caregivers, the child's OCD symptoms may not be obvious. However, other symptoms may emerge much more clearly, such as irritability, fatigue, depressive symptoms, and somatic symptoms. These factors may delay a correct diagnosis and appropriate treatment for the child or adolescent.

Diagnostic criteria

Diagnostic criteria are presented in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (10) and in the International Classification of Diseases 11th Revision (ICD-11) (18). The diagnostic criteria for OCD formulated in the previous edition of the DSM (DSM-IV-TR) (14) were used in the present studies, and are presented in Table 1.

In the DSM-5 (10), OCD is no longer classified as an anxiety disorder, and is instead placed in a new chapter called "Obsessive-Compulsive and Related Disorders" (OCRD). The new chapter also includes body dysmorphic disorder (BDD) and trichotillomania (hair-pulling disorder), as well as two new disorders, hoarding disorder and excoriation disorder (skin-picking disorder). However, the criteria for OCD in the DSM-5 have not been changed from the earlier version, except for a few minor modifications. In the DSM-IV-TR, the person's insight was specified categorically as "poor" or "good", while in the DSM-5 there is a variation in degrees of insight, including good insight, poor insight, and absent insight. Hoarding is classified as a separate diagnosis (10), though hoarding symptoms fully in consonance with DSM-IV criteria are present in pediatric OCD (19).

The change in classification of OCD in the DSM-5 from an anxiety disorder to a placement in the new OCRD chapter has been questioned by Storch et al. (20), who argue that such a change in classification lacks expert consensus and is insufficiently supported by the extant empirical data. Some of the OCRDs are not closely related to one another, for example trichotillomania and hoarding disorder.

Table 1. *Diagnostic criteria for Obsessive-Compulsive Disorder according to DSM-IV-TR.*

A. Either obsessions or compulsions:
Obsessions as defined by (1), (2), (3), and (4):

(1) recurrent and persisting thoughts, impulses or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress

(2) the thoughts, impulses, or images are not simply excessive worries about real-life problems

(3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action

(4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)

Compulsions as defined by (1) and (2):

(1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly

(2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorders; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder)

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition

Specify if:
With Poor Insight**:** if, for most of the time during the current episode the person does not recognize that the obsessions and compulsions are excessive or unreasonable

Prevalence and onset

The prevalence rates of OCD in children and adolescents have been estimated as varying between 0.25% and 4% (21-24). The study that estimated a prevalence rate as low as 0.25% reported data of a younger population aged 5-15 years, and indicated that the prevalence rates differ across age groups, with the prevalence rising with increasing age. A recent study in Greece estimated a prevalence rate of 1.4% in 2427 adolescents aged 16-18 years (25). Prevalence rates of childhood OCD are similar to those reported for adults (2-3%) (26). About 30-50% of adults with OCD developed their illness in childhood (27), showing the importance of the outcome of pediatric OCD. Population-based studies show a gender ratio close to 1:1 (28).

The mean age of onset for pediatric OCD is between 10 and 13 years of age (22, 28-30). However, participants and parents recalled onset of minor symptoms in early childhood (mean=7.0, SD=3.4). Moreover, an earlier age of onset of OCD symptoms fulfilling DSM-IV criteria was 9.2 ± 3.6 years, and the duration of illness was 4.5 ± 3.0 years in a more recent study (31).

Functional areas affected by OCD

Functional impairment

In pediatric OCD, symptoms usually interfere with the children's daily living, causing severe and enduring impairment of psychosocial functioning regard to social, academic, and family functioning. Piacentini and colleagues (32) showed that nearly 90 percent of 151 pediatric OCD patients had significant OCD-related impairment within at least one domain (i.e. social, academic, or home/family), and half of them reported significant dysfunction in all three domains. Valderhaug and Ivarsson (33) found similar functional impairment in a clinical Nordic sample. However, there were consistent gender and age differences, with girls having more severe functional impairment than boys, as well as adolescents having more severe functional impairment than children (33). Furthermore, avoidance behaviors may cause a great deal of suffering and impaired functioning (15, 16). OCD affects a young person's ability to learn in school, and a register-based study with sibling controls has shown that OCD is associated with decreases in educational attainment (4).

Family involvement

Families often accommodate to the OCD symptoms in many different ways. Parents and siblings facilitate avoidance or become involved in the child/adolescent's symptoms, for example, by checking that doors are locked or all electric appliances are turned off, or by repeatedly answering reassurance questions from their child/adolescent. Another way of involvement is that parents or siblings carry out everyday tasks according to the child's request, which are ruled by the obsessions (34-36). Family members often modify their social life based on the young person's OCD symptoms, for example by not leaving home, not inviting guests home, or changing their routines and activities. Pediatric OCD may also have economic consequences, as about half of the mothers and one third of the fathers in one study reported occupational impairment due to their child's OCD symptoms (37).

Quality of life

Quality of life (QoL) in pediatric OCD is notably lower than in a general group of children and adolescents (38, 39), although this improves for those who respond to CBT treatment (39, 40). In childhood, OCD is not only burdensome for sufferers but also for their families. A recent study of burden in caregivers to young people with OCD showed that the former's QoL was also decreased, being negatively affected by the latter's OCD (41).

Sleep-related problems

OCD symptoms may have a direct impact on sleep, as time-consuming rituals at bedtime lead to insomnia. Some children and adolescents do not want to sleep in their own bed due to obsessions that provoke anxiety. Moreover, sleep-related problems (SRPs) such as nightmares, insomnia, sleeping more or less than others, and increased fatigue are common. Approximately 70% of children and adolescents with OCD have one or more SRPs (42-45), which may be associated with greater dysfunction, impairment, and poorer response to CBT. SRPs adversely affect the child's well-being and ability to participate in CBT, although when CBT treatment for OCD is possible, most children's SRPs improved (45).

Comorbidity

The co-occurrence of other psychiatric disorders in pediatric OCD is common, and clinical studies suggest that 40-86% of children have such comorbidities (8, 30, 46-49). The most common co-morbidities are developmental disorders (i.e. ADHD, tic disorders, and autism spectrum disorders), anxiety disorders, and depression (47). Furthermore, some OCD-related disorders occur more frequently in young people with OCD, such as BDD (11.7%) and skin-picking (16.7%). Some of the comorbid diagnoses have symptoms that are similar to those of OCD, both in function and structure (50).

The presence of co-morbidity may aggravate and interfere with the OCD treatment (51). Clinical studies indicate that poorer treatment outcome is often associated with the occurrence of comorbid disorders (46, 52). Given the high rates of comorbidities, it is important to diagnose any comorbidities and be aware of the potential impact they may have on treatment response. In some complex cases, it may be necessary to treat and make adaptive interventions in the child's environment to stabilize the comorbid disorder before starting the OCD treatment (53, 54)

Etiology

OCD has a heterogeneous etiology, and the exact causes and underlying pathogenesis of the disorder are not well understood. It appears that the condition might be caused by a combination of genetic, neurological, behavioral, cognitive, and environmental factors. Several candidate gene association studies have been conducted but have provided only modest insights. Most candidate genes have been related to the serotonin, dopamine, and glutamate neurotransmitter systems (55), although no single gene has been identified as the cause of OCD (56). A review of twin-studies of children and adolescents suggest that OCD symptoms are inherited, with an influence of genetic factors of approximately 40 % (57).

It is conceptualized that in a small subset of pediatric OCD patients with an unusually abrupt and severe onset, OCD symptoms can be triggered by an autoimmune reaction, which causes an inflammation and dysfunction in the basal ganglia. This phenomenon is termed PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) when it is associated with streptococcal infection, and termed PANS (pediatric acute-onset neuropsychiatric syndrome) or CANS (childhood acute neuropsychiatric symptoms) when it is presumed to result from a variety of disease etiologies

(post infectious, autoimmune, and neuroinflammatory disorders to toxic, endocrine, or metabolic disorders). However, the etiology of these conditions (i.e. PANS/PANDAS/CANS) remains unknown, and need to be further investigated before their place in clinical work can be decided (58).

According to learning theory, people in the pathogenic pathway to OCD start to associate certain objects or situations with distress and then learn to avoid those things or to perform compulsions to reduce the distress. This reinforces both these behaviors and cognitions, and once the connection between an object and the feeling of distress becomes established, they become more engrained. Thus, people with OCD increasingly begin to avoid that object and the fear it generates, rather than confronting or tolerating the fear (59) However, little evidence indicates that OCD etiology is caused by such factors, although they seem to be vital with regard to the process leading to worsening of symptoms to a clinical level of severity.
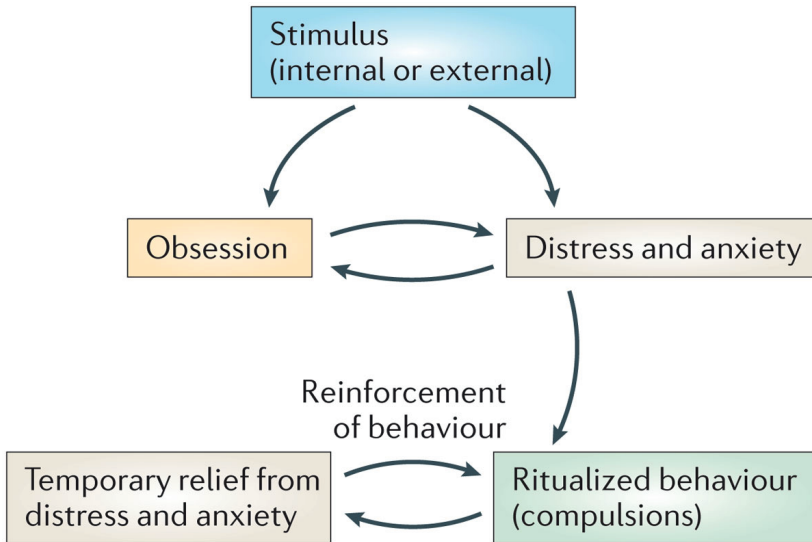
Figure 1. The theoretical basis of obsessive–compulsive behavior (57). Reprinted with permission from Nature Reviews.

Cognitive risk factors

The cognitive theory focuses on how people with OCD misinterpret their thoughts in a way that puts them at higher risk of OCD. Most people have unwelcome or intrusive thoughts at certain times, but for individuals with OCD, the importance of those thoughts are exaggerated. As long as the individual with OCD interprets these intrusive thoughts as disastrous and true, they will continue the avoidance and ritual behaviors (60). There is a discussion whether stress is an independent cause of pediatric OCD, or just a nonspecific factor that can have an adverse effect on the OCD symptoms. One study has demonstrated that there does not seem to be an association between pediatric OCD and serious negative childhood experiences or traumatic attachment experiences (61). Thus, it seems unlikely that such stressful event has a major influence.

Course

There is little known about the naturalistic course of untreated pediatric OCD. Moreover, there is deficient knowledge about the long-term outcome of evidence-based treatments. In the long run, OCD tends to have a fluctuating and often chronic course (40-60%) (62), and even studies of samples with appropriate treatment indicate a persistent risk for a chronic course and relapses of OCD leading to life-long suffering (26, 52, 62). For those with remaining OCD symptoms, the level of these symptoms seems to wax and wane over time between a subclinical and a clinical level (63).

Studies in adults indicate that OCD is a lifelong disorder, with high risk of relapse after treatment (64, 65). The longest follow-up study (over 40 years), consisted of a sample of 144 adults with OCD. Approximately half of the sample continued to have clinically significant symptoms decades later, and a third of them fulfilled the criteria for OCD (64). Studies of adults show that achievement of full remission during follow-up (5-15 years) after treatment, defined as an absence of OCD-symptoms, reduces the risk of relapse considerably (65, 66). Longer illness duration and more severe level of OCD symptoms have been found to increase the risk of a sustained chronic course in adults (67). Therefore, it is inferred to be of importance that treatment is given to prevent chronicity from occurring as well in pediatric OCD.

Individuals with childhood onset OCD appear to have a more promising prognosis than OCD with adult onset, as 44% of the children had remitted by early adulthood (68). On the other hand, a majority (50-80%) of the adults with

OCD had pediatric onset of symptoms (27). There are a number of studies that have examined the long-term outcomes of pediatric OCD. A meta-analysis based on 16 studies (with follow-up periods ranging from 1 to 15.6 years) showed persistence rates of 41% for full OCD and 60% for subclinical or full OCD. Longer duration of OCD at baseline was a predictor of persistent OCD at follow-up (52). The results were limited in that the included studies varied substantially by study types and lengths of treatment. Furthermore, only a few of the included studies had a prospective design and there was a lack of repeated assessments.

In a randomized controlled trial of sertraline with an open extension of the treatment, half of the participants were in remission one year after treatment (69). A seven-year follow-up of a randomized controlled trial evaluated the stability of family-based CBT delivered individually or in a group format, and found remission rates of 79% for individual CBT and 95% for group CBT after seven years (70). There are problematic weaknesses in the extant long-term follow-up studies, including a large variation in the time of the follow-up (1–11 years) (71, 72), small sample sizes (n<77) (31, 70, 73), and a large number of drop-outs from the follow-up (above 50%) (70-73). Moreover, in naturalistic follow-up studies, participants commonly receive mixed treatments (31, 71, 72). All these are serious confounders and consequently lead to difficulties in the interpretation of the results.

Evidence-based treatment of pediatric OCD

Up until the 1980s, OCD was considered to be an untreatable condition. However, since the first report of useful treatment (74), knowledge has increased markedly, and the opinion today is that there are effective evidence-based treatments available. Current international clinical guidelines (13, 75) recommend CBT with exposure and response prevention (E/RP) as the first line of treatment for children and adolescents with OCD. SSRIs are recommended as a second line of treatment if the young person refuses to or is unable to participate in CBT, or when the response to CBT treatment is insufficient (5). More detailed information about the treatment conditions is provided below, along with strategies employed when OCD persists even after combined treatment with CBT and SSRI.

CBT

A number of manuals for the treatment of pediatric OCD have been published, and several studies have investigated the efficacy of such treatment (8, 76, 77). Meta-analyses have shown moderate to large effect sizes for CBT, with moderate to high response rates to treatment (6, 7, 9, 78).

A major component of CBT are psychoeducation, cognitive strategies, E/RP, and relapse prevention. Psychoeducation includes information about OCD and CBT, and it is helpful to use metaphors and analogies to explain exposure, therapeutic relation, and so on. An example of an analogy is describing distress as a "false alarm" (79). Rosa-Alcázar and colleagues (80) have shown that a manual based on multicomponent treatment comprising E/RP, cognitive strategies, and relapse prevention is the most favorable in pediatric OCD. E/RP involves in vivo *exposure* to the obsession provoking stimulus (which could be a situation/object/person, e.g. touching something that triggers the intrusive obsession about dirt and germs), and *ritual prevention* (when the person refrains from performing the compulsions, e.g. not washing despite the obsessions). Exposure is performed gradually and is individually adapted to each patient. It is of importance that the clinician emphasizes that the overarching goal is to gain long-term symptom remission by strengthening inhibitory learning rather than achieving short-term anxiety reduction (81).

In a recent evidence-based update of psychosocial treatment, Freeman et al. (82) found that family support during CBT is well-established and is of great importance for enhancing the treatment outcome. Family support has been evaluated in a number of studies (83-86), yet the character and extent of family involvement differs between them. Thus, the amount of family involvement needed for optimal treatment outcome in pediatric OCD is still unclear (82). Furthermore, a number of modified ways to deliver CBT, including intensive and technology-based methods, have been evaluated, and the results are promising and seem to be effective (82, 87).

Pharmacotherapy

Some children and adolescents may not participate in CBT or do not receive enough benefits from the CBT treatment, and thus are in need of other interventions. SSRIs are recommended as the first-line drug treatment for pediatric OCD (6, 7, 13, 75), and have a substantial evidence base but with a moderate effect size (5). If OCD symptoms increase excessively during CBT, SSRIs may need to be given in addition to CBT to improve the child's ability

to cope with exposures during CBT (13). Switching to SSRIs may also be indicated if the young person is unable or refuses to participate in CBT (5, 9, 78, 88).

In Sweden and Denmark, sertraline and fluvoxamine are approved for pediatric OCD, whereas in Norway only sertraline is approved. Both response and adverse effects vary widely in young people treated with SSRIs for OCD, and so patients should be monitored weekly, then biweekly and then every month to every third month, to evaluate their response to the treatment and any adverse effects. Many of the latter may decrease over time, although some do not and may lead to fore-shortened treatment (69, 89).

Treatment at non-response to initial treatment

There are other "off-label" options when initial pharmacotherapy fails to bring symptom relief. Clomipramine, a tricyclic antidepressant, has evidence for its efficacy, but due to its adverse event profile should only be given in exceptional cases to young patients. Another option is augmenting SSRIs with second generation of antipsychotics (SGA), such as aripiprazole or risperidone, although the evidence for these treatment strategies is limited (90). In the recent Swedish national guidelines, augmentation with risperidone and aripiprazole to SSRIs has the lowest priority (10), meaning that it "may be offered as an exception" (91).

AIM

The overall aims of this thesis are to systematically and prospectively investigate the long-term course of pediatric OCD and the outcome following treatment, in accordance with the Clinical Guidelines for pediatric OCD. The more specific aims of the thesis are to:

- Present the clinical features and background factors of pediatric patients with OCD (Study I)

- Describe the naturalistic treatment of a cohort of pediatric patients with OCD (Study I)

- Examine how the children and adolescents psychosocial functioning is affected by OCD (Studies I and II)

- Investigate if there are changes in depressive symptoms over time (Study II)

- Examine the remission rates (defined as a total score of ≤ 10) and response rates (defined as ≤ 15) on the Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS) (Studies I, II, and III)

- Investigate whether response to the initial CBT in a stepped-care model is an important indicator of outcomes after three years (Study III)

METHOD

In this thesis, two different cohorts of children and adolescents with a diagnosis of OCD according to the DSM-IV-TR (American Psychiatric Association, 1994) were studied.

Studies I and II are consecutive projects that employ the same cohort and can be viewed as naturalistic, prospective studies of the long-term outcome in a clinical sample of pediatric OCD patients.

Study III, or *The Nordic Long-term OCD Treatment Study* (NordLOTS), was an effectiveness study of a stepped-care model with three treatment steps and a long-term follow-up. In this thesis, data are presented from the two- and three-year follow-ups. Data from the three treatment steps and one-year follow-up will not be reported in this thesis, but an overview of the study and a summary of step 1, step 2, and the one-year follow-up are described in paper III and the thesis. An overview of the participants in Studies I-III is provided in Table 2.

	Studies I and II	Study III
Participants (n)	109	269
Age (years)	5-17	7-17
Age, mean	12.9	12.8
Gender (female/male (%))	56/44	51/49
CY-BOCS baseline (SD)	23.0 (6.1)	24.6 (5.1)

Table 2. *Overview of participants in the two studied cohorts.*

Note: CY-BOCS= Children's Yale-Brown Obsessive-Compulsive Scale, SD= Standard Deviation

Measures

The following measures were used for diagnostic work-up, inclusion of patients, and the assessment of treatment outcome. All measures were available in the Swedish language. Measures used in Study III were also available in Danish and Norwegian.

The Kiddie Schedule for Affective Disorders and Schizophrenia – Present State and Lifetime Version (K-SADS–PL) (Studies I, II, and III)

The K-SADS-PL is a semi-structured diagnostic interview for psychiatric disorders based on the DSM-IV, and was used as a diagnostic assessment at baseline. Diagnoses can be classified as "certain," "in remission," "possible," or "not present."

In these studies, only OCD diagnoses and comorbidity classified as "certain" were included (92, 93). The K-SADS-PL has shown good interrater reliability (98%) (93) and an excellent interrater reliability in the Nordic countries (94). Furthermore, it has excellent convergent and divergent validity for child psychiatric disorders in a Nordic pediatric sample (92, 94, 95).

The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Studies I, II, and III)

The CY-BOCS is a widely used, clinician-administered, semi-structured interview that measures the current severity and presence of OCD symptoms. OCD severity is estimated separately for obsessions and compulsions based on: time consumed, level of distress, interference/impairment, resistance to OCD- symptoms, and degree of control over OCD-symptoms. It yields separate severity scores for obsessions and compulsions (0-20), adding up to a total score ranging from 0 to 40 (96). The CY-BOCS has shown good psychometric properties (53, 96, 97). In the NordLOTS sample, interrater agreement as measured by the intra-class correlation coefficients (ICCs) were 0.92 (95% CI= 0.78–0.97) for the total score (98).

The CY-BOCS is the primary outcome measure and also used to develop categorical treatment response, defined as a CY-BOCS total score of ≤15 and clinical remission as a CY-BOCS total score of ≤10 (76, 98).

The Clinical Global Impression-Severity (CGI-S) (Studies I and II)

The CGI-S is a seven-point brief clinician rating of psychopathology severity, with ratings ranging from 0 (no illness) to 6 (extremely severe illness) (99, 100). This clinician-rated scale has been extensively used in treatment studies of OCD in children and adolescents (69).

The Children's Global Assessment Scale (CGAS) (Studies I and II)

The CGAS is an overall rating of the overall global functional ability due to psychiatric disorders. It is rated by the clinician on a numeric scale from 1 to 100, with a higher score indicating better functional ability (101, 102). The scale has shown good inter-rater reliability with ICCs of 0.73 in clinical settings (103). Furthermore, both discriminant and concurrent validity has been demonstrated (102).

The Autism Spectrum Screening Questionnaire (ASSQ) (Studies I and II)

The ASSQ is a 27-item parent-rated form, here used as a dimensional measure of the presence of autism spectrum symptoms. The internal consistency of the ASSQ total score has shown to be $\alpha = 0.86$ (104).

The Child Behavior Checklist (CBCL) (Studies I and II)

The CBCL is a widely used 113-item parent-report assessing a wide range of behavioral and emotional problems in children. Moreover, a child's skills regarding activities, social relationships, and school performance are reported. Parents rate items on a three-point scale (0 = not true, 1 = somewhat or sometimes true, and 2 = very or often true), which has established psychometric properties across a variety of clinical and non-clinical populations REF. The CBCL has shown a mean test-retest reliability between 0.95-1.00 and internal consistency from $\alpha = 0.78$ to $\alpha = 0.97$ (105).

The Children's OCD Impact Scale (COIS) (Studies I and II)

The COIS is a 58-item self- and parent-report that measures the impact OCD has on the psychosocial functioning of children and adolescents at home and in social and academic situations (106). Every item is rated using a four-point Likert scale ranging from 0 to 3 (0 = not at all, 1 = only a little, 2 = pretty much, 3 = a lot). The children/adolescents and their parents both rate the difficulties experiences when performing their daily activities due to OCD. The parent and child versions of the COIS have demonstrated good internal consistency, as well as construct and convergent validity (32, 33).

The Child Depression Inventory (CDI) (Studies I and II)

The CDI is a self-reported 29-item measure that assesses the symptom severity of depression based on the DSM-IV in children and adolescents (107). The CDI are based on DSM-IV diagnostic criteria for major and minor depression. Every item is rated using a three-point Likert scale (0 = not present, 1 = present/mild, 2 = present/obvious) (107, 108).

Psychometric studies have demonstrated adequate internal consistency (Cronbach's a = 0.71 to 0.89), test–retest reliability (r=0.74 to 0.83), and convergent and divergent validity (107). A Swedish version was used in the studies that had shown adequate reliability in a normative study (109).

Wechsler Intelligence for Children (WISC III).

The WISC III is an intelligence test for children and adolescents aged 6–16 years. The scale is individually administrated and consists of different subtests divided into verbal scales and performance scales (110).

Study I. Treatment and 12-month outcome of children and adolescents with obsessive–compulsive disorder: A naturalistic study
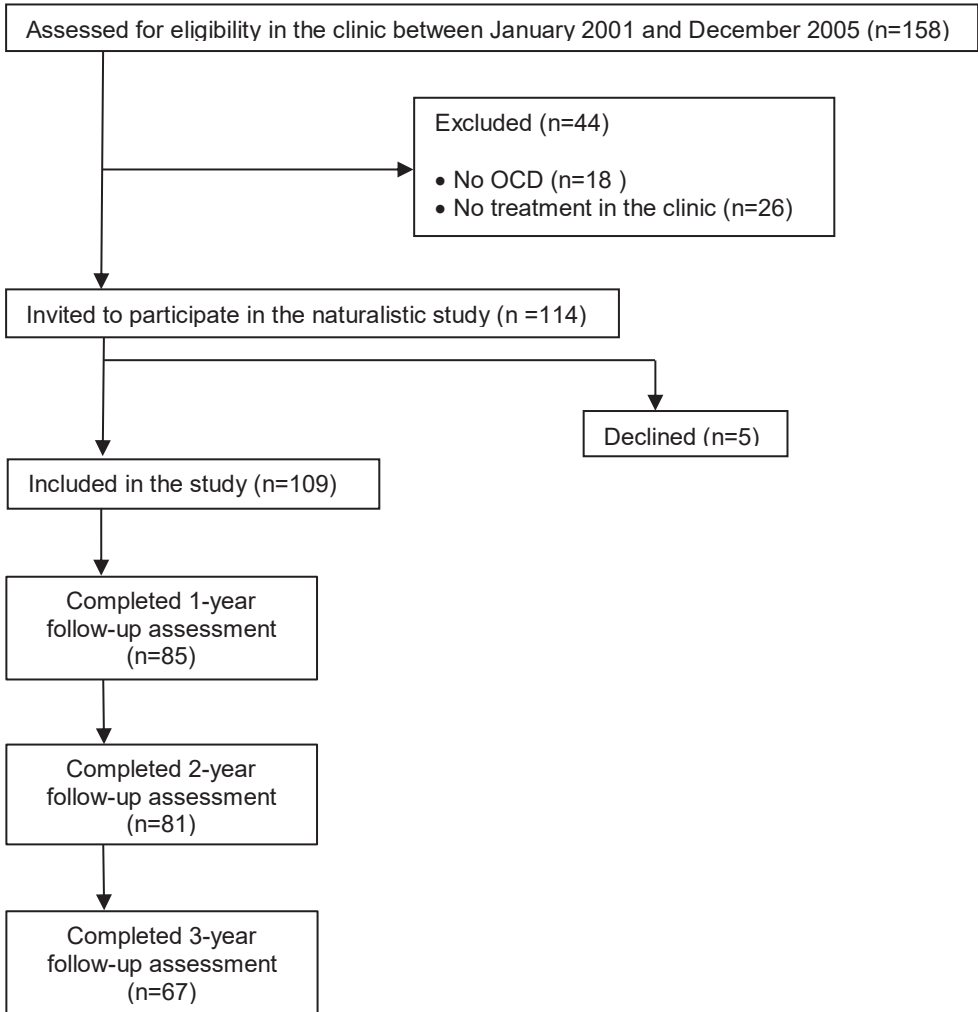
Participants

The study population of Study I, consists of 109 children and adolescents with a primary diagnosis of OCD, recruited at a specialized pediatric OCD clinic for out-patients in West Sweden. Participants were either referred from local Child and Adolescent Psychiatry units (50%) or self-referred by their parents (50%). All were invited to participate in the study if they had an initial assessment during the research period from January 2001 through December 2005 and fulfilled the inclusion criteria. No exclusion criterion was applied.

Inclusion criteria:

- Primary diagnosis of OCD according to criteria in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR);
- Was in need of and accepted treatment for OCD.

During the research period, 158 patients were assessed, 140 of whom had a primary diagnosis of OCD, whereof 114 accepted treatment. In total, 109 children and adolescents gave their consent to participate in this research. The mean age of the participants at baseline was 12.9 years (range 5–17 years). Gender distribution was slightly uneven, with 61 girls (56%) and 48 boys (44%). A flowchart of the studies I and II is presented in Figure 2.

Figure 2. Flowchart over the studies I and II.

Procedure

All children and adolescents (≥11 years old), together with their parents signed a written informed consent to participate in the study. Clinical comprehensive assessments were done at baseline prior to treatment. Diagnostic assessments for determining a primary diagnosis of OCD and any other psychiatric comorbidity were performed using KSADS-PL (93). The diagnostic evaluations were performed by an experienced child psychiatrist or a resident physician supervised by the experienced child psychiatrist. Severity and occurrence of OCD symptoms was assessed by a therapist in the team (including specialist nurses in psychiatric care, social worker, licensed psychotherapists, psychologists and child psychiatrist) using the CY-BOCS and CGI. Psychological assessments of the children and adolescents were conducted by a psychologist using the WISC III. Furthermore, baseline assessments included several self- and parent questionnaires, assessing assessment of OCD related functional impairment (COIS), symptoms of depression (CDI), autism (ASSQ) and general psychiatric symptoms (CBCL). These measures were given out by the therapist.

All 109 children and adolescents were invited to participate in the follow-up assessments. The outcome assessments followed a fixed windows scheme, six-month and one-year following the baseline assessments. Follow-up assessments was performed by an independent rater, a therapist at the clinic whom was not responsible for the patient's treatment. The CY-BOCS, COIS and CGI was used as outcome measures at follow-up assessments.

Treatment

The treatment was based on the current clinical guidelines for treatment of pediatric OCD and individually adapted for each patient (111). Appropriate adaption of the treatment was conducted, based on the child's age, developmental maturity and the presence of any psychiatric comorbidity. The first choice of treatment was CBT with E/RP, which except for exposures with response prevention included psychoeducation and relapse prevention as well. Each patient had two therapists in charge, who alternated to participate in the CBT sessions. In most cases the CBT were administrated as home-based treatment (72.5%), although some were offered at the clinic (27.5%). Pharmacotherapy with SSRI was used as single treatment when the participant rejected to or cannot participate in the CBT treatment. Moreover, when the CBT response was insufficient, SSRI was used as combined treatment to

enhance CBT. In case of insufficient effect following treatment with an SSRI plus CBT, augmentation with an SGA was used.

Statistical analysis

The total sample of 109 was included in analyses. Initial analyses compared the baseline demographic and clinical characteristics between the two genders. Pearson's χ2 test was used for the analysis of categorical variables and one-way analysis of variance (ANOVA) for continuous measures. When comparing between participants with missing data and those with no missing data, we identified no significant differences. Therefore, in subsequent analyses, data were assumed to be missing at random.

The primary outcome measure was a change in the CY-BOCS total score, and as a secondary outcome measure we used the change in total score of COIS-C/P. The scalar total scores of treatment outcome measures were analyzed using linear mixed-effects models (LMEs). The tests were two-tailed, and a *p*-value of less than .05 was considered to indicate statistical significance. No multiple imputations for missing values were made prior to the LME analysis, as simulation studies have shown that LME models deal with missing data in an appropriate way (Peters et al., 2012). However, multiple imputation was used to replace missing data before generating and analyzing categorical outcome data. A total of 10 data sets were generated to make the estimates. The outcomes were combined using Rubin's rules (112).

IBM SPSS 21 was used to perform the statistical analyses (113).

Ethics

Ethical approval for was granted by the internal review board (IRB) in Gothenburg, Dnr Ö 373-02.

Study II. A solid majority remit following evidence-based OCD treatments: a 3-year naturalistic outcome study in pediatric OCD

Participants

In total, 109 children and adolescents with a primary diagnosis of OCD were recruited in Gothenburg, Sweden. The participants were the same as those who participated in Study I. A flowchart of the study is presented in Figure 2.

Procedure and Treatment

If participants were in need of further treatment during the period from the one-year follow-up to the three-year follow-up, they were offered additional periods of treatment based on the current clinical guidelines for treatment of pediatric OCD, as described above in Study I. The outcome assessments following the fixed window scheme were conducted two and three years following the baseline assessments. Follow-up assessments were performed by an independent rater, who administered both interviews and questionnaires.

Statistical analysis

The primary outcome measure was a change in the CY-BOCS total score, and as a secondary outcome measure we used the change in the total score of COIS-C/P and CDI. The scalar total scores of treatment outcome measures were analyzed in the same way as described in Study I. Multiple imputation was used to replace missing data before analyzing categorical outcome data. Before multiple imputation, missing data from the two- and three-year follow-ups were analyzed for randomness using ANOVA. Comparisons were made based on OCD-severity at baseline, age, gender, age of OCD onset, and OCD severity at follow-up timepoints (six months, one-year, and two-years) between participants with missing data and those with non-missing data. None of these comparisons showed any significant differences, thus data were assumed to be missing at random. The prerequisites for using multiple imputation were consequently met. A total of 20 data sets were generated to

make the estimates. The outcomes were combined using Rubin's rules (112), and statistical analyses were performed in IBM SPSS 22 (114).

Ethics

Ethical approval for was granted by the internal review board (IRB) in Gothenburg, Dnr Ö 373-02.

Study III Treatment Gains are Sustainable in Pediatric Obsessive-Compulsive Disorder: Three-Year Follow-Up from the NordLOTS

The Nordic Long-term OCD Treatment Study (NordLOTS) is a collaboration between Swedish, Norwegian, and Danish researchers and clinicians. It is a multicenter study, in which a total of 20 clinics cooperated, including both general community CAP units and specialized OCD-clinics. There were five main study sites that cooperated in the study: Gothenburg and Stockholm in Sweden, Aarhus in Denmark, and Oslo and Trondheim in Norway

Participants

The study population of Study III comprised of 269 children and adolescents, all of whom had been included in the NordLOTS between September 2008 and June 2012. The last follow-up data were collected in December 2015.

Inclusion criteria:

- Primary diagnosis of OCD according to criteria in the DSM-IV-TR
- CY-BOCS total severity score of ≥16
- Age range of 7-17 years
- Patients with ADHD were included if they were stabilized on medication for at least three months

Exclusion criteria:

- Comorbid disorders with higher treatment priority than OCD (i.e. psychosis and depression with suicidality)
- Mental retardation or autism spectrum disorder (although PDD-NOS was allowed if the CGI score for this was ≤ 3)
- Treatment for OCD with either CBT or SSRI within the last six months prior to inclusion
- Parent or child could not understand the language in the country where the study was carried out

The most common exclusion criteria were: did not meet diagnostic criteria for OCD, or did not have sufficient OCD severity (i.e. CY-BOCS ≤15). The included participants had an average age of 12.8 years (ranging from 7 to 17 years; see (8). A flow diagram of the NordLOTS is presented in Figure 3.
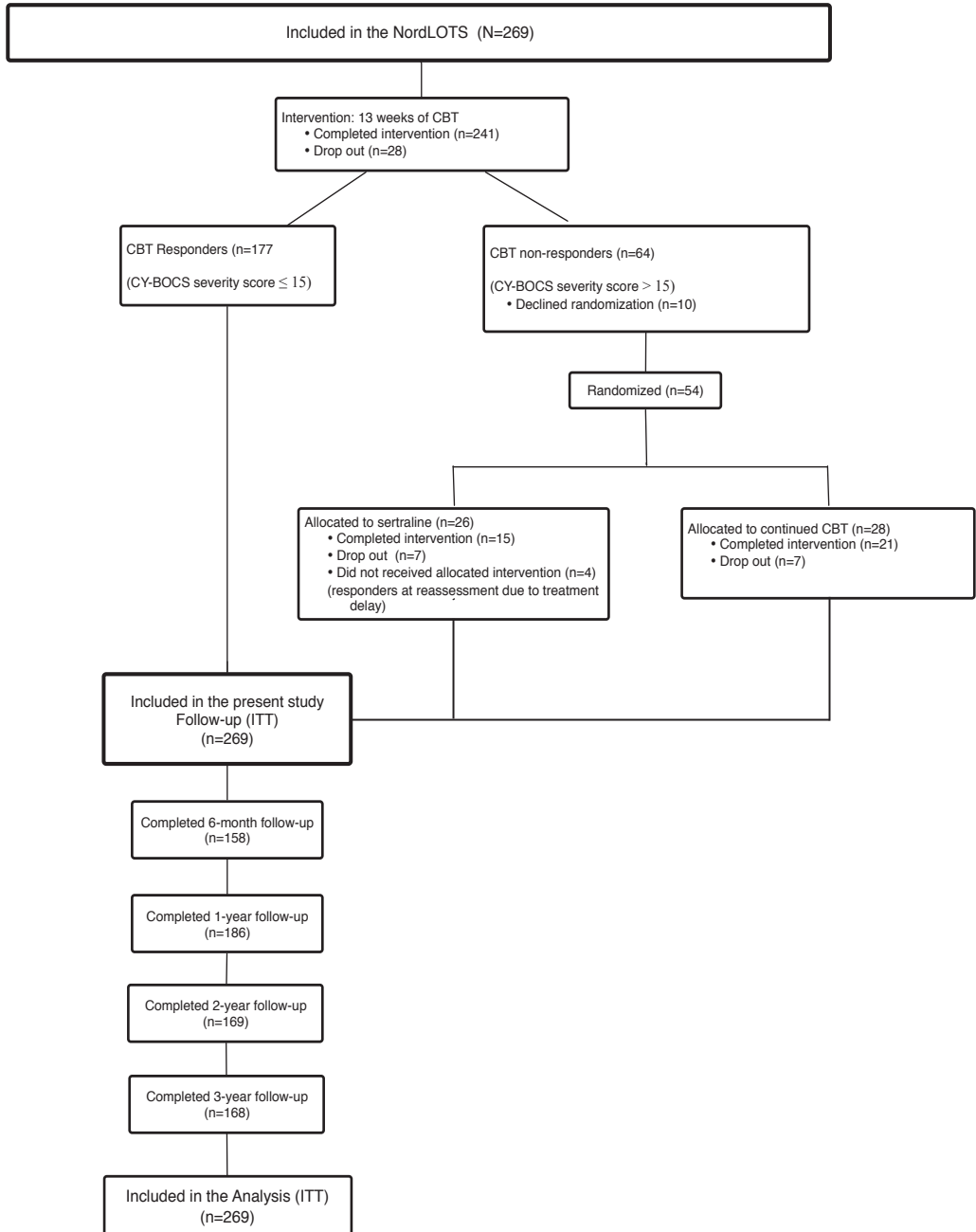
Figure 3. *Flow diagram of The Nordic Long-term OCD Treatment Study (NordLOTS)*

Procedures

Extensive assessments were conducted at baseline prior to treatment, and all young people and their parents participated in the assessments. To make the OCD diagnosis and possible comorbid psychiatric diagnoses, a semi-structured diagnostic interview was conducted using the KSADS-PL. The CY-BOCS was used to measure the severity of OCD symptoms.

All 269 study participants were invited to take part in the follow-up assessments. The outcome assessments followed a fixed window follow-up scheme of two- and three-years post-treatment of the first step CBT. The CY-BOCS was used as an outcome measure at the follow-up assessments. The assessments were performed by an independent rater, who was a therapist at the clinic but not responsible for the patients' treatment.

Treatment

The first-step of CBT was based on a Nordic manual for pediatric OCD (79). A former manual by March and Mulle (115) was translated into Nordic languages and adapted to Nordic conditions. Furthermore, the manual was extended with additional family interventions, from a customized version of a manual by Piacentini. The main parts of the CBT included psychoeducation about OCD and CBT, goal formulation, exposure and response prevention, and relapse prevention. All included participants were offered 14 weekly sessions, with a minimum requirement of at least seven sessions. An overview of the CBT treatment sessions is presented in Appendix 1.

The CBT sessions were audio taped and treatment fidelity was evaluated regard to three categories; manual adherence; relationship competence, and an aggregated evaluation of the session. The treatment fidelity was found to be very good (8, 98).

Non-responders to the first-step CBT (CY-BOCS total score ≥16 post treatment) were randomly assigned to 16-week extended treatment of either continued CBT (10 sessions using the same CBT manual) or pharmacotherapy with sertraline (6 sessions), according to a pharmacotherapy manual based on the manual used in the POTS study (76). An overview of the pharmacotherapy sessions is presented in Appendix 2.

At non-response to the second-step CBT, participants were offered pharmacotherapy with CBT and SSRI. A third step of the treatment for those

with non-response to the second step of treatment was based on pharmacotherapy augmenting aripiprazole (an SGA) to sertraline. Only three participants were offered and accepted this treatment. Thus, this extension has not been analyzed nor published.
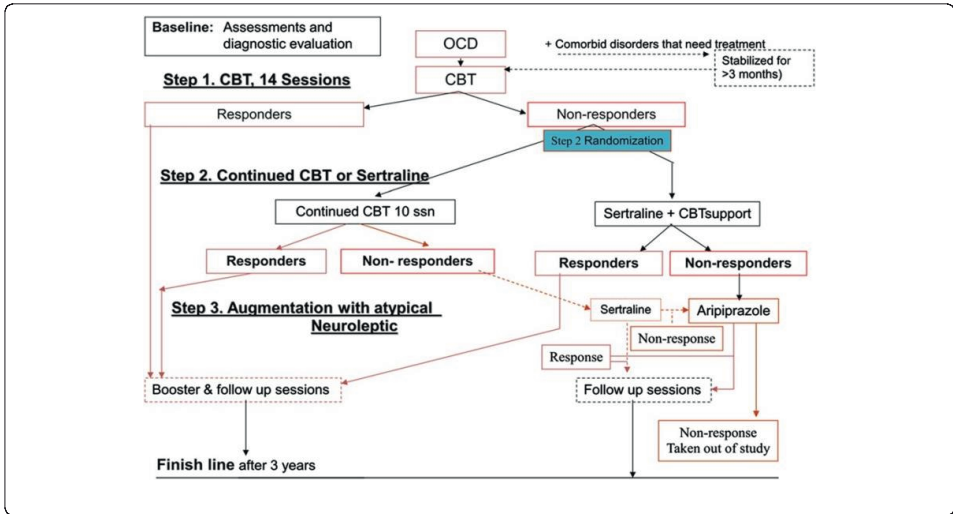

Figure 4. *Overview of the NordLOTS study flow.*

Statistical analysis

The total sample of 269 participants was included in the analyses according to intent-to-treat (ITT) principles. Comparisons of the baseline demographic and clinical characteristics between two groups were performed: those who responded (n=241) and those who did not respond (n=64) to initial CBT treatment. For analyses of categorical variables we used $\chi 2$ tests, and ANOVA was used to analyze the continuous measures.

There was some attrition to the follow-up assessments, with 37.2% (n=100) at two-years follow-up and 37.5% (n=101) at three-years follow-up. None of the comparisons showed any significant differences between participants with missing data and those with non-missing data, with regard to the baseline CY-BOCS total score, age of onset, gender, age, socioeconomic status, and estimated treatment outcomes. Consequently, we assume that data were missing at random in subsequent analyses, and the requirements for using multiple imputations are consequently met.

The statistical method we applied for the primary outcome of the CY-BOCS as a continuous measure was piecewise regression (116, 117). This method was used to investigate the reduction of the primary outcome measure of the CY-BOCS total score during first-step CBT compared with the three-year follow-up period. The model estimates whether there is a change in outcome trajectory after a known occurrence, which in this study is posttreatment of the first-step CBT. The LME model was conducted and included two random effects (intercept and weeks since baseline) and two fixed effects (group of the first-step CBT response and interaction of time and group of response). Tests were two-tailed, and a *p*-value of less than .05 was considered to indicate statistical significance.

Missing data were handled with multiple imputations with a sequential regression multivariate imputation algorithm (112), before analyzing the categorical outcome data. The imputation model included all baseline demographics, outcome measures, treatment indicators, stratification variables (sex and tic disorder), time in weeks, and all feasible predictors and moderators.

In accordance with the guidelines, a total of 20 data sets were generated to make the estimates, confidence intervals, and *p*-values reliable (118, 119). The outcomes were combined using Rubin's rules (112). Additional analyses of categorical outcomes were performed of those participating in the three-year follow-up assessment (n=168) as well.

Statistical analyses were performed in IBM SPSS 23 (120), except for the LME and multiple imputation of dichotomous outcome values that were conducted in SAS Statistical Software, Version 9.4 (121).

Ethics

Ethical approval was granted by the IRB in Gothenburg, Dnr 487-07, and by respective local IRBs in and Denmark Norway.

Trail registration

Clinical trial registration was conducted at www.controlled-trials.com; ISRCTN66385119 Nordic Long-term Obsessive-Compulsive Disorder (OCD) Treatment Study.

RESULTS

Study I

Initial analyses of the participants in study I (and II), compared the baseline demographics and clinical characteristics between gender. These results are presented in Table 3.

Variable	Total	Girls	Boys	*p*-value
N	109	61	48	-
Age, year, mean (SD)	12.9 (2.6)	13.3 (2.4)	12.2 (2.6)	.046[a]
Age of OCD onset, year (SD)	9.8 (2.9)	9.6 (2.9)	11.2 (3.0	.341[a]
CY-BOCS, mean (SD)				
Total baseline	23.0 (6.1)	23.7 (5.6)	22.2 (6,6)	ns.[b]
Obsessions baseline	11.6 (3,7)	12.0 (3.1)	11.1 (4.4)	ns.[b]
Compulsions baseline	11.4 (3.3)	11.7 (3.1)	11.1 (3.5)	ns.[b]
CGI	4.2 (1.1)	4.2 (1.0)	4.2 (1.2)	ns.[b]
COIS child report	41.9 (30.3)	46.4 (31.0)	36.1 (28.7)	ns.[b]
COIS parent report	55.0 (32.5)	57.3(31.8)	51.9(33.5)	ns.[b]
CBCL total	43.0 (20.3)	42.8 (19.4)	43.2(21.7)	ns. [b]
Internalizing	14.7 (7.8)	15.4 (7.7)	13.8 (8.0)	ns.[b]
Externalizing	10.2 (8.5)	9.8 (7.4)	10.7 (9.8)	ns.[b]
ASSQ	7.5 (5.9)	6.9 (5.4)	8.3 (6.5)	ns.[b]
CDI	11.8 (9.0)	12.3 (9.0)	11.0 (8.9)	ns.[b]
CGAS	50.8 (10.3)	50.2 (8.8)	51.6 (12.0)	ns.[b]
WISC	100.6 (13.1)	100.2 (1.8)	101.2 (12.9)	ns.[b]

Note: Significant differences (p < .05) are indicated with boldface.
[a] One-way Analysis of variance of groups [b] Pearson Chi-square of groups

Table 3. Pretreatment Demographics and Clinical Descriptive Statistics of Pretreatment Demographics and Clinical Descriptive Statistics of participants of study I and II.

The majority of the participants (95.4%) received CBT up to the one-year follow-up assessment, with an average of 14 sessions (range 1-42, Mdn 12). The CBT treatment was completed for most participants (55%) at that time. Five (4.6 %) participants were treated with SSRI only, either by their own choice or if they were unable to participate in the CBT. In total 54.1% of the participants were medicated with SSRIs at some stage prior to the one-year follow-up. However, there was substantial variation, as some were on medication when they came to the first assessments, some started during the process, and others terminated their medication usage during the first year. The most common drug was Sertraline, with a median daily dose of 100 mg. A minority of the participants (n=9, 8.3 %) received augmentation with SGA alongside their SSRI. Eight patients were as well treated as inpatients due to inadequate treatment response.

The majority of the participants were assessed at the six-month (76.1%) and one-year (78%) follow-up. Analysis with LME of the CY-BOCS total score showed a significant reduction of OCD-symptoms across time (F [2, 86.169]=80.118, $p < .001$). The estimated CY-BOCS total score at baseline was 23.0 (95% CI 21.8–24.2) with a decrease from baseline to the one-year follow-up by an estimated average of 11.8 points. Figure 5 illustrates the estimated CY-BOCS severity scores over time for Study I and II.

At the one-year follow-up, two out of three patients (67%) were responders (CY-BOCS ≤15) and almost half (47.7%) were in remission (CY-BOCS ≤10). Out of these, one-third (16.7% of the full sample) had a CY-BOCS total score of 0, meaning that they had no OCD symptoms. However, about one third (33%) of the total participants had continued moderate to severe OCD symptoms at the one-year follow-up, out of which 86% had continued therapy with CBT and/or SSRI at the one-year follow-up. Severity of OCD symptoms from baseline to the three-year follow-up (study I and II) are illustrated in Figure 6.

Participants had improved their psychosocial functioning between the baseline and the one-year follow-up, according to both the self- and parent-ratings. Analyses with LME of secondary outcome measures with regard to impairment (COIS-C and COIS-P) showed significant reduction over time (F [2, 65.739] 18.014, p < .001 and [F 2, 77.433] 23.681, p < .001, respectively). Psychosocial functioning, the estimated COIS-C and COIS-P total scores from baseline to three-year follow-up (Study I and II) are illustrated in Figure 7.

Study II

By the three-year follow-up, the participants had received 22 (SD = 19.1, Mdn =16) CBT sessions on average (distributed over 1-3 periods of treatment), including treatment during the first year. However, the majority (65%) of participants had only one period of CBT treatment with an average of 16 sessions (SD = 15.9). Up until the two-year follow-up assessment, most participants (66%) had completed the CBT treatment, and at the three-year follow-up, only 10% of the participants were still receiving CBT. Moreover, at the three-year follow-up almost a third (32%) were on continuing pharmacotherapeutic treatment with an SSRI. One participant initiated combined treatment with SSRI and SGA and three received inpatient care during the second and third year after baseline.

During the study, all participants were invited to each follow-up assessment. Three out of four participated (74.3%) in the two-year follow-up assessment, while 61.5% participated in the three-year follow-up.

Analyses with the LME model of the longitudinal CY-BOCS total score revealed a significant reduction in OCD symptoms with a significant effect of time [$F(4, 329.743) = 101.439$, $p < 0.001$]. The estimated mean CY-BOCS total score at baseline was 23 (95% CI 21.8–24.2) and had decreased to 6.9 (95% 5.2–8.7) at the three-year follow-up. Almost four out of five (78%) of the participants had at least a 35% reduction of the CY-BOCS total score at the three-year follow-up. The mean CY-BOCS total score reduction from baseline to the three-year follow-up was 64% (SD = 32.9). Estimated CY-BOCS total scores are illustrated in Figure 5.
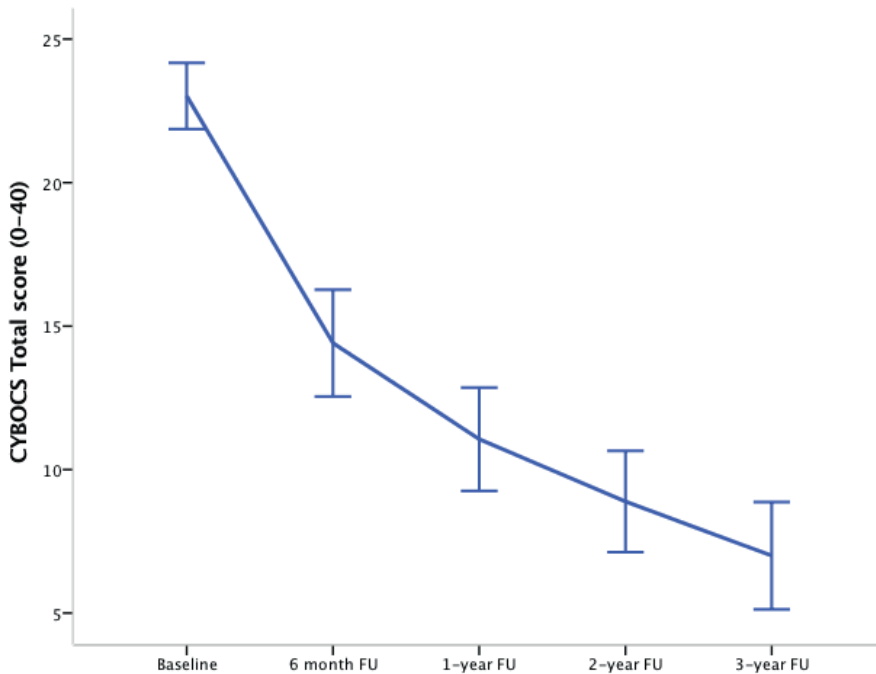
Figure 5. *Estimated Children`s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) total scores, from baseline to three-year follow-up in children and adolescents (ITT, n=109) in study I and II, with 95% CI.*

Note: p < 0.001

At the two-year follow-up, 56.9 % of the participants were in remission (CY-BOCS total score $\leq$ 10), and the remission rate increased to 66.1% until the three-year follow-up. Response to treatment based on a CY-BOCS total score of $\leq$15 at the two-year follow-up was 69,7%, which increased to 85.3% up until the three-year follow-up. There was no significant difference ($p = .50$) in remission status between those with mild (CY-BOCS $\leq$15) and those with moderate to severe OCD (CY-BOCS 16-40) at baseline. Severity of OCD symptoms from baseline to the three-year follow-up (study I and II) are illustrated in Figure 6.
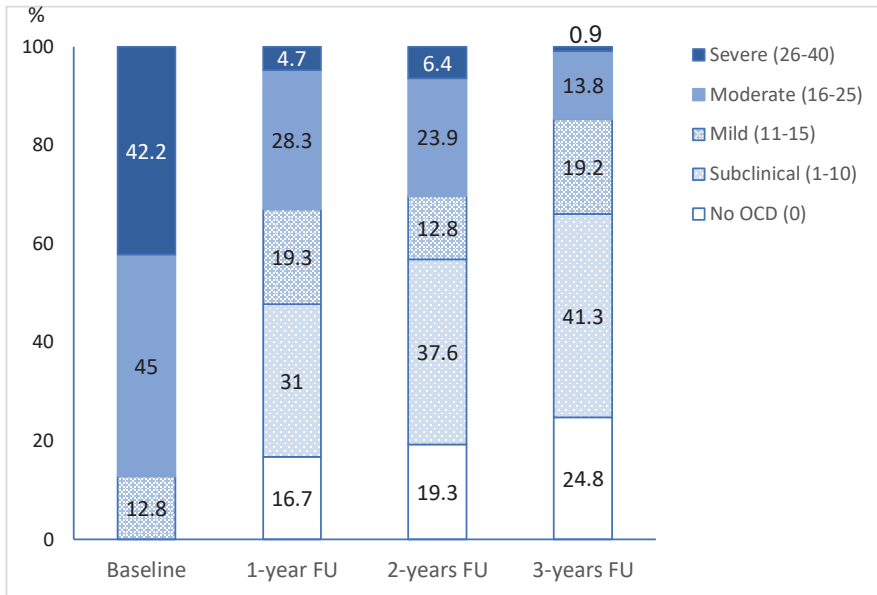
Figure 6. *Severity of OCD symptoms at baseline and at one-year, two-year and three-year follow-up (Study I and II).*

The OCD impact on the participants' psychosocial functioning was measured by the COIS-C/P, and was found to be reduced during the follow-up. Longitudinal analyses with LME showed significant reduction with an effect of time $[F(4, 67.586) = 19.419, p < 0.001]$ on the COIS-C total score and with an effect of time $[F(4, 81.447) = 26.382, p < 0.001]$ for the COIS-P total score. The estimated mean of the COIS-C total score at baseline was 41.3 (95% CI 35.0–47.6), with a reduced score of 13.2 (95% CI 9.5–16.9) and 14.4 (95% CI 9.4–19.5) at the two- and three-year follow-ups, respectively. The mean COIS-P total score at baseline was estimated to be 54.4 points (95% CI 47.7–60.5) and was reduced to 20.7 (95% CI 15.9–25.6) and 16.6 (95% CI 11.4–21.8) at the two- and three-year follow-ups, respectively. Pairwise comparisons showed significant differences across time from baseline to the two- and three-year follow-ups ($p < .001$) for self-ratings and parental ratings. However, there was no significant reduction of the impairment between the two- and three-year follow-ups. Psychosocial functioning, the estimated COIS-C and COIS-P total scores from baseline to three-year follow-up (Study I and II) are illustrated in Figure 7.
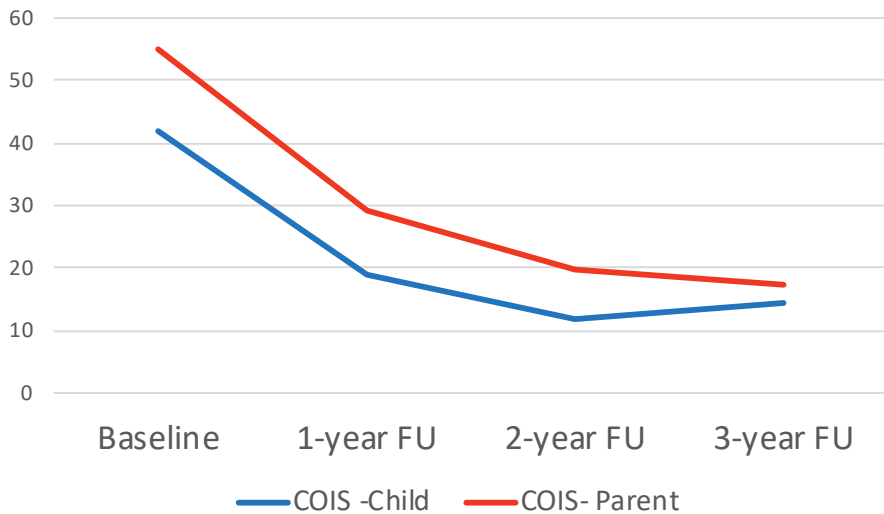
Figure 7. *Psychosocial functioning, estimated Children's OCD Impact Scale (COIS-C)/ (COIS-P) total scores from baseline to three-year follow-up (Study I and II).*

Longitudinal analysis with LME of self-reported depressive symptoms were measured with CDI, and revealed a significant effect of time [$F_{(4, 57.160)}$ = 6.571, $p < 0.001$]. The estimated mean total score of CDI at baseline was 11.8 (95% CI 9.9–13.7) with a reduced score of 7.7 (95% CI 6.1–9.2) at the two-year follow-up, and a similar reduced score of 7.6 (95% CI 5.8–9.3) at the three-year follow-up.

Study III

Most participants (89.6%), completed the first step of treatment with manualized CBT, with 73.2% responding well to this first stage of CBT, including two additional responders not reported in original outcome paper, due to that data for these two patients were initially missing (8, 122). Non-responders were randomly assigned to a 16-week second treatment stage, with some offered continued CBT (10 sessions) and others pharmacotherapy with sertraline. Approximately half of them (50% in the CBT group and 45.4% in

the sertraline group) responded well to the second step of treatment (123). The one-year follow-up of those who responded to the first step of CBT showed that the improvement that had been achieved was maintained, and that they continued to improve further during the first year after treatment (122).

All 269 participants were invited to each follow-up assessment, with the majority participating in the two-year (62.8%) and three-year (62.5%) assessments. Pre-treatment demographics and clinical descriptions of the sample are presented in Table 4.

Table 4. Pre-treatment Demographics and Clinical Descriptive Statistics (Study III).

Variable	Total	Responders to first-step CBT	Non-responders to first-step CBT	*p*-value
n	269	177	64	-
Age, year, mean (SD)	12.8 (2.7)	12.6 (2.8)	13.2 (2.6)	.077[a]
Age of OCD onset, year (SD)	11.65 (2.99)	11.4 (3.05)	11.9 (2.92)	.308[a]
Female participants	138 (51.3)	84 (47.5)	37 (57.8)	.156[b]
Male participants	131 (48.7)	93 (52.5)	27 (42.2)	
Family status, n (%)				
Parents living together	173 (64.3)	114 (64.4)	44 (68.8)	.440[b]
Divorced	91 (33.8)	59 (33.3)	20 (31.3)	
Other	4 (1.5)	4 (2.3)	0 (0.0)	
CY-BOCS, mean (SD)				
Total baseline	24.6 (5.1)	23.8 (5.0)	26.4 (5.3)	**.001**[a]
Obsessions baseline	12.3 (2.8)	11.9 (2.7)	13.1 (2.9)	**.005**[a]
Compulsions baseline	12.3 (2.7)	11.9 (2.6)	13.3 (2.7)	**.001**[a]
Baseline comorbid disorders (K-SADS PL), n (%)				
Any anxiety disorders	52 (19.3)	31 (17.5)	15 (23.4)	.311[b]
Any depressive disorder	10 (3.7)	4 (2.3)	4 (6.3)	.129[b]
ADHD	24 (8.9)	17 (9.6)	7 (10.9)	.836[b]
ODD/CD	10 (3.7)	8 (4.5)	1 (1.6)	.282[b]
Tic	49 (18.2)	32 (18.1)	13 (20.3)	.708[b]
Number of co-occurring diagnoses, n (%)				
None	163 (62.8)	110 (64.0)	36 (56.3)	.130[b]
1	62 (23.0)	39 (22.7)	16 (25.0)	
2	25 (9.3)	14 (8.1)	11 (1.6)	
≥3	13 (4.9)	9 (5.2)	1 (1.6)	

Note: Significant differences (p < .05) are indicated with boldface. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; CY-BOCS =Children's Yale-Brown Obsessive-Compulsive Scale; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version; OCD =obsessive compulsive disorder; ODD = oppositional defiant disorder.
[a] One-way Analysis of variance of groups of response and non-response to initial CBT differences.
[b] Pearson Chi-square of groups of response and non-response to initial CBT differences.

The longitudinal trajectories of OCD severity by CY-BOCS total score were investigated using LME models. Analyses of the ITT sample (n=269) showed a significant reduction of the estimated mean CY-BOCS total score from baseline 24.7 to the three-year follow-up 5.0 (p=.001). Analyses of those (n=177) who responded (CY-BOCS ≤15) versus those (n=64) who did not respond (CY-BOCS ≥16) to first-step CBT as a grouping variable, revealed a significant (p<.001) difference between the groups at the two-year assessment, although no significant (p=.998) difference was found at the three-year follow-up. Furthermore, no significant difference was found (p=.169) between the extended treatment conditions of either CBT or pharmacotherapy with sertraline at the three-year follow-up.

Treatment following the one-year follow-up was not directed by the study design, but any type of treatment that the participants received in between follow-ups was recorded. However, the study's standard operating procedure prescribed how CBT booster sessions should be offered during the follow-up, and how extra treatment was to be offered at relapse. So even after the one-year follow-up, any OCD-treatment was performed in accordance with the study manuals for CBT and pharmacotherapy, as far as possible.

During the follow-up period (i.e. second and third years after first-step CBT), 6% (n=16) of the patients relapsed (CY-BOCS ≥16) and received supplementary treatment. Five of the them were given additional CBT (6-17 sessions) and the other 11 received pharmacotherapy with sertraline. At the three-year follow-up, only 4.8% (n=13) of all participants had continuous treatment with sertraline. One to five booster sessions of CBT were given to 11.9% (n=32) of the participants, due to an increase of OCD-symptoms, but these patients did not fulfill the criteria for a relapse.

Moreover, analysis showed a significant difference (p<.001) between those receiving further treatment (i.e., from initial CBT posttreatment – three-year follow-up) and those receiving no further treatment for OCD during the second and third years of the follow-up assessment period (i.e. following step 2 of the treatment). The estimated CY-BOCS mean score for those with no further treatment was 3.8 at the three-year follow-up, and for those with further OCD treatment the estimated CY-BOCS mean score was 7.8.

Throughout the follow-up period, 11.2% (n=30) of the patients received additional treatment for psychiatric disorders other than OCD, such as medication for ADD/ADHD (6.7%, n=18), and CBT or medication for depression, oppositional defiant disorder, sleep disturbance, anxiety disorders, or trauma (4.5%, n=12).

The estimated CY-BOCS severity scores at different assessment points (baseline, posttreatment of first-step CBT, and all time points during follow-up) for the total sample and divided in groups of responders/non-responders to first-step CBT are presented in Table 5. Figure 8, illustrates the estimated CY-BOCS severity scores by response status at posttreatment following first-step CBT.

Table 5. Outcomes Across Follow-up Assessments Points.

	Mean	SE	95% CI	
			Lower Bound	Upper Bound
Total (n=269)				
Baseline	24.7	0.32	24.1	25.3
Post CBT	10.9	0.44	10.0	11.7
1-year FU	8.2	0.37	7.5	8.9
2-year FU	6.6	0.36	5.9	7.3
3-year FU	5.0	0.46	4.1	5.9
Responders to first-step CBT (n=177)				
Baseline	23.8	0.39	23.1	24.6
Post CBT	7.9	0.37	7.2	8.6
1-year FU	6.1	0.34	5.5	6.8
2-year FU	5.6	0.39	4.8	6.4
3-year FU	5.0	0.52	4.0	6.1
Non-responders to first-step CBT (n=64)				
Baseline	26.6	0.74	25.2	28.1
Post CBT	19.4	0.75	17.9	20.9
1-year FU	14.2	0.70	12.9	15.6
2-year FU	9.6	0.85	8.0	11.3
3-year FU	5.0	1.15	2.8	7.3

Note: Estimations of CY-BOCS severity score based on linear mixed-effects model. Post first-step CBT was measured at week 13. CBT= Cognitive behavior therapy; CY-BOCS =Children's Yale-Brown Obsessive-Compulsive FU= Follow-up; SE= standard error.
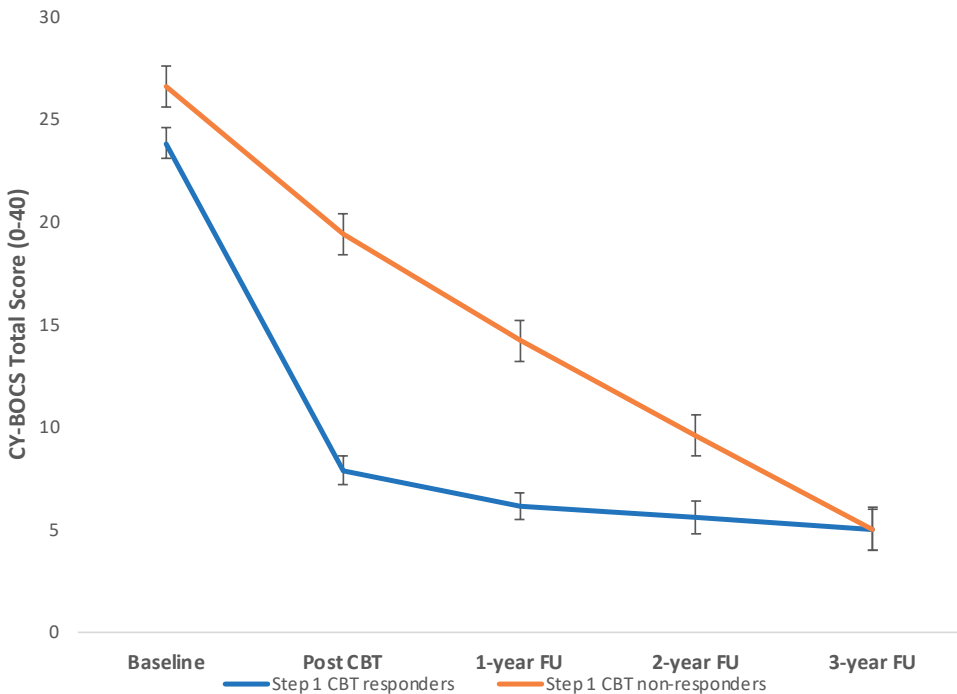
Figure 8. *Long-term outcome over three years. Estimated Children`s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) total scores in children and adolescents (ITT, n=269), by groups of responders/non-responders to the first-step CBT with a 95% CI.*

The estimated score of the overall impairment measured by CGAS at baseline was 54.0, with an increase during first-step CBT to 71.3. Analysis of the overall impairment found a significant (p<.001) increase from the posttreatment of first-step CBT to the three-year follow-up to an estimated score of 77.6, and with an average increase in functioning of 6.3 points.

Moreover, 90% of the participants were rated as responders and 73% were in clinical remission at the three-year follow-up. Analyses of treatment response (CY-BOCS ≤15) and clinical remission (CY-BOCS ≤10) at this stage of the ITT sample (n=269) were based on imputed data. Additional analyses of those participating in the three-year follow-up (n=168) showed an outcome slightly

better than that for the ITT sample, in that 94% (n=157) of the patients were responders to treatment and the rate of clinical remission was 81% (n=136) at the three-year follow-up. Figure 9. Illustrates remission rates across the follow-up period.
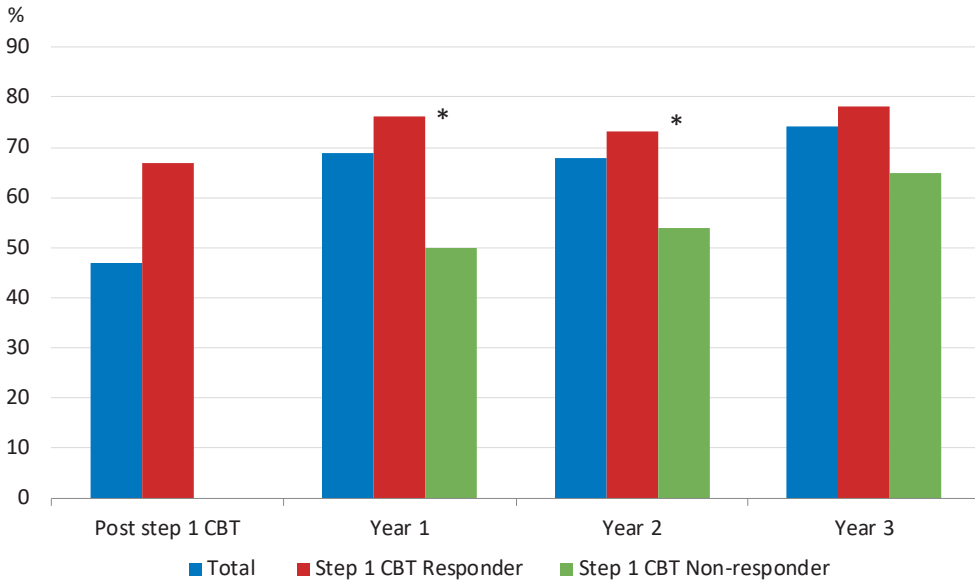
Figure 9. *Remission Rates Across Follow-up Assessments.*

Note*: *p < .01 First-step CBT post-treatment responder status associated with increased likelihood of remission at post-treatment, 1, 2, and 3-year follow-up. CBT = cognitive-behavioral therapy, FU = follow-up.*

DISCUSSION

The focus of this thesis is to study the long-term course of pediatric OCD and its outcome three years following evidence-based treatment. The concept was to follow the children and adolescents prospectively and to investigate whether they improved over time with regard to symptom severity, impairment, psychosocial functioning, and depressive symptoms. Additional treatments received during the follow-up period was described. The study aimed to improve the knowledge about the long-term outcome of evidence-based treatments for pediatric OCD. This may hopefully contribute to the improvement of future treatment strategies.

Main findings

The overall findings of the three studies presented in this thesis suggest that most children and adolescents diagnosed with OCD have a positive long-term outcome following evidence-based treatment for pediatric OCD, based on expert consensus guidelines. The results are characteristic both for the individually adapted treatment based on the clinical consensus guidelines in Studies I and II as well as for the stepwise treatment procedure applied in Study III.

OCD symptom severity

In Study I, we found that a majority of young people with OCD had improved and had fully or partially recovered from the OCD-symptoms after one year after baseline assessments. These results are in line with other studies of pediatric OCD described in meta-analyses (78, 124). Our findings show a better outcome at the one-year follow-up where the mean CY-BOCS total scores of 11.2 compare favorably with the mean scores of 14.1 shown in another naturalistic long-term follow-up study (71).

Study II used the same sample as Study I, and results indicate that the improvements achieved after one year were maintained and that the young people with OCD were further improved during the extended follow-up period (i.e. second and third year after baseline assessment). After three years, 66% of the patients were in remission, and approximately five out of six (85.3%) had responded to the treatment. However, 14.7% still had a persistent diagnosis of full OCD, whereof 14 (13.8%) had moderate severity and only one (0.9%) had severe OCD. These results are far better than those shown in previous long-term follow-up studies, where both remission rates (53%) (125) and response rates (67%) were much lower (125, 126). However, comparisons with other naturalistic studies are confounded by methodological issues: their wide range of follow-up periods (1-11 years); the age of the participants in their follow-up samples (11-28 years); and large variation of additional treatments received during the follow-up period (71, 72, 126). Despite the high degree of co-morbidity in our sample (48), response to treatment is more favorable than in other studies, as described in a meta-analysis of follow-up studies (52).

The low age of the participants in our sample at follow-up may have affected our results, as higher rates of remission have been shown among young people versus adults with OCD have been shown (125). Furthermore, about one-third of our sample had ongoing OCD-treatment at the three-year follow-up. Among those with ongoing treatment at three-year follow-up, SSRI medication was used in most cases (32%), whereas two participants received a combination of CBT and SSRI, and four participants (3.7%) received CBT at the three-year follow-up. However, the rates of ongoing treatment in our cohort were lower in comparison with those described in a previous study of OCD (125). Our findings also differ from those of a UK-based study, where OCD was shown to take an episodic or more waxing and waning course, with a high risk of chronic OCD symptoms (71). The findings of previous studies indicate the need for us to follow up and assess patients into adulthood, in order to verify whether relapse rates rise in late adolescence or early adulthood.

Study III is the first multinational and multicenter study of pediatric OCD, and remains the largest study that has systematically investigated the long-term outcomes of pediatric OCD with repeated assessment points over a three year follow-up period. The treatment was delivered in a stepped care model with those not responding to first-step CBT (14 weeks) being randomized to a second step with either continued CBT or pharmacotherapy with sertraline, both of which are viable treatments for CBT non-responders (123). Attrition was moderate, as we completed assessments at the clinics, with 63% and 62%

of the 269 participants returning for the two-year and three-year follow-ups, respectively.

The main findings of the study were that three-fourths (73%) of the participants were in clinical remission (CY-BOCS≤10) at the three-year follow-up assessment, indicating a better long-term outcome of pediatric OCD as compared with that reported in previous studies (52). Furthermore, another 17% had responded to treatment, even though they still had mild OCD symptoms (CY-BOCS=11–15), thus the overall response rate was 90% at the three-year follow-up. These results extend the findings reported in the one-year follow-up of responders to initial CBT in the NordLOTS, where a large majority (92%) of participants remained in remission at the one-year follow-up (122). Treatment gains were maintained and improved further during the follow-up period (i.e. second and third year after the first treatment step), in that the mean CY-BOCS total score at baseline of 24.7 had decreased to 5.0 a mean CY-BOCS score of after three years. These findings are characteristic both for those who responded well to initial CBT and for those who needed extended treatment with CBT or sertraline. Hence, the symptom level at the three-year follow-up did not appear to be influenced by either early response to treatment, the duration or the sequence of treatments. Those with more severe OCD symptoms at baseline were more likely to get extended treatment, however the differences in severity levelled out over time. Furthermore, a minority of the participants (6%) received treatment for OCD (CBT and/or sertraline) during the follow-up period, and in addition 11.9 % had 1-5 booster sessions. Thus, approximately 5% of participants were receiving ongoing OCD-treatment with sertraline at the three-year follow-up. These rates of ongoing treatment were much lower than those described in a previous study of OCD (125), and also lower than those in Study II.

The substantial stability of treatment gains and long-term rates of mild OCD (17%) or chronic moderate–severe OCD (10%), as demonstrated in Study III, are much better than the pooled mean persistence rate for full OCD of 41% reported in a meta-analysis by Stewart *et al.* (52). Our findings are in accordance with those of O'Leary *et al.* (70), who assessed patients seven years after they received CBT. However, their result could be confounded by methodological issues, such as more than 50% attrition to follow-up, and that most of the follow-up assessments were performed by telephone interviews (70); in contrast, our data were collected via interviews conducted in person at the clinic. Furthermore, the results in Study III are in accordance with and even slightly better than the long-term remission rate of 66% and response rate of 85% that were demonstrated in Study II

Taken together, these three studies may indicate that when good quality CBT is used in pediatric OCD, the long-term outcome is correspondingly good. Furthermore, our findings of the long-term outcomes in children and adolescents are far better than those described in adult samples (29, 64). The duration between onset of OCD and start of treatment could be more than 17 years in adult samples, while the mean duration between onset of OCD and treatment in our samples was 2.9 years (Studies I and II) and 1.2 years (Study III). The short illness duration before treatment could be one reason why our results were more favorable compared to studies with adults. Moreover, it is promising that the results found in Study III indicate that the prognosis does not differ between responders to first-step CBT and those who needed extended treatment. These are important findings, in view of the lack of studies investigating the long-term outcomes of extended treatment for non-responders to initial CBT.

Psychosocial functioning

Studies I and II found that the patients suffered from substantially impaired psychosocial functioning caused by OCD. Findings from baseline assessments with both the parent and child versions of COIS showed more severe impairment at baseline in comparison with findings from a previous study of childhood OCD (33). However, the participants' psychosocial functioning significantly improved between the baseline assessment and the six-month and one-year follow-ups, as well as the two- and three-year evaluations. Study II showed that after three years, most participants had only little remaining impairments due to OCD symptoms. Even those individuals with moderate or severe OCD at baseline showed improved psychosocial functioning after three years.

Depressive symptoms

Few of the participants in Studies I and II had CDI scores indicating moderate to severe depression at baseline, and even fewer showed elevated levels on CDI scores after three years. This may indicate that for most of the sample the reported depressive symptoms at baseline were related to their OCD illness and did not constitute a primary affective disorder.

Methodological considerations

Study participants representativeness

This thesis comprises two different clinical groups of children and adolescents with OCD. Participants in Studies I and II were children and adolescents with OCD assessed and treated at a specialized clinic for outpatient care in Gothenburg, Sweden. The clinic has a primary position in the chain of care in that a majority of the sample was parent referred, or directly referred from local Child and Adolescent psychiatric (CAP) clinics without having received previous treatment. Compared with other studies where the unit was a tertiary national OCD clinic, it is likely that our sample is more representative of patients with OCD in ordinary CAP clinics. Comorbidity was common in the sample, as 78% percent of the participants had one or more comorbid diagnoses (48). This is reasonably in line with comorbidity rates found in other studies. (26, 47). Furthermore, few exclusion criteria were applied, and almost all of the potential study participants gave their consent. Hence, we conclude that these results are representative of patients with OCD at CAP clinics in general.

In Study III, participants were recruited from Denmark, Norway, and Sweden, with two main study sites in the latter country, in Gothenburg and Stockholm. Furthermore, we included patients from various settings, both from outpatients in community-based clinics and from specialized OCD clinics. Including participants from various settings and keeping the exclusion criteria to a minimum suggests that our results are fairly representative of patients at CAP clinics as well.

Attrition to follow-up assessments

There was some attrition at the follow-up assessments in all three studies, however, more than three-fourths of the participants in Study I and nearly two-thirds in Studies II and III participated at the follow-up assessments. For dichotomic outcomes, we used multiple imputation to handle missing data. Comparisons of descriptive data between participants with missing and non-missing data at follow-up showed no significant differences between the groups. Thus, we assume that data were missing at random and therefore prerequisites for using multiple imputation are met. However, there is a risk that attrition skewed our results in ways that we cannot entirely estimate. For instance, drop-outs to follow-up may have responded less well to the

treatments than completers. Analyses in Study III of only the participants that completed their follow-up assessments gave even more positive outcomes than the ITT analysis showed. On the other hand, if many of those who dropped-out at the follow-up assessments had responded well, the outcome from the ITT analysis may have underestimated the long-term treatment effects. However, due to the completer analysis in Study III, we do not believe this to be the case.

Limitations and strengths

The main limitation of the studies is the lack of a "no treatment" control groups, as we cannot say whether the outcome is due to our treatments or to spontaneous change, possibly reflecting developmental maturation. However, as previous long-term naturalistic outcome studies have indicated worse outcomes (71, 72, 126), we believe that it is unlikely that the long-term improvements can be attributed exclusively to spontaneous recovery. Since we have established and effective therapies for OCD today, it is not ethically to replace these effective methods with placebo that is known to be ineffective. Such a "no treatment control" could have shown whether the treatments or spontaneous recovery was the more important factor. However, aside from the ethical problem, it would have been methodologically difficult to realize.

Another limitation is that the follow-up assessments did not include any semi-structured diagnostic instrument. However, the symptoms and severity of OCD were assessed by a standard clinical interview with the young people and their parents using the CY-BOCS, which was administered by trained independent assessors. Furthermore, not all the participants or their parents participated in all assessment points throughout the follow-up period. In Studies I and II, however, 74.3–78% of the young people participated in the six-month, one-year, and two-year follow-ups, and 61.5% completed their three-year assessment. In Study III, 63% and 62% completed the two- and three-year follow-up assessments, respectively. It should be noted, however, that the analyses of attrition showed no difference in severity of illness at baseline between those who participated versus those who did not participated in the follow-up assessments. Thus, the presence of selection bias seems unlikely. Furthermore, the attrition rate was less than attrition rates found in previous long-term studies (70-72).

Another limitation of Study II is the difference in sample size between responders and non-responders to the initial treatment, which may have biased the results of the comparative analyses between the groups somewhat. Moreover, all three studies were conducted in Nordic societies, which are socially stable with limited ethnic heterogeneity and limited socioeconomic differences. Therefore, our results may not generalize to populations with larger ethnic heterogeneity or socioeconomic divergence.

Limitations aside, the three studies included in this thesis are the largest studies that have systematically evaluated the long-term outcomes of pediatric OCD within a prospective longitudinal design, and with repeated assessments during the three-year follow-up period. The main strengths of the studies are the repeated assessments during the follow-up period and well-characterized samples of outpatients. Further, the follow-up assessments were performed by independent raters at clinics. Symptom severity at baseline was similar to the level of symptom severity reported in other studies. These strengths, along with the fact that few exclusion criteria were applied in the studies, give a solidity to the results and make them generalizable to ordinary CAP units. Further strengths for Study III are that the sample consists of outpatients from various settings and that the manualized stepwise treatment is described robustly.

CONCLUSIONS

- The majority of children and adolescents diagnosed with OCD have a long-term positive outcome following evidence-based treatment for pediatric OCD, which was individually adapted following expert consensus guidelines (i.e., CBT and SSRI, when indicated).

- The long-term stability of treatment gains for children and adolescents with OCD, participating in a stepwise manualized treatment, is excellent. The immediate improvements after a first step of manualized CBT (and, if needed, extended treatment with CBT or a switch to pharmacotherapy with sertraline) are excellent, and continued improvement ensues over time.

- Long-term improvements were also found with regard to psychosocial functioning, and there was a reduction in depressive symptoms. Further, the achieved improvements during treatment in these areas were also maintained over time.

FUTURE PERSPECTIVES

Clinical implications

Our findings suggest that the majority of patients respond well to treatment for pediatric OCD, and that treatment gains are maintained and further improved several years after treatment. Single treatment with CBT, preferably manualized, seems to be the most beneficial and safe treatment to offer young persons with OCD. Therapists need to be up-to-date regarding research on current treatment methods (e.g., further CBT advances), and on the development within assessments and diagnostic methods.

Moreover, for some young persons, OCD-symptoms seem to wax and wane over time, and a small number of participants need additional treatment with either CBT or SSRI during the years following initial treatment. Thus, it is of importance to assess patients regularly for at least two years following effective treatment and, if needed, offer booster sessions and additional treatment. This is based on our clinical impression, but we consider that the outcome of our studies I and II sample and the three-year outcome of our NordLOTS sample support such a practice, as reported in this thesis.

Conventionally, standardized CBT protocols for OCD range between 12 and 16 weekly sessions. The optimal number of sessions, however, is unknown and may need to vary based upon individual patient characteristics. This study suggests that those who did not respond well to initial CBT could benefit from extended treatment protocols. The staff responsible for child psychiatric care should take into account the possibility of extending CBT treatment as an alternative to medication with SSRI, as the long-term effects of both treatment forms seem to be similar. It is of importance that the choice of SSRIs as treatment is based on person-centered care. The decision must be based on the patients' and/or their parents' preferences rather than, for example, a shortage of CBT resources or clinical routines.

Restrictions of current CBT are not given by nature but are due to historical traditions. The rationale for the exposure-based CBT has historically been based on the emotion processing theory, in which habituation, is described as

the main process for successful exposure-based CBT. Recently, more attention has been focused on inhibitory learning as the explanatory model for successful exposures. This model focuses on the acquirement and strengthening of non-fear associations during non-reinforced exposures. The change of theoretical explanatory model may challenge therapists when performing exposure-based treatment.

Future research

Treatment of pediatric OCD shows favorable outcomes both post-treatment and at long-term follow-up. However, we do not know if the improvement persists into adulthood. We particularly lack knowledge about second-line treatment for pediatric OCD patients, in case of insufficient response to CBT. Thus, there is a need for considerably more long-term studies of childhood OCD to further understand the stability of treatment effects and consequences of the disorder throughout the child's development and into adulthood. Hopefully, strategies for early diagnosis and step-wise treatments used for early onset psychosis and schizophrenia can serve as models and be developed for pediatric OCD as well. Such treatment strategies could be helpful in the development of person-centered care.

Future CBT research should examine procedural changes (e.g., exposures based on the inhibition theory), and not allow historical approaches to set the limits on how to do CBT. The clinical usage of these strategies remains limited even if there is an interesting theoretical base for the emotional processing paradigm. Furthermore, there is a need for studies that assess these strategies in child clinical populations in order to evaluate the clinical outcomes and to verify whether these strategies improve on the extinction learning.

Furthermore, it is important to try to identify predictors and mediators of long-term outcome in order to be better able to individualize and personalize treatments more effectively, so that children are quickly allocated to the most likely beneficial interventions.

The effect of treatment is usually evaluated based on measures of symptom level, and sometimes on other factors such as functional ability or quality of life. It is important to identify other factors that can affect the child's well-

being and ability to cooperate with treatment, such as lifestyle and family factors. Moreover, it is particularly important to examine lifestyle factors such as sleep, eating habits, and physical activity, both with regard to their impact on the child's OCD symptoms and ability to benefit from the OCD treatment. This is of vital concern, as there is an increase in the number of children who sleep poorly, are physically inactive, or are malnourished (either eating too little or too much). Future studies need to assess such domains more closely.

As demonstrated in this thesis, effective treatments for pediatric OCD have been developed. However, we need further collaborative care interventions, large multicenter studies, RCTs, and registry-based studies, to be able to improve present treatment interventions to help even more of those suffering from childhood OCD and to evaluate the short-term and long-term outcomes.

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APPENDIX

Appendix 1.

An overview of the CBT treatment sessions in Study III.

Content of CBT-sessions and assessments

Time	Assessment	Assessment instrument	Parents involved in
0	Assessment by independent evaluator	K-SADS, CBCL, CY-BOCS, CGI, MFQ, ASSQ, COIS, CGAS, FAS, EAS, SCARED-R	Whole session
1	Psycho-education: Model for understanding and treatment	CGI-I, Compliance	Whole session
2	Externalising of OCD	CGI-I,	Whole session
3	Cognitive training and further assessment of OCD	CGI-I,	30 min
	Parents: *Negative attributions on OCD and the child*		
4	Test-exposure and tool box	CGI-I,	30 min
	Parents: *Parents' role, guilt-feeling and self-reproach*		
5	E/RP; fight against OCD	CGI-I,	30 min
	Parents: *The family's involvement in OCD*		
6	E/RP; get more control over OCD	CGI-I,	30 min
	Parents: *The child's own responsibility for the treatment*		
7	E/RP; support the child or the OCD?	CGI-I, Compliance, CY-BOCS, CGAS, to bring home: MFQ, COIS	Whole session
	Joint hour with parents: *Repetition of parents' role, milestones*		
8	E/RP; comorbidity and special therapeutic needs.	CGI-I,	30 min
	Parents: *Secondary winnings and other obstacles*		
9	E/RP; continue the fight against OCD	CGI-I,	30 min
	Parents: *Separate OCD from other problems*		
10	E/RP; continue the fight against OCD	CGI-I,	30 min
	Parents: *Unity and taking care of the family*		
11	E/RP; Going through the treatment session	CGI-I,	Whole session
	Parents: *Group-gathering – problem solving*		
12	E/RP; turning point	CGI-I,	30 min
	Parents: *How can parents prevent relapse*		
13	E/RP; prevent relapse	CGI-I, Compliance, CY-BOCS, CGAS.	30 min
	Parents: *What to do in case of relapse*	CBCL, MFQ, COIS, SCARED-R.	
	Check that date for independent evaluation is set		
14	Closing ceremony	CGI-I,	Whole session
	Getting together with the parents: *Going through the treatment process*		

Appendix 2.

An overview of the pharmacotherapy sessions in Study III.

Assessments and dosing schedule in sertraline step 2

Week	Dose (mg)	Range (mg)	Assessments	Actions
				Check Adverse Events Scale (baseline) (AE), Somatic assessment (SA), Clinical Global Impression (CGI)
0	25 × 3 days, then 50	25-50	CY-BOCS incl. CGI (use CY-BOCS at step 1 session 13 if < 3 weeks, else reassessment in point 10c above), CGAS, blood pressure (BP), pulse, weight, length, side effects (AE)	AE, SA, CGI, Clinical Global Impression - Improvement (CGI-I)
2	75	50-75	CGI-I, CGI, BP, pulse, weight, length, side effects, treatment credibility	AE, SA, CGI, CGI-I
3-4	100	75-100	CGI-I, CGI, BP, pulse, weight, length, side effects	AE, SA, CGI, CGI-I, dose correction based on response
5-7	150	75-150	CGI-I, CGI, BP, pulse, weight, length, side effects, treatment credibility, KINDL ("independent rater")	AE, SA, CGI, CGI-I, dose correction on response
8-12	200	75-200	CGI-I, CGI, BP, pulse, weight, length, side effects, treatment credibility	AE, SA, CGI, CGI-I, dose correction based on response
12-16	200	75-200	CY-BOCS incl. CGI/CGI-I, CGAS, Scared-R, MFQ, COIS, FAS, KINDL ("independent rater"), BP, pulse, weight, length, side effects, treatment credibility	AE, SA, CGI, CGI-I, dose correction based on response