STUDY PROTOCOL: PREVENTION OF CHILDHOOD ANXIETY DISORDERS IN OFFSPRING OF ANXIOUS PARENTS

Presentation of research group

The members of the research group have extensive experience from clinical work with both children and adults with anxiety disorders as well as experience of psychotherapy research.

Johan Åhlén, the Principal Investigator (PI) is a licensed psychologist and has a PhD in psychology. He has experience in clinical work and research regarding the prevention of childhood anxiety. He will be involved in the research design, recruitment, and running groups, data-analysis, and report writing.

Ata Ghaderi is a licensed psychologist, licensed psychotherapist, and professor in clinical psychology. He has done a significant number of RCT on the treatment of eating disorders, and parent--training for conduct problems, as well as prevention of obesity, eating disorders, and internalizing problems among children and adolescents. Ghaderi will mainly be involved in the research design, ethical considerations, data--analysis, and report writing.

Christina Dalman is a professor of psychiatric epidemiology and research group leader for the Epidemiology of Psychiatric Conditions, Substance use and Social Environment (EPICSS) research group at the Department of Public Health Sciences at Karolinska Institutet. She has done extensive research on risk factors of psychiatric conditions, using register--data from population--wide cohorts.

Inna Feldman is a health economist and Associate Professor at the Child Health and Parenting Research group at Uppsala University. She has extensive experience in economic evaluations of interventions for parents and children in the field of mental health. She will be responsible for the economic evaluation analysis of the trial, together with Filipa Sampaio, and report writing.

Filipa Sampaio is a health economist and a post--doctoral researcher at the Child Health and Parenting Research group at Uppsala University. She has experience in within trial economic evaluations of parenting interventions targeting behavior problems in children. She will be responsible for the economic evaluation analysis of the trial, together with Inna Feldman, and report writing.

Sigrid Elfström, PhD student, licensed psychologist, has clinical experience from working with anxiety disorders as well as experience of clinical research. Sigrid will be the study-coordinator, and she will be involved in several parts of the trial (i.e., recruitment, assessment, running groups, data collection, data-analysis, and report writing.

Study site

The project take place at the Department of Global Health at Karolinska Institutet, located Solna vägen 1, 113 65 Stockholm, Sweden.

Background

Objective

The current project aims to expand the evidence of prevention of anxiety disorders in children. We will take a novel approach to prevent childhood anxiety disorders by evaluating the Confident Parents - Brave Children (CPBC) program, a parent program targeting anxious parents, in a randomised controlled trial (RCT).

Research questions

- Is the CPBC-program effective in preventing childhood anxiety disorders within a period of 12 and 36 months respectively, compared to a self-help parenting book?
- Is the CPBC-program effective in preventing childhood anxiety symptoms within a period of 12 and 36 months respectively, compared to a self-help parenting book?
- Is the effect moderated by severity of parental anxiety, child anxiety symptoms at baseline, or gender or age of the child?
- Is the CPBC effective in increasing parental self-efficacy?
- Is the effect of CPBC-program mediated by changes in parental criticism and rejection, overprotection, parental modelling of anxiety or parental accommodation?
- Is the CPBC-program cost-effective?

Method

Participants

Study participants will be parents with elevated anxiety living in Sweden. Children aged 5-9, who do not meet criteria for anxiety disorder, will be included in the study together with their parents.

Sample size

To have an 80% power to detect a significant ($p \leq 0.05$) small to moderate difference (standardized mean difference = 0.4) the investigators will need to recruit 194 children. Given an anticipated attrition of 10%, the investigators will aim at including a total of 216 children. Participants will be recruited through advertisements. The participants will be randomly allocated to either (1) CPBC-program or (2) reading a self-help book.

Inclusion criteria:

- The parent suffers from exaggerated worry or anxiety
- The parent speaks and reads Swedish
- The child is 5-9 years old
- The child receives a clinicians assigned clinical severity rating (CSR) of 1 to 3 on anxiety disorders in ADIS-C (subclinical symptoms of anxiety)

Exclusion criteria:

- Current or recent parental alcohol or substance abuse

- The parent suffers from severe psychiatric conditions (e.g. current or recent psychotic or manic/hypomanic symptoms, severe depression or increased risk of suicide)
- Social conditions that would obstruct from participation (e.g. ongoing custody dispute, domestic violence, ongoing investigation of child neglect through social services)
- The child suffers from/is currently in treatment for an anxiety disorder or depression
- The child is currently undergoing a neuropsychological evaluation
- The child has no symptoms of anxiety at all (the child receives a clinicians assigned CSR of 0 on all anxiety disorders in the ADIS-C interview)
- The child meets criteria for an anxiety disorder (the child receives a clinicians assigned CSR of 4 or above on any anxiety disorder in ADIS-C interview)

Procedure

Recruitment of study participants will be done through advertisements in local newspapers and on Facebook. Interested parents will be able to read more about the study at Karolinska Institutets webpage and to complete a screening questionnaire online. All parents who have answered the screening questions will be contacted by email. Those eligible will be booked for a short phone interview to further screen for eligibility according to the inclusion and exclusion criteria. Parents who clearly meet exclusion criteria will be excluded after the phone screening interview, while those who are still judged to be eligible participants are invited to a diagnostic assessment via a video conferencing application (Zoom).

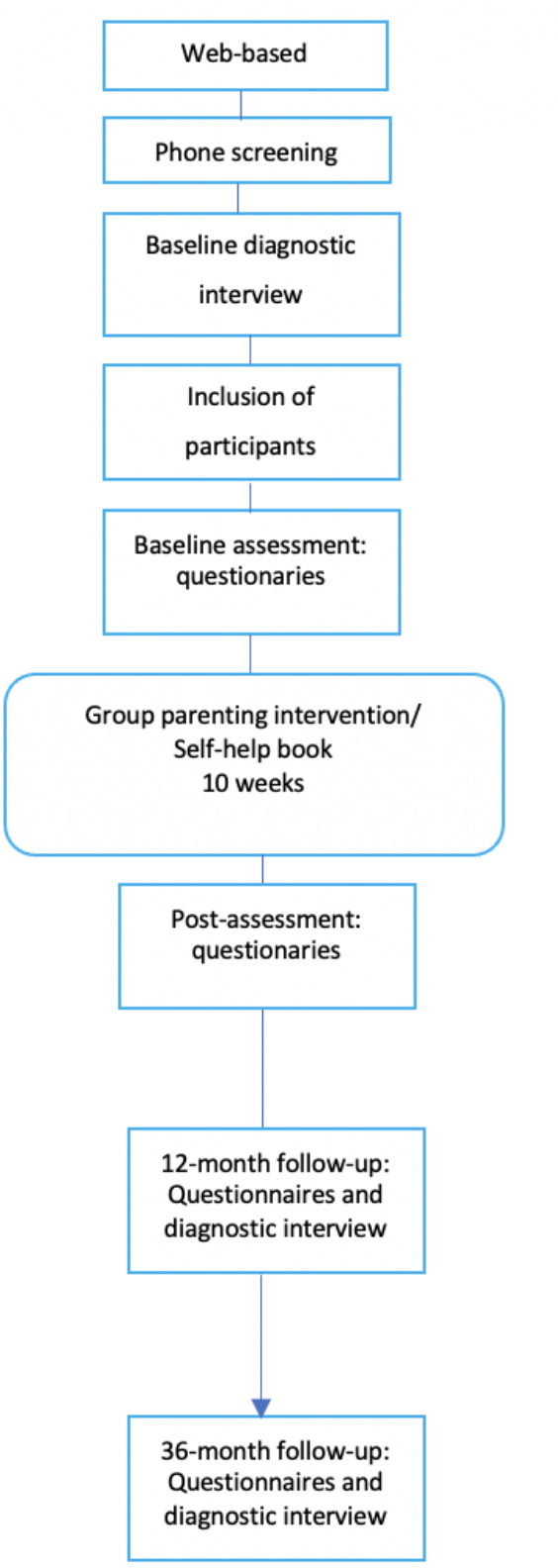
Before the video assessment, potential participating parents and children will be provided with both written and oral information about the study. If willing to participate, we will collect written informed consents from the parents and oral informed consents from the children. Oral consents from children will be collected during the video conferencing call. During the video call, parents will answer questions about their own and their children's mental health. A licensed psychologist will administer two semi-structured diagnostic interviews (M.I.N.I. and ADIS) to collect information about anxiety disorders as well as other psychiatric disorders. After the diagnostic video interview, the research team will decide if the parents meet inclusion criteria or not.

Parents who are included will receive an email with personal login information to a battery of questionnaires (baseline assessment). The parents are then randomly assigned to either (1) the intervention group, *Confident Parents - Brave Children* (CPBT) or (2) the active comparator group (reading a self-help book).

The CPBT will contain 6 group sessions during a period of 10 weeks. Individual booster sessions with all participants will be scheduled one month after the last group session. All group leaders will be licensed psychologists.

At the end of the intervention phase (after the booster session), the participants will receive an email with personal login information to complete a battery of questionnaires (post assessment).

Follow-up, semi-structured diagnostic interviews are conducted 12- and 36-month post-treatment. The participants will also complete a battery of questionnaires at 12- and 36-month follow-ups. An overview of the study is provided in figure 1 below.


Web-based
Phone screening
Baseline diagnostic interview
Inclusion of participants
Baseline assessment: questionaries
Group parenting intervention/ Self-help book 10 weeks
Post-assessment: questionaries
12-month follow-up: Questionnaires and diagnostic interview
36-month follow-up: Questionnaires and diagnostic interview

Measures

Primary outcome measure

The primary outcome will be change in severity of childhood anxiety disorder, as rated by clinician at 12- and 36-months follow-up. Clinical Severity Ratings (CSR) range from 0 to 8, where a value of 4 and higher indicate that the child meets criteria for an anxiety disorder. The CSR is extracted from the Anxiety Disorders Interview Schedule - Schedule for Children (ADIS-C). The CRS is rated by clinician based on interviewing with primary caregiver.

Secondary outcome measures - parent reported

EQ5D

EQ5D is a validated self-rated questionnaire of the parent's quality of life, including 5 items (each item scored 1-3 where lower scores indicates better quality of life). EQ5D will be used in the cost-effectiveness analysis and measures changes in health-related quality of life (HRQoL) in parents on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression

Time frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

Child Health Utility 9D (CHU9D)

CHU9D is a validated parent-rated questionnaire of the child's quality of life, including 9 items (each item scored 1-5 where lower scores indicates better quality of life).

Time frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

Expressed Emotion Adjective Checklist (EEAC)

The EEAC is a validated self-rated questionnaire of the parent's positive and negative emotions directed towards the child. The EEAC include 20 adjectives (each scored 1-8 where 1 indicates never and 8 always).

Time frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

Revised Parental Overprotective Scale (RPOS)

RPOS is a revised version of the validated self-rated questionnaire of the parent's overprotective behaviors, including 11 items (each item scored 1-5 where higher scores indicates more overprotective behaviors).

Time frame: RPOS at post-intervention, 12-month, and 36 month follow-up.

Modelling of Parental Anxiety Questionnaire (MPAQ)

MPAQ is a self-rated questionnaire of the parent's modelling of anxious and non-anxious behaviors (two different sub-scales), including 7+9 items (each item scored 1-5 where higher scores indicates more modelling).

Time Frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

Screen for Child Anxiety Related Disorders Revised (SCARED-R)
SCARED-R is a validated parent-rated questionnaire of the child's anxiety symptoms including 41 items (each item scored 0-2 where higher scores indicates more anxiety symptoms).
Time frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

Patient Health Questionnaire (PHQ-9)
PHQ-9 is a validated self-rated questionnaire of the parent's depression symptoms, including 9 items, (each item scored 0-3 where higher scores indicates more depressive symptoms).
Time frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

PROMIS-Anxiety Short Form
The PROMIS Anxiety Short Form is a validated self-rated questionnaire of the parent's anxiety symptoms, including 8 items, (each item scored 1-5 where higher scores indicates more anxiety symptoms).
Time Frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

Family Accommodation Scale-Anxiety Parent Report (FASA-PR)
The FASA-PR is a validated self-rated questionnaire of the parent's accommodation to the child's anxiety, including 13 items (each item scored 0-4 where higher scores indicates more accommodation).
Time frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

Parenting Sense of Competence Scale (PSOC)
PSOC is a validated self-reported questionnaire of the parent's sense of competence, including 11 items (each item scored 1-6 where higher scores indicates more sense of competence).
Time Frame: Base-line assessment, post-intervention, 12 month follow-up, 36 month follow-up.

The Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P)
The TiC-P is a measure aimed at assessing resource use and other costs associated with psychiatric or behavioral conditions. It includes questions on healthcare social support, social support parental absence from work, absence from school and productivity loss in school.

Assessment points

Participants will be assessed at pretreatment, baseline, post intervention and at 12- and 36-month follow-up.

Timeline / Measure	Online screening	Phone screening	Video assessment	Base-line measures	Post measures	12-moth follow-up	36-month follow-up
Clinician assessed							
Demographic data	X						
ADIS			X			X	X
MINI			X				
Child CSR			X			X	X
Parent CSR			X				
Parent reported							
EQ5D				X	x	X	x
EEAC				X	x	X	x
RPOS				x	X	x	X
MPAQ				X	X	x	X
SCARED-R				X	X	x	X
PHQ-9	x				X	x	X
PROMIS Anxiety short form	x				X	X	x
FASA-PR				X	x	X	x
PSOC				X	x	X	x
CHUD-9				x	x	x	x

Table 2. Overview of measures and time points.

Intervention

*Intervention (*CPBT*)*
Previous research on parenting styles involved in the transmission of anxiety between the parent and the child could be summarized into three main themes: (1) criticism and low warmth, (2) overprotection, (3) modelling anxiety and avoidance and (4) accommodation of anxiety.

We hypothesize that helping parents gain more knowledge of childhood anxiety and use more positive parenting skills would produce warmer parenting and more acceptance of the child. We hypothesize that helping parents understand the consequences of overprotective behaviour and find opportunities to help their child in challenging/approaching behaviour would increase the autonomy of their child. We believe that helping parents challenge their own fears and remember to reward their child for approaching behaviours would increase modelling and reinforcement of approaching behaviours. Subsequently, we hypothesize that parental warmth and acceptance, increased autonomy of the child, and modelling and reinforcement of approaching behaviour would, in the long term, decrease the risk of developing an anxiety disorder. CPBT comprise six 120-minute group sessions and one individual booster sessions. All sessions will be carried out using Zoom.

Participants in the active control group will receive a parenting book containing research-based strategies for handling children's anxiety [12]. They will be instructed to read the book within the 10 weeks from baseline to post assessments but will receive no other guidelines. They will not receive any help from the research team while working with the book.

Efficacy: Data-Analysis

The efficacy of the CPBT will be evaluated in a series of regression analyses. The primary outcome measure (child CSR) will be evaluated in a generalized linear mixed model (GLMM). The measures EEAC, OP, FASA-PR and MPAQ will be evaluated separately as dependent variables using the linear mixed model (LMM).

Cost-Effectiveness

Two types of analyses (cost-utility analysis and cost consequence analysis) will be performed. The cost-utility analysis will be expressed as an incremental cost effectiveness ratio given as the difference in costs divided by the difference in quality-adjusted life years (QALYs) for parents and children between the two conditions (i.e. the cost for one additional life year with full health gained). In the cost-consequence analysis, incremental costs and outcomes per parent and /child between the conditions will be presented for each cost and outcome item. Costs in both trial arms will be estimated from a limited societal perspective. Costs will be calculated for each participant based on resource items and associated relevant unit costs. Costs to deliver the intervention will be estimated based on practitioners' time to

deliver the intervention, costs for materials, etc., using a micro-costing framework. The use of other societal resources by children and their parents will be collected at baseline and at 12 months follow -up. This comprises information on the use of resources related to healthcare and productivity losses due to absence from school for children, and productivity losses due to absence from work for parents, which will be collected using an adapted version of the questionnaire on healthcare consumption and productivity losses (TiC-P) [29]. The TiC-P is a feasible and reliable instrument for collecting data on medical consumption and productivity losses in individuals with mild to moderate mental health problems. Total costs will be aggregated by trial arm.

As the economic data are likely to be missing at random, multiple imputation methods will be used in the base case analysis. Total QALY gains for parents and children over the trial period will be estimated using the area under the curve method. Cost data and QALYs will be analyzed using generalized linear models (GLM) to account for non-normal distribution. The GLM approaches allow the consideration of other distributions and functional forms to fit the costs data. Data will be analyzed while controlling for covariates and adjusting for baseline values.

Safety procedures and adverse events

If a child meets criteria for an anxiety disorder when the first diagnostic interview is carried out, the family is excluded and referred to health care. If the parent suffers from substance or alcohol abuse or severe psychiatric illness, or in case of domestic violence, the family will be excluded and referred to health care or social services.

Parents and children are free to seek care for mental health problems while participating in the study. Only licensed psychologists will carry out the diagnostic assessments and be responsible for leading the parenting groups. To prevent any possible concern about data safety among the participants, there will be information on how data is securely handled. All participant data will be handled confidentially. Data will be imported to a coded data file and the investigators will perform all analysis.

In case of an adverse event, the members of the research team will inform the study coordinator (Johan Åhlén) who will be responsible for deciding what actions are appropriate to take. Any adverse events will be described in the planned publication.

Project schedule

Spring 2021: Recruitment and assessment of cohort 1
Fall 2021: Recruitment and assessment of cohort 2
Spring 2022: Recruitment and assessment of cohort 3, and follow up cohort 1
Fall 2022: Follow up cohort 2
Spring 2023: Follow up cohort 3

Summer-fall 2023: Publishing results

Presentation of results

The study results will be presented in several articles submitted for publication in scientific journals.