



Prevention for Children at Familial Risk of Severe Mental Illness - The VIA Family Study



PhD Thesis

Anne Dorothee Müller

This thesis has been submitted to the Graduate School of Health and Medical Sciences,
University of Copenhagen, 1 December 2023

Title:

Prevention for children at familial risk of severe mental illness – the VIA Family project

Author:

Anne Dorothee Müller, MSc

Affiliation:

Child and Adolescent Mental Health Center, Research Unit, Copenhagen University Hospital
Mental Health Services CPH, Copenhagen, Denmark

Enrolment:

Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of
Copenhagen, Copenhagen, Denmark

Supervisors**Principle supervisor**

Professor Anne Amalie Elgaard Thorup, MD, PhD

Child and Adolescent Mental Health Center, Research Unit, Copenhagen University Hospital – Mental Health Services CPH,
Copenhagen, Denmark.

Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Co-supervisors

Professor Merete Nordentoft, MD, PhD

Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre
Copenhagen, Copenhagen, Denmark

Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Associate Professor Nicoline Hemager, MSc, PhD

Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre
Copenhagen, Copenhagen, Denmark

Department of Psychology, University of Copenhagen, Copenhagen, Denmark

Professor Geneviève Piché, MSc, PhD

Centre de recherche universitaire sur les jeunes et les familles (CRUJeF), Québec, Canada

Department of Psychoeducation and Psychology, Université du Québec en Outaouais, Saint-Jérôme, PQ, Canada

Assessment Committee**Chairperson**

Professor Annamaria Giraldi, MD, PhD

Department of Clinical Medicine, University of Copenhagen, Denmark

Professor Celso Arango, MD, PhD

Universidad Complutense, Madrid, Spain and Kings College, London, UK

Dr Melinda Goodyear, MBSc, PhD

Monash University, Warragul, Victoria, Australia and Emerging Minds, Hilton, SA, Australia

Abbreviations

CBCL: Child Behavior Checklist

CGAS: Children's Global Assessment Scale

HOME: Home Observation Measurement of the Environment

ITT: Intention to Treat

K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version

NGO: Non-governmental organization

TRF: Teacher Report Form

Preface

On a spring day in 2017, I started my journey in the VIA Family research project. I was intrigued by the study's prospect that preventive interventions can potentially prevent potential disadvantages for children and their families. In the first years of my PhD, I spent time learning how to conduct a clinical trial: formulating applications for ethical approval, writing statistical codes, and playing card games with children while doing data assessment.

However, my quantitative focus changed when I started working part-time as a practitioner in the family-based prevention program 'Family Talk' alongside my research work. Engaging with children and parents in a clinical setting revealed the diversity of families and the subtle yet potent changes possible through intervention. This experience prompted me to question if the impact of the VIA Family intervention on families' lives could be measured or comprehended differently than through traditional randomized trial design. Consequently, in the summer of 2019, I started planning a qualitative study to provide a more nuanced evaluation of the preventive intervention. However, after integrating findings from both studies in autumn 2022, a new research question emerged — how does change come about? Possibly influenced by my background in psychology, I ventured into studying mechanisms underlying change. Concluding this thesis on a sunny winter day, the concept of prevention still intrigues me, even though its' challenges have become apparent. This thesis reflects my scientific journey and my encounters with families and children. I am grateful for this journey and my experiences from engaging in clinical research. Although collecting data from a clinical population is time-consuming, it provided me with valuable insights.

This thesis may be a waterdrop in the big ocean of science. Nevertheless, I still hope it can inform future studies, motivate aspiring researchers, and inspire future generations to delve into the fascinating realm of science.

I dedicate this thesis to my children Fridtjof, Øjvind and Ejnar

Acknowledgements

First, I want to say thanks to all the participating families. Thanks for opening your homes and telling me your stories. I could not have done this study without your trust, time and wisdom.

Next, thanks to my supervisors. Thanks to Anne Thorup for the opportunity to work on this project and for supporting my ideas. Thank you for your positive attitude and your encouraging belief in me. Thanks to Merete Nordentoft and Nicoline Hemager for your guidance, supervision, and constructive feedback. A special thanks to Geneviève Piché for welcoming me warmly in snowy Quebec, giving me feedback and input and inspiring me to ask new questions.

I also want to thank all my colleagues from the research unit: Kate H Jønsson, Mette Eigil, Henriette Andreasen, Anna I Printzlau, Amalie F Kristensen, Signe S Nielsen, Lisbeth J Mikkelsen, Sofie H Christensen, Helene K Kristensen, Abisha Visnu, Johan S Kristensen, Marianne Melau, Kirstine Fischer, Sophie K Jørgensen, and Michella Heinrichsen. A special thanks to Mala Moszkowicz for clinical guidance and for sharing your wisdom. Thanks, Sidsel Ingversen, for encouraging me and reminding me what the intervention could do for the families. A special thanks to Ida Gjøde for being a fantastic PhD buddy and inspiring me to question the status quo of what is possible.

Also, thanks to Jakob Thorsen for guidance on English grammar and language, Nikolaj Thams, Felix Müller, and Julie Forman for being R-code-crisis hotlines and for guidance with statistical questions. Thanks to the funders of the three studies: Satspuljen, TRYGFonden, the Research Unit of the Child- and Adolescent Mental Health in the Capital Region, and Tværspuljen.

A special thanks to my family and friends for your encouragement. Thanks to my brother Felix for your help with everything from Redcap to R-statistics, for helping me restructure my thoughts, and for believing in me. Thanks to my mother, Katharina, for being so ambitious on my behalf and caring for my home and children when I was working late. Last but not least, thanks to my husband, Kristian, for supporting me, encouraging me, and showing me that life moves on beyond this thesis – your support and love mean the world to me.

Summary (English)

This thesis explores a preventive intervention for children at familial risk of severe mental illness, VIA Family, through three studies. We defined severe mental illness as recurrent moderate or major depression, bipolar disorder, or schizophrenia spectrum disorder. Children of parents with severe mental illness have an increased risk of developing a lifetime mental illness compared with children with parents without mental illness. Following the transgenerational model of transmission, mental illnesses in children with a familial risk develop along trajectories which are influenced by risk and protective factors. Hence, preventive interventions focusing on changing modifiable factors of risk and protection hold the potential to prevent the development and the functional consequences of mental illness.

The thesis consists of three studies investigating the VIA Family Intervention from three perspectives. The objective of all three studies is to examine the efficacy and mechanisms of change related to a preventive intervention for children at familial risk for severe mental illness: VIA Family. The intervention was family-based, complex, multi-component, and individually tailored, aiming at decreasing modifiable risk factors and increasing modifiable protective factors.

The first study is based on the VIA Family trial. The trial was pragmatic, rater-blinded, and randomized, with a two-arm parallel-group design testing for the superiority of VIA Family over treatment as usual. We assessed children's global functioning (primary outcome), emotional and behavioural problems, and absence from school at baseline and after 18 months (secondary outcomes). The trial included 95 families with 113 children, randomly allocated to VIA Family or treatment as usual. The results showed no superior efficacy of the VIA Family intervention compared with treatment as usual.

The second study is based on the discrepancies between the null findings of the VIA Family trial and the positive narratives from the participating families. We aim to understand possible underlying mechanisms of change within the VIA Family

intervention. The study has an exploratory sequential mixed methods design. We conducted 4 focus group discussions with children and parents, including 8 children and 8 parents. We analysed the collected data using an abductive thematic analysis within a theoretical framework of a health-belief model and a self-determination theory. We find that parents perceived a change through the intervention when they perceived a *need for support*. Children's motivation to engage in the intervention was intrinsic and based on their families' participation.

In the third study, we use the qualitative findings to generate a hypothesis to be tested in a post hoc subgroup analysis of secondary data from the VIA Family trial. The integrated findings highlight the crucial role of participants' perception of need and motivation in driving change within preventive interventions, impacting the levels of support and stimulation in the home environment. However, no significant differences in children's global functioning were observed.

In conclusion, we do not find a superior effect of the VIA Family intervention compared with treatment as usual. The short intervention period, follow-up timepoint, measurement biases, and sample heterogeneity might explain the null findings. Furthermore, we find that participants' perceptions of need and quality of motivation are important mechanisms of change. The exploratory findings need to be confirmed in future studies. Nevertheless, an emphasis on families' perceived need for prevention might improve recruitment, maintain long-term changes, and inform future preventive interventions for children at familial risk for severe mental illness.

Summary in Danish (Dansk resumé)

Denne afhandling er en sammenfatning af tre studier, der undersøger en forebyggende indsats til børn med øget familiær risiko for alvorlig psykisk sygdom. En alvorlig psykisk sygdom defineres her som en tilbagevendende moderat eller svær depression, en bipolar lidelse eller en skizofrenispektrums-forstyrrelse. Børn af forældre med alvorlig psykisk sygdom har en forøget risiko for at udvikle psykisk sygdom sammenlignet med børn af forældre uden psykiske sygdomme. Ifølge den tværgenerationelle transmissionsmodel (engelsk: model of transgenerational transmission) har mængden og typen af risiko- og beskyttelsesfaktorer afgørende betydning for udviklingen af psykiske sygdomme hos børn med øget familiær risiko for udviklingen af alvorlig psykisk sygdom. Derfor har forebyggende indsatser, der har fokus på at nedbringe effekten af risikofaktorerne og at styrke beskyttelsesfaktorerne, ifølge modellen, potentiale til at forebygge psykisk sygdom.

Formålet med alle tre studier er at undersøge effekten af en specifik forebyggende indsats for børn i familier med øget risiko for alvorlig psykisk sygdom: VIA Family interventionen. Interventionen indeholdt flere komponenter og havde et familiebaseret, komplekst og individuelt tilpasset design. Målet med interventionen var at reducere risikofaktorerne og at styrke beskyttelsesfaktorerne for børnene. Afhandlingen består af tre studier, der på hver sin måde undersøger interventionen: 1) forskel i effekt i forhold til sædvanlig behandling, 2) interventionens forandringsmekanismer og 3) virkninger af interventionen på subgrupper.

Det første studie undersøger effekten af VIA-Family-interventionen sammenlignet med det sædvanlige behandlingstilbud for børn med øget familiær risiko for alvorlig psykisk sygdom efter 18 måneder. Studiet er et randomiseret klinisk studie. Familierne blev tilfældigt randomiseret til henholdsvis VIA Family og sædvanlig behandling. Det primære effektmål er forskellen i ændringerne af børnenes globale funktionsniveau efter interventionen sammenlignet med gruppen ændringerne hos børn i den sædvanlig behandling. De sekundære effektmål er forskellene imellem de to gruppers følelsesmæssige og adfærdsmæssige problemfelter samt skolefravær efter

interventionen. Studiet inkluderer 95 familier med deres i alt 113 børn. Resultaterne viser ingen forskel i forandring i det primære og de sekundære effektmål imellem de to grupper.

Det andet studie tager udgangspunkt i den diskrepans, der er imellem resultaterne fra det randomiserede studie og de positive beretninger, der kom fra de deltagende familier. Formålet med dette studie er at forstå mulige underliggende forandringsmekanismer, som bidrog til effekten i VIA-Family-interventionen. Til dette studie indsamlede vi kvalitative data igennem fire fokusgruppediskussioner med otte børn og otte forældre, som havde deltaget i VIA-Family-interventionen. Studiet er en abduktiv tematisk analyse og bygger på teorier fra self-determination theory og health-belief model. Resultaterne viser, at forældrene oplevede en positiv forandring under interventionens hvis de oplevede at de havde et behov for hjælp. Børnene beskrev, at deres motivation for deltagelse var baseret på familiens deltagelse i interventionen.

I det tredje og sidste studie anvendes de kvalitative fund fra det andet studie til at generere en ny hypotese. Hypotesen afprøves i en post-hoc-subgruppeanalyse af sekundære data fra det randomiserede studie. Studiet integrerer de kvalitative fund ved hjælp af et eksplorativt og sekventielt mixed methods design. Studiet viser, at de forældre, der ved interventionens begyndelse var motiverede for at deltage på baggrund af et udtalt behov for hjælp, havde effekt af interventionen i form af en højere score af børnenes hjemmemiljø. Resultaterne viste ingen forskel i børnenes globale funktion imellem de to grupper igennem interventionens forløb.

Sammenfattende viser de tre studier ingen bedre effekt af VIA-Family-interventionen sammenlignet med den sædvanlige behandling. Interventionens indhold, længde samt det tidlige opfølgningstidspunkt efter interventionen kan, sammen med målebaseret bias og heterogenitet i samplet, være med til at forklare dette fund. Derudover viser studierne, at børnenes motivation var afhængig af forældrenes medvirken i interventionen, og at forældrenes opfattelse af familiens behov for hjælp var en afgørende forandringsmekanisme. Disse eksplorative fund kan med fordel tænkes med ind i designet af fremtidige forebyggende indsatser. Et forøget fokus på forældrenes oplevede behov for hjælp til forebyggelse kan forbedre fremtidige interventionsstudiers rekruttering og være med til at skabe og opretholde langvarige positive forandringer hos børnene.

Table of Contents

Preface	iii
Acknowledgements	iv
Summary (English)	v
Summary in Danish (Dansk resumé)	vii
List of papers	1
Introduction	2
Children at Familial Risk of Severe Mental Illness	2
Transgenerational Transmission of Mental Illnesses.....	3
<i>Risk and protective factors and transmission mechanisms</i>	5
<i>Vulnerability, resilience, and potential child outcomes</i>	9
Preventive Interventions	10
<i>Universal, selective, and indicated prevention</i>	10
<i>Preventive interventions in usual care– Globally and in Denmark</i>	11
<i>Components in preventive interventions</i>	12
<i>Multicomponent Interventions</i>	14
<i>Complex Interventions</i>	15
Mechanisms of Change in Preventive Interventions.....	16
Aims and Objectives	18
Objectives of this Thesis	18
Study 1 - Aim and Hypotheses.....	18
Study 2- Aim and Research Question.....	18
Study 3- Aim and Hypothesis	19
Methods	20

<i>The VIA Family trial</i>	20
<i>Sequential Mixed Methods Study</i>	20
Interventions.....	22
<i>VIA Family intervention</i>	22
<i>Treatment as Usual</i>	26
<i>Participants and recruitment</i>	28
<i>Study 1 – Data Collection and Measures</i>	32
<i>Study 2 - Data collection and generation</i>	39
<i>Study 3 - Data and measures</i>	41
Analyses	42
<i>Study 1 - Statistical Analyses Plan</i>	42
<i>Study 2 – Abductive Thematic Analysis</i>	44
<i>Study 3 - Mixed Methods Integration and Subgroup Analyses</i>	47
Results	49
Recruitment and Flow in the VIA Family Trial.....	49
Results Study 1: Differences in Change between Groups.....	54
Results Study 2: Qualitative Findings.....	60
Results from Study 3: Subgroup analyses	66
Discussion	69
Summary of Main Findings	69
Interpretation of Results	70
Limitations, Strengths and Future Directions.....	74
Conclusion.....	78
Ethical considerations.....	78
Clinical Implications.....	80
References	83
Paper 1	97
Paper 2	138

Supplementary Material 167

S1 Trial Protocol

S2 Number of referrals from VIA Family to social services or mental health centres

S3 Guide for focus group discussion – Children and Parent.....

S4 Mixed methods grouping of categories

S5 Use of VIA Family components

S6 Use of elements in usual care

List of papers

This thesis encompasses two papers of three studies.

Paper 1 reports Study 1 and Paper 2 combines Study 2 and Study 3 in a sequential mixed methods paper.

Paper 1

Müller, Anne D; Gjøde, Ida C T; Thams, Nikolaj; Ingversen, Sidsel; Moszkowicz, Mala; Jepsen, Jens R M; Mikkelsen, Lisbeth J; Nielsen, Signe S; Hemager, Nicoline; Nordentoft, Merete; and Thorup, Anne A E (2023) *Family-based preventive intervention for children of parents with severe mental illness: A randomized clinical trial*

Accepted for publication at JCPP-Advances

Paper 2

Müller, Anne D; Gjøde, Ida C T; Christensen, Sofie; Jørgensen, Sophie K; Fischer, Kirstine Moszkowicz, Mala; Hemager, Nicoline; Nordentoft, Merete; Piché, Geneviève; and Thorup, Anne A E (2023) *"It was a need that we did not think we had": a mixed methods study of mechanisms of change in mental illness prevention.*

Prepared for submission

Introduction

Children at familial risk of severe mental illness have an increased risk of developing a mental illness compared with their peers¹. The term *severe mental illness* serves as an umbrella term to categorize recurrent moderate and severe depression, bipolar disorder, and schizophrenia spectrum disorders^{2,3}. Parental severe mental illness can severely affect the individual and their children due to the high chronicity of the illnesses, the large functional impairment, and the risk of transmission of mental illness from parent to child^{1,2}.

Preventive interventions aim to reduce the incidence, prevalence and recurrence of mental illness⁴. According to the World Health Organization (WHO), preventive interventions have a promising potential to cost-effectively and sustainably improve global mental health². In the field of mental health, prevention of mental illness refers to not merely reducing the prevalence of mental disorders but also reducing the functional impact, timely onset and chronicity of mental illness⁴. Globally, mental illness has a high impact: It affects societies through loss of income, the economy through enormous economic expenses, and distresses the individual and their families^{2,5,6}.

Children at Familial Risk of Severe Mental Illness

Globally, a systematic review estimated that approximately 20-39% of patients with *any* mental illness within the adult mental health services are parents to a child under 18 years⁷. In Northern Europe, the estimates of parents in adult mental health services with any mental illness and children under 18 years are around 10-30%^{5,8,9}. The estimates vary depending on criteria defining mental illness, geographical location, measurement methods applied, and the inclusion of levels of care of the parent (primary, secondary or tertiary care)^{5,7,8}.

Regarding severe mental illnesses, in Denmark, approximately 2.2 % of all patients in treatment for a severe mental illness are parents to at least one child between 0 and 16 years⁸. The chronicity and functional impairment associated with severe mental illness can significantly affect their children³. Severe mental illness is linked to various genetic and environmental risk factors, potentially heightening the risk for their children³. Consequently, children of parents with severe mental illness face an increased risk of developing not only the same mental illness as their parent but also other mental health problems¹. Scientifically, these children are therefore described and categorized as being at familial risk for severe mental illness³.

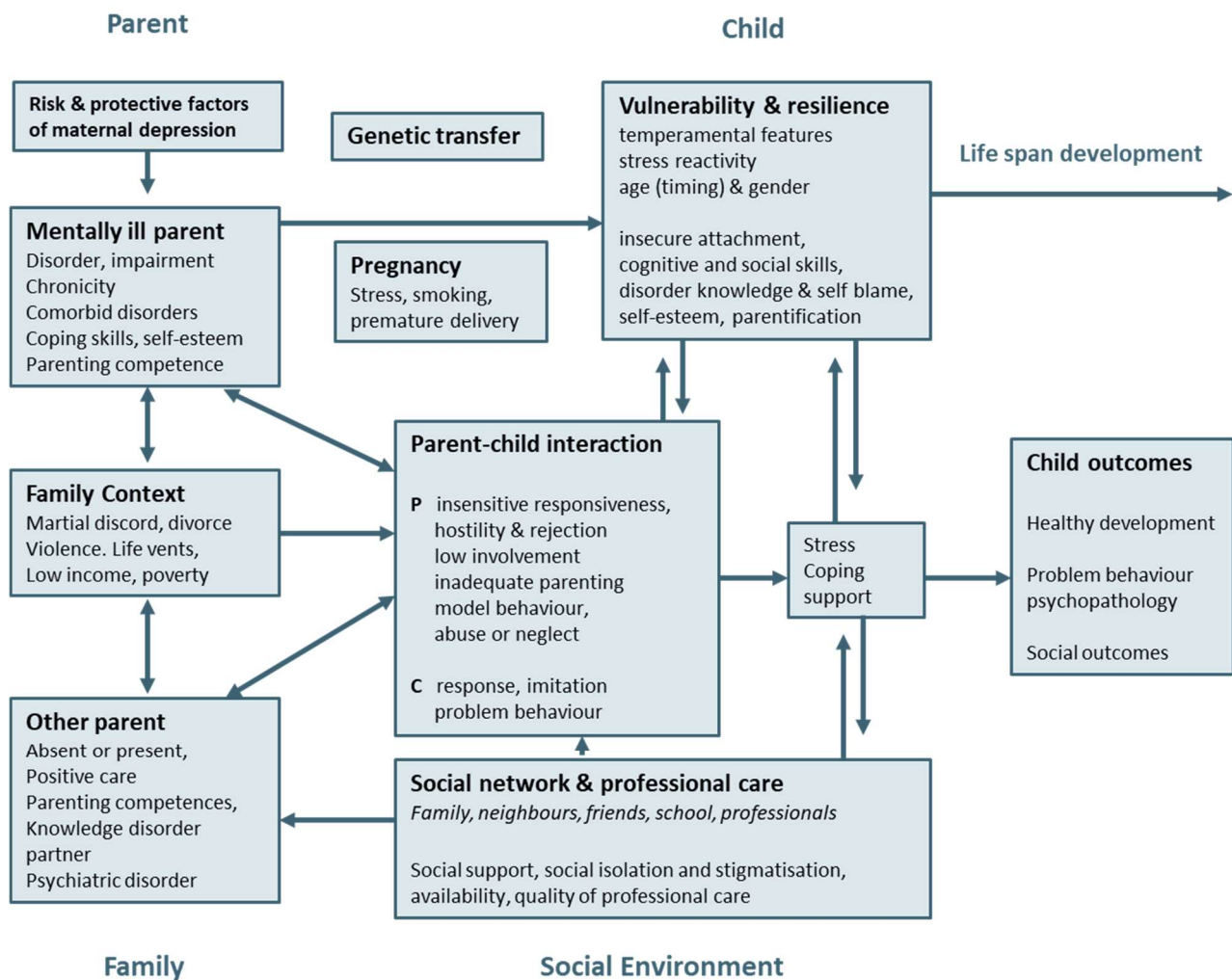
However, not all children with a familial risk for severe mental illness develop mental health problems. Many children thrive despite adversities; this highlights the role of resilience. Resilience is a child's ability to adapt effectively after exposure to adversities¹⁰. Protective factors within and around the child contribute to developing and enhancing resilience.

Therefore, the keys to understanding and changing the impact of parental severe mental illness on their children are to comprehend how severe mental illness transitions from parent to child and identify what risk and protective factors are at play. This understanding can inform preventive strategies promoting mental health.

Transgenerational Transmission of Mental Illnesses

The developmental model of transgenerational transmission of psychopathology proposed by Hosman, van Doesum and van Saantfort (2009) illustrates the interaction of internal and external risk and protective factors in children of mothers with depression¹¹(see Figure 1). In this thesis, I use the model to describe the transgenerational transmission of mental illness for children of parents with severe mental illnesses.

Figure 1. The transgenerational transmission model of mental illness in children at familial risk for mental illness (by Hosman, van Doesum and van Saantfort (2009)¹¹)



Developmental psychopathology

The model builds on a developmental psychopathology framework¹¹. It assumes that mental illnesses develop along individual trajectories through multiple risk factors and transactional and reciprocal associations between mental illness of parents and children's characteristics (e.g., neurocognitive functioning and temperament)¹¹. Consequently, the risk of developing a mental illness is non-linear and multifactorial, and it cannot be comprehended through a basic cause-and-effect relationship¹¹. Multiple trajectories and risk factors can lead to the same mental illness (equifinality). Additionally, the same factors can lead to different mental health problems (multifinality). For example, children can develop the same illness as their parents, they can develop a different mental illness, and finally, they can develop no mental illness at all. The concepts of multifinality, equifinality and individual trajectories in mental illness development have been empirically supported by findings from, e.g., high-risk studies, twin studies and gene-environment studies^{1,12}.

Throughout a child's life, specific sensitive periods and developmental stages arise, each associated with specific developmental tasks for the child^{3,11}. These stages include the prenatal period, infancy, early childhood, puberty, and early adulthood^{3,11}. Each stage involves different risk and protective factors and mechanisms of transmission of these factors to develop vulnerability or resilience within the child¹¹. Notably, the impact of risk factors on a child's mental health tends to be more severe the younger the child is³.

Risk and protective factors and transmission mechanisms

The transgenerational transmission model illustrates four key domains of risk and protective factors affecting transgenerational transmission mechanisms: parent, child, family, and the social environment¹³.

Certain characteristics apply to risk and protective factors. Factors can be intrinsic (often biological), e.g., a child's temperamental features or neurocognitive skills, and extrinsic (often environmental), e.g., adverse events^{3,4,11}. Further, intrinsic and extrinsic factors can mutually influence each other. For example, epigenetic mechanisms can

result in environmental-caused genetic alterations, while genetic factors can also influence a person's environment ^{4,14}. Moreover, the same risk or protective factor can originate from various sources. For example, high levels of parental stress can stem from the demands of parenting a child, whether or not the child has a mental illness, stem from tackling a mental illness, or from the difficulties of socioeconomic adversities^{3,11,15,16}.

Additionally, risk and protective factors tend to cluster, contributing to a cumulative effect ^{4,12}. An accumulation of risk factors, together with a lack of protective factors, provides a synergistic effect that intensifies the increased likelihood of developing a mental illness⁴. Reducing modifiable risk factors and supporting the development of protective influences can start healthy developmental trajectories³.

The transgenerational transmission mechanisms are mutually shaped by risk and protective. Transmission mechanisms include genetics, prenatal factors, parent-child interaction, family dynamics, and social factors. Collectively, these mechanisms can contribute to the emergence of early signs of vulnerability and resilience. Their interplay ultimately leads to diverse outcomes, i.e., multifinality and equifinality.

The following section summarizes both the empirical evidence from quantitative studies and findings from qualitative and mixed methods studies that support the transmission model. Risk and protective factors and their associated transmission mechanisms are grouped into domains within the model according to their origin (see Figure 1).

Importantly, the factors are interrelated and affect each other.

In the next section, I will present risk and protective factors and transmission mechanisms within five main areas: parents, child, parent-child interaction, family, and social environment.

Parents

As outlined earlier, the impact of parental severe mental illness on transgenerational transmission is a combination of multiple biological and environmental factors^{3,4,11}.

While genes account for an important part of risk transmission, environmental factors contribute too ^{17–21}.

During pregnancy, maternal severe mental illness is associated with numerous risk factors which also affect their (unborn) child. For example, mothers with severe mental illness have a higher risk of experiencing trauma, a higher risk of substance misuse, and a higher risk of premature delivery^{3,22,23}. All of these factors affect their child. Moreover, both the comorbidity and chronicity of parental mental illness and the degree of functional impairment augment risk. However, protective factors also affect transmission mechanisms, e.g., parent's positive coping skills²⁴ and high self-esteem¹¹.

The co-parent can contribute to various protective factors. This contribution can potentially buffer the effect of modifiable risk factors from the parent with the mental illness and the child. Especially if the other parent, for example, has supportive parenting skills, a good social network, and, if needed, receives professional help¹¹. However, the literature indicates that people with mental illness more often find a partner who also has a history of mental illness compared with people without mental illness (i.e., assortative mating)^{25–27}. In these cases, the co-parent potentially contributes with the same risk factors as the 'ill-parent'. For their children, this adds to the polygenetic and environmental risks.

Children

Children contribute to the risk transmission with their own factors of risk and protection, respectively.

There are numerous protective factors within the child. For example, positive temperamental traits, low-stress reactivity, high self-esteem, constructive coping strategies, and good cognitive and social skills^{3,28,29}. However, children with a familial risk of severe mental illness are often more impaired in these areas compared with children of parents without severe mental illness. Moreover, children of parents with severe mental illness more often experience extrinsic risk factors, e.g., bullying¹¹. As a consequence of these various risk factors, children at familial risk for severe mental illness often show early signs of vulnerability, such as low global functioning, low self-esteem, and the experience of adverse life events^{3,30,31}. Notably, the absence of these risk factors serves as protective factors for transgenerational transmission and may potentially influence the development of resilience^{3,11}.

Parent-child relationship

Both parental and child factors contribute to the quality of the parent-child relationship¹¹. This relationship is crucial in the model, as it mediates the transgenerational risk transmission during childhood ¹¹.

Parents' main contribution to a positive parent-child relationship is through positive parenting behaviour^{32,33}. This encompasses, e.g., sensitive responsiveness (including mentalization), good model behaviour, and the absence of abuse and neglect^{11,32}.

Children, on their part, contribute to the relationship with factors such as adaptable temperamental traits, positive responsiveness imitation, and positive mental health ¹⁶. A positive and good parent-child relationship positively associates with a child's chance of developing a secure attachment pattern, creating a supportive and stimulating home environment and numerous other resilience-enhancing factors^{3,11}.

Consequently, the other way around, the absence of a good parent-child relationship serves as a risk factor for the later development of mental illness^{3,34}. Parental severe mental illness negatively affects the parent-child relationship by impacting parenting competencies, contributing to the overall risk transmission³⁵⁻³⁷.

Family context

High family functioning and a stimulating home environment are protective factors in the transgenerational transmission of mental illness. Nevertheless, in families with severe parental mental illness, both family functioning and the home environment are often impaired^{3,38}. This impairment further affects the quality of the interparental relationship and communication, which, when weakened, contributes as a risk factor to the risk transmission^{3,11}.

Social Environment

Parents' and children's social and cultural environments substantially impact both and can potentially contribute to numerous protective factors. Good examples are families' social networks, peers and friends, schools or day-care, and, in some cases, professional care, which can all positively influence children's social environment¹¹.

Prosperous socioeconomic circumstances likewise serve as protective factors³⁹.

Research has shown that low-income socioeconomic circumstances impact interparental relationships, parental stress levels, and the home environment^{3,11,15}. This

highlights the fact that poverty is both a significant risk factor for the development of mental illness and a potential consequence of it^{3,11,15}. In general, parents with severe mental illness and their children more often live in low socioeconomic circumstances, including poverty, than parents without a mental illness^{5,40}.

Vulnerability, resilience, and potential child outcomes

The result of cumulative risk factors is that children of parents with severe mental illness who face adversities tend to exhibit a greater disposition to vulnerability rather than resilience. According to the model, stress, coping, and support can act as 'triggers' for the outcomes¹¹.

Following the principle of multifinality, severe mental illness can lead to multiple outcomes for children, influenced by the amount of risk and protective factors present along with signs of vulnerability and resilience of the child. Nevertheless, potential long-term outcomes for children at familial risk of severe mental illness are, e.g., low global functioning, mental illness, academic impairment, socioeconomic disadvantages, and somatic morbidity^{1,3,5,11,41–44}.

However, the interactional processes can also lead to long-term positive mental health for the children, often due to the presence of several protective factors. This makes the transgenerational model a promising framework for informing and designing preventive interventions^{11,13}.

To sum up, the transgenerational transmission model describes how risk and protective factors within and around the parents, the family, and the children contribute to the development of individual mental health trajectories.

Preventive Interventions

Universal, selective, and indicated prevention

Historically, medical and somatic disease prevention models informed prevention models for mental health. The WHO uses a classification system that groups preventive strategies in mental health into universal, selective and indicated prevention – based on the risk of the population and the costs and benefits of delivering a preventive intervention⁴⁵.

Universal prevention

Universal prevention strategies target an entire population or a specific group within a population². Universal prevention within mental health aims to promote general mental health and well-being and to reduce the overall risk of developing mental health problems⁴⁶. Examples are public health campaigns for healthy eating and exercise, anti-bullying initiatives at schools or stigma-reducing mental health educations^{2,46}. Universal mental health programs aim to encourage people to engage in healthy behaviours, create supportive environments, and change culture (e.g., anti-stigmatisation campaigns) to benefit an entire population or group.

Selective prevention

Selective prevention strategies focus on individuals or groups who have a higher risk than others of developing specific health issues due to identifiable risk factors or characteristics⁴⁶. Selective programs are designed to reduce risk for high-risk groups, e.g., for children with familial high-risk for severe mental illness. Hence, selective programs are designed for groups that benefit the most from the intervention(e.g., high-risk groups)⁴. However, selective preventive intervention programs typically do not target people who already show symptoms but those at high risk of developing symptoms^{4,46}.

Indicated prevention

Indicated prevention focuses on individuals who already show signs of vulnerability^{4,46}. These interventions aim to provide early treatment and support to interrupt the progress of illness. In children with elevated familial risk, indicated preventive interventions are early interventions for children showing early signs of vulnerability (e.g., mental illness symptoms)^{45,47}.

Preventive interventions in usual care– Globally and in Denmark

Globally, preventive initiatives for mental health are often underrepresented and underfinanced compared to remedial and rehabilitative interventions³. Child and adolescent mental health services and adult mental health services have an individualized and therapeutic focus rather than a family-based and preventive one³. Moreover, the primary focus in social services is on preventing abuse and neglect³. Although these areas are important, numerous other risk and protective factors need to be addressed in the prevention of mental illness, as outlined in the transgenerational transmission model.

In Denmark, children of parents with severe mental illness rarely receive preventive support through usual care. In social services, e.g., despite the existence of legal provisions for preventive care outlined in the Danish Social Service Law (§11 and §52), families with parental mental illness are rarely offered support based on the child's familial risk status alone.

Within the adult mental health services, clinicians can offer family meetings to their patients and their patients' next-of-kin. Moreover, clinicians can refer children to child support groups within the mental health services. However, clinicians rarely inform their patients about these offers.

Clinicians have explained this lack of support offering, resulting from their own experience of lack of skills or time constraints alongside their regular duties⁴⁸. Families,

on the other hand, have described that they experience that their practitioners do not take a family view or that the parent's mental disorder overshadows their child's needs as next-of-kin^{3,49}. As a result, many families of parents with severe mental illness describe that they feel left alone and experience that support for children at familial risk of severe mental illness is fragmented³³

Components in preventive interventions

Meta-analytic evidence suggests that preventive interventions for children of parents with any mental illness have a significant effect on children^{50,51}. However, most preventive intervention trials for children at familial risk of severe mental illness have only included children of parents with depression or bipolar disorder^{50,52}, whereas randomized studies of preventive interventions for children of parents with psychosis are few^{37,50}. Of these, none have looked at child outcomes in a randomized design³⁷. Within the last decades, several preventive interventions and programs have emerged. Many interventions are based on a system theory, e.g., Bronfenbrenner's ecological system theory⁵³, where multiple interacting systems affect a person's development⁵⁰. Consequently, not all interventions include components for children and parents because a change in one family member could potentially positively affect the whole system around the child ⁵⁰.

In the following, I will describe some of the elements or components frequently applied to and studied in preventive interventions for children at familial risk of severe mental illness. I have restricted my search to interventions for children of parents with severe mental illness, which target the whole family and which have been tested in randomized trials, including quantitative and qualitative evaluation studies. The main components are psychoeducation, cognitive behavioural therapy, parenting advice, and peer support groups.

Psychoeducation

Educating children about parental mental illness is one of the most prominent elements in preventive interventions for this group^{37,50,52,54–56}. Psychoeducation presupposes that knowledge and understanding of parental mental illness may act as a protective factor that can help children cope, reduce internal stigmatization and feelings of guilt and responsibility, and strengthen resilience when faced with difficult periods due to the mental illness of the parent^{11,37,50,57,58}.

One of the most widely studied programs with a psychoeducational focus is the Family Talk program, developed by William Beardslee⁵⁹. The program has shown efficacy in different countries (e.g., the US, Finland and Greece ^{60,61}) and is currently being tested in Denmark⁶². Psychoeducation has been proven to be effective when addressing the whole family or parents alone (who then educate their children)^{60,61,63}. Findings from qualitative and mixed studies indicate that children feel relieved from knowledge about their parent's mental illness and perceive substantial benefits from the interventions^{57,64}. Parents described how the intervention, in some instances, would contribute to a normalization of the illness within the family⁶⁵. Psychoeducational components are often included in or combined with other components in preventive programs, e.g., with cognitive behavioural therapy-based components ^{50,52}.

A different approach to educating children about parental mental illness is through improving mental health-literacy, either online or through books, which has been perceived as effective, acceptable and cost-effective in enhancing protective factors^{4,58,66,67}.

Cognitive Behavioural Therapy

Interventions based on elements from Cognitive Behavioural Therapy (CBT) include, e.g., cognitive restructuring. They have been used for parents, children or the whole family^{37,50,52,54}. CBT-based programs for children with a familial risk of severe mental illness have been studied in group and individual settings^{37,50,52,54}. Moreover, CBT-based programs have targeted either only the parent with mental illness ⁶⁸, only the child (children > 13 years)^{69,70}, or the whole family^{71,72}. In the family-based CBT interventions, both children and parents are involved.

The most widely studied program is the manualized family group cognitive-behavioural intervention (FGBI) by Compas⁷¹. The program applies components of psychoeducation

and CBT-techniques, including sessions for parents and children alone and joint sessions. This method has shown efficacy for children, e.g., in the PRODO study in Germany^{73,74}. The parent-focused CBT-based interventions mainly focus on parenting strategies, either alone or as an add-on to the existing treatment for psychopathology^{50,52}.

Parenting

Enhancing parenting is a frequently studied component for prevention purposes in this group that targets both the risk and protective factors associated with parenting. Similar to psychoeducation and CBT-based programs, parenting components are often integrated with other elements in the same preventive program that can mediate change in preventive interventions for parents with mental illness^{32,52}. An example is the PRODO study for families with parental depression, which showed both short-term and mid-term effects of parenting on child-outcomes^{73,74}. Within parenting programs, one of the most widely used parenting programs for preventive programs is the positive parenting program (Triple P)^{37,75}.

Peer support groups

Peer support for children aims to enhance protective factors for children, such as self-esteem, coping, and prosocial behaviour skills^{48,54,76}. It has shown promising results for children at familial risk of SMI^{77,78}.

Multicomponent Interventions

Finally, while most referenced studies include more than one component, they often focus on *one* component. However, the needs of families are diverse and dynamic, i.e. they can change over time⁷⁹.

Evidence from a systematic review highlights that some families' have a need for parenting support and others a need for support for a child's early signs of vulnerability⁷⁹. The transgenerational transmission model suggests that risk and

protective factors operate at multiple levels and support the possibility of a multi-level preventive intervention. Even though practitioners, parents and children emphasize this, only a limited number of interventions consider the diversity of families by providing components tailored to each family's specific risk and protective factors ⁸⁰.

An example of such an intervention is the *Preventive Basic Care Management* intervention tested in a Dutch study by Wansink and colleagues⁸¹. The multicomponent intervention aimed to reduce risk factors and enhance protective factors by focusing on positive parenting, support coordination, strengthening families' support systems and social networks, and monitoring signs of vulnerability in children and parents⁸¹. The intervention was based on case management with the goal of assisting families in coordinating the numerous preventive and psychiatric services available to parents with mental illness and their children⁸¹.

Families were in regular contact with their case manager for a mean period of 18 months⁸¹. The intervention was compared with the effect of receiving a brochure with information about potential risks for children of parents with mental illness in a randomized clinical trial ^{81,82}. At the end-of-treatment assessment, there were no differences between groups over time on parenting skills for the experimental intervention group and no differences in child outcomes (prevention of child behavioural problems).

Complex Interventions

Multicomponent and individually tailored interventions imply a high degree of complexity and are therefore often defined as 'complex interventions'. In this thesis, complexity in an intervention is defined by the number of interacting intervention components within the intervention, the degree of individuality in intervention delivery, and the multiple ways change can be evaluated ^{83–85}. A complex intervention often seeks to induce change in different systems (e.g., at the individual, family and community levels) ⁸⁴. However, although probably no mental health intervention is a simple intervention, researchers may define an intervention as non-complex, i.e. simple, to explore a linear pathway from intervention to outcome⁸⁵.

Like 'simple' interventions, research on complex interventions is measured and evaluated by assessing efficacy, fidelity and feasibility⁸⁴. The United Kingdom's Medical Council and the National Institute of Health Research have developed a framework for developing and evaluating complex interventions⁸³.

Following this framework, complexity occurs at different levels. It starts at the design phase of the study: the formulation of the research question is typically complex itself⁸³. As a result, the research question often extends beyond efficacy and causality to address processes of change and mechanisms of change⁸³. Complex interventions emphasize the importance of theory and theoretical frameworks to operationalize change, often defined as program theories to accommodate complexity. The complexity of the design and research questions often leads to the inclusion of qualitative and mixed-methods methodologies⁸³. Including both qualitative and quantitative methods and integrating their results enhances the understanding of the underlying mechanisms that lead to change in people in complex interventions⁸⁶.

Following the transgenerational model of transmission of mental illness, preventive interventions that aim to reduce modifiable risk factors and enhance modifiable protective factors might need to operate at various levels, depending on the specific needs of the family or child in question. This calls for preventive interventions with multiple components tailored to the individual needs of the specific child and the rest of the family.

Mechanisms of Change in Preventive Interventions

The study of mechanisms of change is the study of processes through which an intervention operates to bring about a change in an outcome⁸⁷. Mechanisms of change are the time-causal relationship between intervention components and change - they extend beyond mediators and moderators^{83,88}. Due to methodological restrictions, the first step in quantitative analyses in identifying mechanisms of change is often through moderators and mediators^{87,88}. Qualitative researchers commonly define mechanisms of

change as underlying processes or factors that trigger change through engagement in the interventions and thereby contribute to change⁸⁹. In this thesis, I define mechanisms of change as *contextual mechanisms that interact with the intervention to bring about change*^{89,90}.

Evidence of possible mechanisms of change in mental health prevention for children at familial risk for severe mental illness is scarce^{50–52,74}.

In quantitative studies, mechanisms of change have mostly been studied through mediators and moderators⁸⁶. The most prominent findings of mediators are specific intervention components as underlying mechanisms leading to a treatment effect^{52,74,91}. For example, cognitive problem-solving and negative parenting in cognitive behavioural therapy mediate the effect of family-based interventions for children at familial risk for depression^{74,91}.

Qualitative studies of mechanisms of change have investigated participants' own understanding of processes enabling change. Findings suggest that, e.g., building parental agency acted as a mechanism to bring about change in parenting⁹².

Despite rigorous research in the broader field of psychotherapeutic interventions for children, there is no empirical evidence of specific mechanisms of change⁹³. However, there are findings of mediators and moderators of change after psychotherapy for children and adolescents, which can inform the study of mechanisms of change⁸⁷. A review from 2023 identified changes in family functioning, parenting skills, and successful engagement in therapy activities as the most promising mediators for future studies of mechanisms of change in psychotherapy for adolescents⁸⁷. Successful child engagement is likewise of interest, both within the field of family-based therapies and family-based preventive interventions, as it presupposes parent engagement. Given the complexity of the transgenerational transmission model, multiple mechanisms of change presumably operate across various levels. Identifying different mechanisms of change can enhance the understanding of how an intervention brings about change for different people in different contexts and how it can improve interventions^{52,56,92}.

Aims and Objectives

Objectives of this Thesis

The aim of this thesis is to investigate the impact of a preventive family-based intervention, VIA Family, on children whose parents have a severe mental illness. The thesis is based on three sequentially separated studies.

Study 1 - Aim and Hypotheses

The aim of the first study was to explore the effect of VIA Family compared with treatment as usual for the participating children⁹⁴. The study reports the effect of a randomized clinical trial, VIA Family, on differences in children's outcomes between allocation groups at post-intervention ⁹⁴.

The hypothesis was that VIA Family was superior to treatment as usual to a) improve children's global functioning (Children's Global Assessment Scale (CGAS))⁹⁵, primary outcome ⁹⁴) and b) reduce signs of risk and early vulnerability for mental illness in the participating children⁹⁴.

Study 2- Aim and Research Question

The aim of the second study was to explore mechanisms of change associated with participation in VIA Family intervention. We aimed to explore if, how and when participating children and their parents experienced change when engaged in the experimental intervention in a qualitative study. The study generated data from focus group discussions with a subsample of families participating in the VIA Family intervention.

The research question was: *What mechanisms of change, if any, did participants experience within the intervention?*

Study 3- Aim and Hypothesis

The aim of the third study was to identify a variable and conduct a subgroup analysis based on the findings from Study 2 (participants' description of change).

We hypothesized that, within the VIA Family group, children subgrouped along a variable that most closely aligns to a 'need for support' subgroup would show greater improvements in global functioning (CGAS, primary outcome in VIA Family trial⁹⁴) and a higher increase in levels of support and stimulation in the home environment (HOME, secondary outcome in VIA Family trial⁹⁴) compared to children in the 'contributing to science' subgroup from baseline to the end of the intervention. The variable defining 'need for support' or 'contributing to science' was based on a baseline interview on motivation for participation with children's primary caregivers in the VIA Family trial. Studies 2 and 3 were conducted in a sequential mixed methods design and prepared for publication within the same manuscript.

Methods

The VIA Family trial

The background of this thesis is the VIA Family trial that we conducted in the Capital Region of Denmark between 2017 and 2021.

The trial had a two-armed and randomized design to test for superiority of the experimental intervention, VIA Family, over treatment as usual^{94,96}. The allocation ratio of the groups was 1:1, solely stratified for parents' severe mental illness diagnoses⁹⁴. At baseline and at the end of the intervention (after 18 months), we assessed and analysed data blinded to allocation and allocation sequence⁹⁴. Before data collection ended, we published a trial protocol⁹⁴ (see supplementary material S1) and registered the trial at clinicaltrials.gov (NCT03497663).

We gained ethical approval for the trial by the Danish Regional Committee for Health Research Ethics in the Capital Region of Denmark (Approval number H-17000450)⁹⁴.

The Danish Data Protection Agency approved the trials' compliance with rules for protecting personal data⁹⁴.

Trial outcomes at end-of-treatment constitute study 1.

Sequential mixed methods study

To explore participants' experiences within the VIA Family intervention, we did a qualitative study with a subgroup of children and parents in the VIA Family group in parallel with the trial. We sequentially collected, analysed, and integrated qualitative data for Study 2. Then, we used the findings of Study 2 to conduct a subgroup analysis on secondary data from the VIA Family trial.

The findings of Studies 2 and 3 explore possible mechanisms of change within VIA Family with a sequential mixed methods approach⁹⁷. The premise of mixed methods is

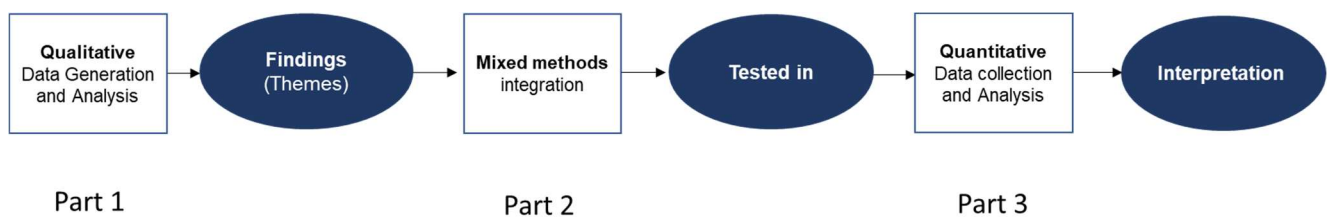
that the combination of quantitative and qualitative data and methods increases insight into the research problem beyond what each method can provide independently⁹⁷. In addition, this integration enables exploring pathways and underlying mechanisms by which an intervention will generate outcomes^{84,86}. This is especially valuable for complex interventions which operate in complex systems^{83,86,98,99}.

Consequently, a mixed methods approach provides great potential for complex intervention research to explore the efficacy and underlying mechanisms of the effect^{83,86}. In complex intervention research, applying mixed methods may enhance the ability to explain the results, help refine interventions and assist in implementing interventions^{86,98}.

Sequential exploratory design

A sequential design in mixed methods is a sequence of several study parts, i.e. sub-studies. Results from one part inform the next (see Figure 2). A sequential design is often used to explore a new or unknown phenomenon or inform a new variable⁹⁷.

Figure 2. *The Exploratory Sequential Design (Adapted from Creswell & Plano Clark (2018)⁹⁷)*



The exploratory design starts with a qualitative study (see Figure 2)⁹⁷. Commonly, this is the most emphasized part because the exploratory design aims to *explore* the unknown⁹⁷. Thus, in this part, the researcher intends to investigate the depth, context and meaning of how people experience and engage in their world. The next part is a mixed-method integration, where the qualitative findings inform the following quantitative part (see Figure 2). The mixed methods integration part (part 2 in Figure 2)

aims to develop a quantitative measure, typically an intervention, questionnaire or a new variable, rooted in the findings of thoughts and meanings of participants ⁹⁷. The last part (part 3) is, typically, a quantitative study testing for feasibility, validity or efficacy⁹⁷. Since quantitative research relies on variables to measure and analyse relationships in data, prior identification of meaningful variables is crucial in quantitative research.

Study 2 constituted the initial part of the sequential mixed methods study. Here, we explored participants' experiences of potential mechanisms of change within the intervention. Building upon the findings from study 2, we formulated a hypothesis and introduced a novel variable (part 2), which we explored quantitatively in study 3. The final part included subgroup analysis, exploring the hypothesis that intervention effects significantly differed among subgroups defined by the novel variable.

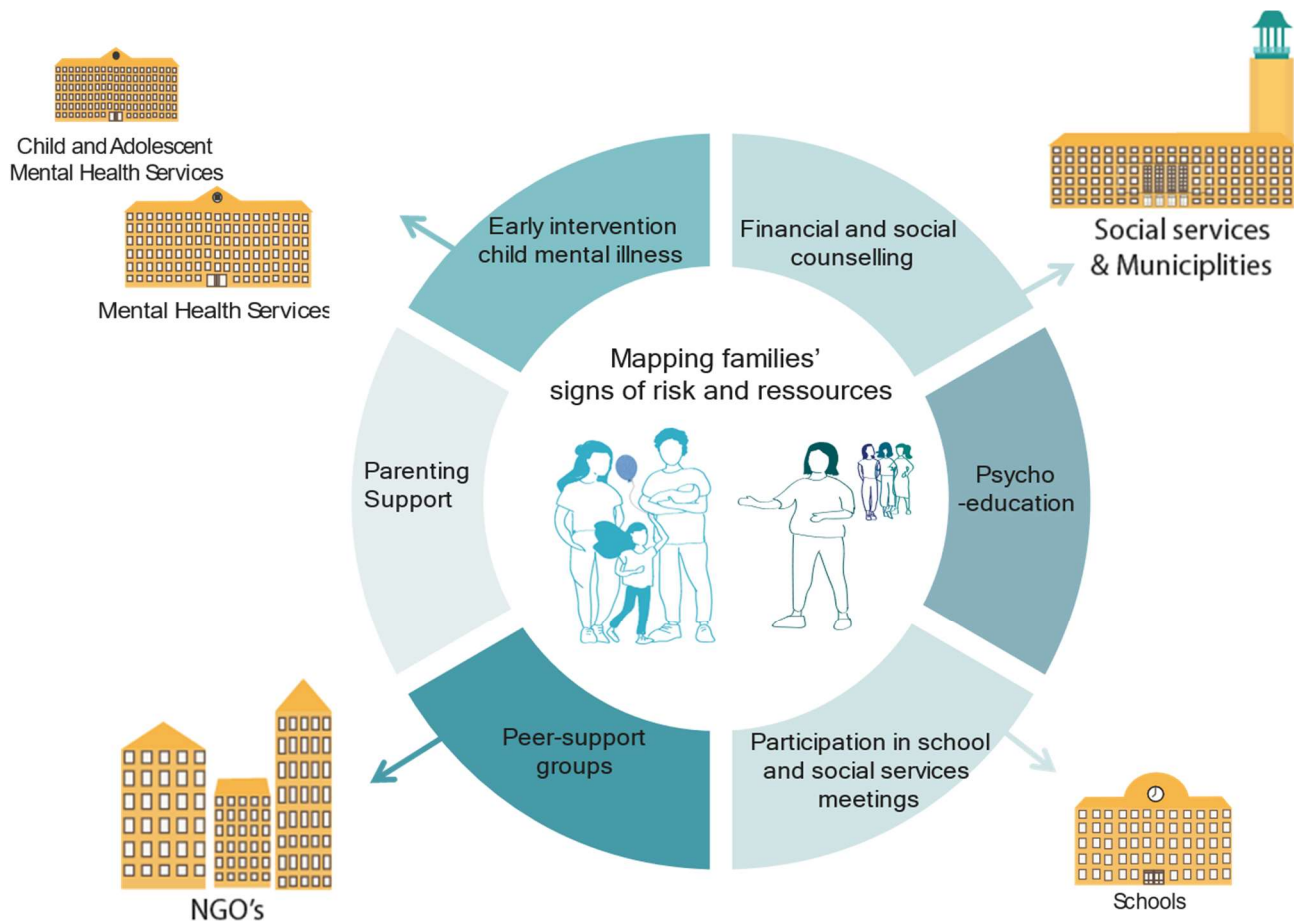
Interventions

VIA Family intervention

VIA Family was a family-based intervention aiming to enhance children's protective factors and reduce early signs of vulnerability and modifiable risk factors (see Figure 1) ⁹⁴. A multidisciplinary team supported parents and their children with their individual needs. Moreover, if indicated, the team identified relevant support within usual care and referred families to them ⁹⁴. Families were involved in the intervention for 18 months to facilitate transformative changes, which can take time⁹⁴.

The intervention aimed to address the individual needs of the family and the multiple risk and protective factors. Consequently, VIA Family was a multicomponent intervention but individually-delivered and flexible⁹⁴.

Figure 3. VIA Family was a family-based intervention centred around case-management and multiple components tailored to the individual families' needs. (Part of Figure 1 in Paper 1)



The intervention team

To address the diverse needs of the family, VIA Family involved a multidisciplinary service delivery team offering family-centred case-management. The team consisted of a social worker, a family therapist, a psychologist, and a nurse⁹⁴. All four team members had extensive experiences with child and adolescent mental health services, adult mental health services or social services⁹⁴. Team members had weekly meetings to profit from each other's multidisciplinary experiences and expertise. Moreover, the team received regularly specialized supervision and counselling by, e.g., a child and adolescence psychiatrist.

Each family was assigned a case-manager. However, based on the individual needs of the family (and each family member), the families could work with several team-members aside from their case-manager.

Multiple components

All components were chosen due to their theoretical assumption to decrease the impact of risk factors or decrease those that are modifiable and increase modifiable protective factors. All families received the introductory sessions with *basic components* followed by additional *optional components*.

The aim of the introductory sessions, which included the basic components, was to determine which components were suitable and acceptable for the individual family. Moreover, the aim was to build an alliance. Basic components were psychoeducation about parental mental illness or, in the case the family did not want disclosure on parental diagnosis, psychoeducation about family members' ways of communicating and recognizing each other's feelings. Additionally, basic components included *mapping signs of resources and risk* in the family (including each child) and creating a *family lifeline* to illustrate families' perceptions of how parental mental illness affects each family member. Introductory sessions varied between three and eight sessions.

Next, a flexible and tailored approach followed the initial core elements. Here, families could choose from a variety of components based on their motivation, relevance and dialogue with their case manager (see Figure 1 for illustration of some of the components).

Peer-support groups. Children, adolescents and parents could participate in peer-support groups. The groups were led by two team-members and based on principles of peer support, where children meet and exchange experiences with other children who are in a similar situation (having a parent with a SMI)⁸⁰. Each group met for seven sessions.

Support children with mental health problems. Children and parents could get advice or support for transient mental health problems, e.g., anxiety symptoms, stress

reactions or (children's) psychotic-like experiences. However, a family member's potential treatment for a mental health condition in the mental health services the treatment continued in the mental health services. The psychologist could screen and assess symptoms of mental illness (e.g., Autism Spectrum Disorder) and assist with transfer to the relevant mental health services. Moreover, the case-manager would help families to contact private psychologists or psychiatrists.

Parenting support. Parenting support was based on the Positive Parenting Program (Triple P)⁷⁵. All team-members were trained in Triple P levels 2, 4 (standard), and 5, and in Stepping Stones¹⁰⁰ (for families where the child has some kind of developmental impairment). If parents asked for parenting advice but did not want to participate in the Triple P group sessions, their case manager could offer individual parenting support sessions.

Financial, Legal and Social Counselling: Families could get counselling on what financial, legal and social support is available within usual care (i.e., social services or NGOs). For example, the social worker would help families apply for financial support, which they were entitled to. Moreover, if indicated, all team-members referred children in need to social services or child protection services (see S2 supplementary material for the number of referrals).

Participation in meetings with school or social services: Team members could facilitate or participate as support persons in meetings with, e.g., the school, social services or the job centre.

Other optional components: Team-members' expertise and experience supported families with optional components, e.g., mapping a safety plan for the family, optimization of the lifestyle of the ill-parent, and mental health treatment.

Families decided with their case-manager which components of the intervention were suitable and relevant for them and matched their motivation. The family also decided who would participate, e.g., parents could participate without their children. Nevertheless, the case manager would encourage the family to get all family members involved in some way.

The intervention delivery was flexible. This means that families could meet with the case-manager or the team members at home, in the off-clinic rooms of VIA Family or in other places (e.g., a park or playground). Furthermore, the case-managers were in contact with the families through physical meetings, mail, text messages, and phone- and videocalls. However, all intervention components were offered in person.

Treatment adherence

Adherence to the intervention was defined as having a minimum of 15 interactions with the case-manager and the intervention team over the 18-month intervention period. This criterion included a prerequisite for at least 8 face-to-face meetings, active participation in the initial sessions, and involvement in a minimum of 2 additional components⁹⁴. The intervention team registered all interactions with enrolled families in the REDCap system^{94,101}. We conducted a preliminary pilot test of the intervention elements in a limited sample before the commencement of the study⁹⁴.

Treatment as Usual

To explore the effect of VIA Family, we compared the exploratory intervention with usual care.

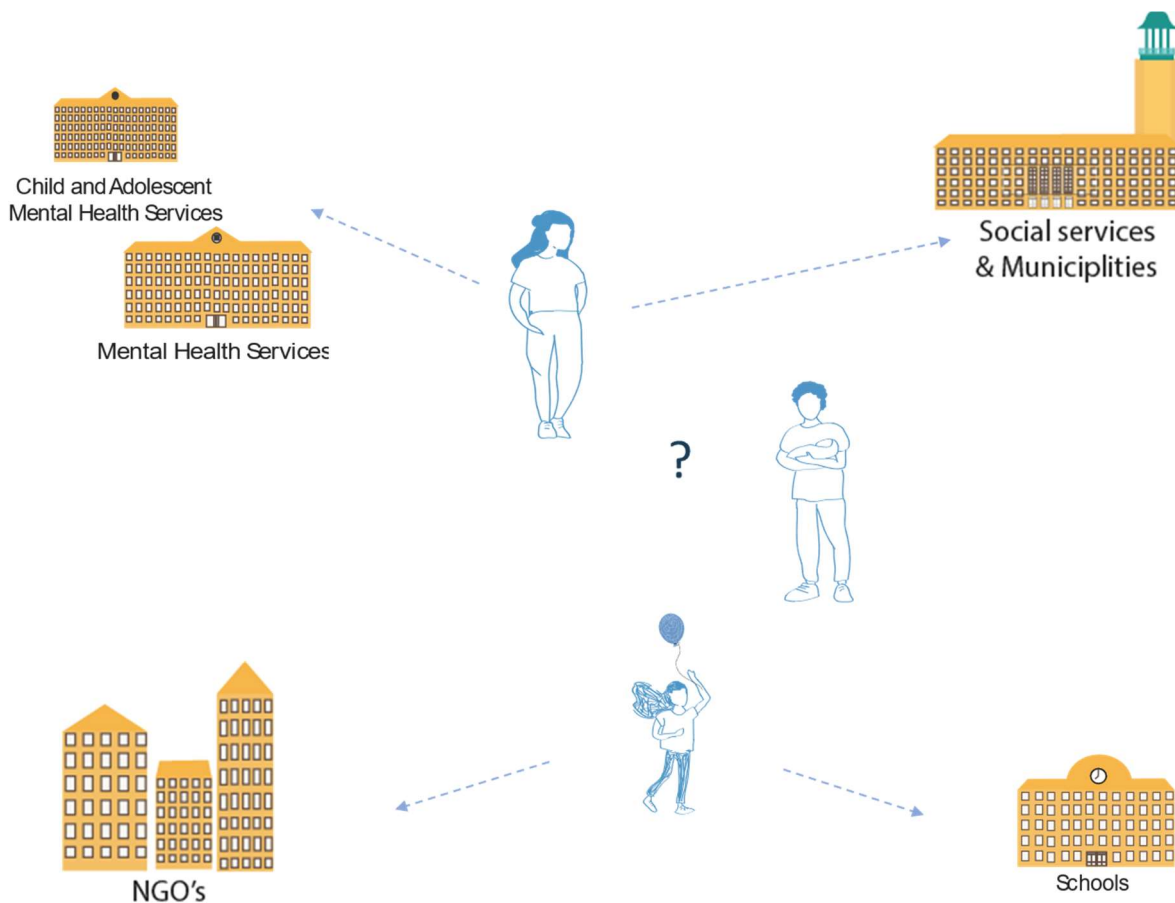
Notably, at the time of the study, there was no coordinated support for families with children with a familial risk for severe mental illnesses within the catchment area (see also an introduction on usual care in Denmark)(see Figure 4). Families with parental severe mental illness who were in psychiatric treatment could be offered a family

meeting. If families were in need of financial or social support, the social services within the municipalities were responsible for offering it.

Significantly, there was a lack of coordination of the support between adult mental health services, child and adolescent mental health services, and social services.

Additionally, none of the support services offered by the centres and the social services considered the specific needs of families with children at familial risk of severe mental illness.

Figure 4. Usual care for children with familial high-risk is often fragmented and individualized (Part of Figure 1 in Study 1)



Participants and recruitment

Study 1

Participants

The trial included families with at least one parent diagnosed with severe mental illness and at least one child between 6 and 12 years⁹⁴. Moreover, eligible parents must have been in contact with the secondary sector of public mental health services in Denmark in relation to their severe mental illness diagnoses at least once from one year before their child was born to present-day ⁹⁴.

In the research setting, we named the eligible parent with a severe mental illness diagnosis and a child within the eligible age range and address: 'Index-parent'. In the cases where there was more than one parent, we called the other parent 'other-parent'. The other-parent could also have a severe mental illness diagnosis. The Index parent was then defined as the parent who appeared first on our recruitment list of possible participants.

We defined a severe mental illness diagnosis as having either schizophrenia spectrum, bipolar disorder, or recurrent major depression⁹⁴. We used the ICD-10 and ICD-8 codes as inclusion criteria: Schizophrenia Spectrum Disorder: ICD-10: F20, F21, F22, or F25, or ICD-8: 295, 297, 298.29, 298.39, 298.89, 298.99, or 301.83. Bipolar Affective Disorder: ICD-10: F30 or F31, or ICD-8: 296.19 or 296.39. Recurrent Major Depressive Disorder: ICD-10: F33.1, F33.2 or F33.3, or ICD-8: 296.0, 298.0 or 300.4. All diagnoses were confirmed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)¹⁰². In the rare case where it was not possible to conduct a diagnostic interview, we asked for access to the parent's health records for retrospective confirmation of inclusion diagnosis and time⁹⁴.

Eligible children had to live with at least one of their biological parents⁹⁴.

At the beginning of the recruitment period, we restricted the catchment area to the municipality of Frederiksberg in the Capital Region of Denmark⁹⁴. Later, we expanded the geographical catchment area to include more municipalities because we were not able to contact as many participants as initially anticipated. All the areas were within the inclusion area of the Mental Health Services of Copenhagen (Psykiatrisk Center København, Frederiksberg and Amager).

Recruitment

We used two strategies for recruitment:

First, we used data from the Danish registries to contact eligible families⁹⁴. We used data from a) the Civil Registration System¹⁰³ (data on a person's address and their children, including age of children) that were linked with data from b) the Danish National Patient Register for Psychiatry¹⁰⁴ (data on treatment in the public mental health services) and linked with data from c) the Danish Psychiatric Central Research Register¹⁰⁴.

We sent a physical and an electronic letter of invitation to the Index parent's registered home address and their digital mailbox (e-boks)⁹⁴. The first contact was with the Index parent. With their permission, we contacted the other parent with a letter of invitation⁹⁴. If possible, we obtained their phone number through online phone registries (e.g., www.118.dk) and contacted them by phone.

Second, we contacted relevant mental health services and social services to inform them of our study⁹⁴. We held information meetings for employees and their leaders and handed out recruitment material. If they identified an eligible and interested parent, they obtained informed consent for the research team to contact the parent.

We invited all interested parents to an information meeting where we informed them about the aim of the project, their legal rights as research participants, and that they could be informed about the outcomes of the child's assessment if they wished to. If families were interested, the parents signed written informed consent for their own participation⁹⁴. Caregivers signed written consent for their children's participation⁹⁴. Next, we invited them for eligible screening.

Study 2

Participants

The sample for the qualitative analysis consisted of a sub-group of parents and children randomized to the VIA Family intervention.

Inclusion criteria for participation in the substudy were: 1) having recent experience with participation in different elements from the VIA Family intervention and 2) participants were familiar with members in their focus group (i.e., from the same peer support groups). Due to inclusion criteria, we used a purposive sampling method¹⁰⁵. We aimed to include both Index-parents, co-parents, and mothers and fathers in the adult sample. Moreover, we aimed to balance the children sample regarding age and gender. Nevertheless, these were not inclusion criteria.

Recruitment

We invited all families currently participating or recently completing the intervention (within the last 4 weeks) in the VIA Family intervention. However, social gathering restrictions during the COVID-19 pandemic at the time of data collection constrained our inclusion of participants. Hence, we only invited participants for focus groups who were currently in social contact with each other through participating in the same support groups (11 children and 12 parents). The research team (ADM and IG) and two graduate students of anthropology (SKJ and KF) jointly developed an invitation letter, which the VIA Family team distributed to all eligible families (see Paper 2, page 139 for description of initials). Parents and children interested in participating were then contacted by SKJ and KF and orally informed about the study and their rights as study participants. All parents signed consent for their participation and their children's participation. Each family member received a gift card (30 US\$) for participation.

All invited participants accepted the invitation. However, three children and two parents were not able to join the interview due to COVID-19 restrictions. Therefore, we included eight parents (three/five parents per focus group, respectively) and their eight children (four children per focus group) in the focus group. Within the parents' focus groups, five participants were mothers, and three participants had a mental illness diagnosis. In

one of the groups, two parents from the same family participated. Within the children's focus groups, children were aged 8 – 14 years, and five children identified as female. In one group, two siblings from the same family participated. We pseudonymize all names in the results section.

Study 3

Participants

We used secondary data from the VIA Family trial for the quantitative analysis. All participants from the VIA Family trial were eligible for inclusion. We only excluded participants with no data on motivation for participation at baseline. Consequently, we excluded children of families who did not give a reason for their motivation to participate (n= 3).

Measures and Procedures

Study 1 – Data Collection and Measures

Procedures and informants

We included multiple informants in the trial to describe the participating children's well-being and signs of risk and protective factors: all eligible children from a family (i.e., including siblings within the eligible age range), their index parent, their primary caregiver and their schoolteachers⁹⁴. The child's parents decided who the child's primary caregiver was in collaboration with the researchers. The primary caregiver could be the index or the other parent. Further, we asked all families for consent to contact the child's/children's primary teacher for information on signs of risk and protective factors⁹⁴. Parents decided who was to be labelled primary teacher. Furthermore, we gained information on absence from school from the municipalities or, when children went to private schools, directly from the children's schools⁹⁴.

All children and their parents were assessed at the research site at Frederiksberg Hospital and in their homes. Parents could answer the questionnaires online (using the electronic data system RedCap¹⁰¹) or in a hard copy version. With the parents' consent, we sent questionnaires to the schoolteachers by email or in hard copy. Due to the youngest children's lack of reading proficiency and to ensure consistency in the procedures, the researcher read aloud and registered the answers from the children's questionnaires⁹⁴.

The assessment team consisted of psychologists, a child and adolescent psychiatrist, a nurse, an anthropologist, and psychology students. The psychologists were the only ones to conduct diagnostic interviews. All assessors had prior relevant training and received relevant regular supervision from specialists in child and adolescent psychiatry and a specialist in clinical child psychology ⁹⁴.

Measures

We collected data at two time points: at baseline, i.e. inclusion into the study, and after 18 months, i.e. end-of-treatment⁹⁴.

Assessments at baseline only

Baseline assessment included a structured sociodemographic interview with the child's primary caregiver and a short neurocognitive screening of all children (see Figure 5 for all measures at baseline assessment) ⁹⁴.

Assessment of change from baseline to end-of-intervention

At baseline and after 18 months of intervention, we assessed all children and their primary caregivers with various measures. See Figure 6 for an overview of primary and secondary outcome measures and Figure 7 for exploratory outcome measures.

We gathered information on service use in usual care for both groups through data from the municipalities for the use of service 6 months before study entry and during the whole study period (18 months). Additionally, we collected parental reports of service use in mental health centres, social services, and the private sector at both timepoints (6 months before study entry and 6 months before study endpoint).

Figure 5. Measures at baseline assessment (Figure 2- Paper 1)

Variable &References	Instrument
Family and Child Sociodemographic Information	
Demography and family relations Interview data <i>The guide was adapted from a demographic interview in a study on children at risk from parents with schizophrenia and bipolar disorder (VIA 11)¹⁰⁶.</i>	Semi-structured interview <i>The interview covered themes around the child, the caregivers and the family:</i> 1. <i>Child's primary caregiver</i> 2. <i>Sociodemographic information about the family</i> 3. <i>Significant events during child's life (such as divorce, family members mental health problems)</i> 4. <i>Significant events during the primary caregiver's childhood</i> 5. <i>Child's early development: motoric, language, social</i> 6. <i>Child's psychosocial functioning</i> 7. <i>Disclosure of parental mental illness and motivation for participation</i>
Quality of the home environment Caldwell & Bradley ¹⁰⁷	Home Observation for Measurement of the Environment (HOME) <i>A semi-structured interview and observation measure to rate the quality and quantity of a stimulating and supportive home environment that is available to a child. The interview is in a natural setting at the child's home with the child and the primary caregiver present. We used the version for middle childhood and early adolescence.</i>
Family functioning Epstein & Bishop (1983) ¹⁰⁸	Family Assessment Device (FAD) <i>A 60-item questionnaire that measures family members' perceptions of their family. All caregivers completed the questionnaire. We assessed the general family functioning scale. It is based on the McMaster model of family functioning.</i>
Children's neurocognitive functioning	
Estimate of General Intelligence Reynolds & Kamphaus (2003) ¹⁰⁹	Reynolds Intellectual Screening Test (RIST) <i>Brief screening tool for an estimate of a child's general intelligence. The test consists of two subtests: verbal and non-verbal intelligence. We used standardized scores based on age and sex using Danish norms.</i>
Verbal memory (Immediate and delayed) Reynolds & Voress (2007) ¹¹⁰	Test of Memory and Learning (TOMAL), 2 nd Edition (Memory of Stories) <i>Test to measure immediate and delayed verbal memory. We used standardized scores based on age and sex using US norms.</i>
Processing speed Wechsler (2003) ¹¹¹	Coding subtest from Wechsler Intelligence Scale for Children, 4 th Edition (WISC-IV) <i>Test to measure processing speed. We used standardized scores based on age and sex based on a Danish population.</i>
Visual memory Meyers & Meyers (1995) ¹¹²	Rey Complex Figure Test and Recognition Trial (RCFT) <i>We used T-scores based on age and sex on norms from a US sample.</i>

Figure 5 - continued. Measures at baseline assessment (Figure 2- Paper 1)

Variable &References	Instrument
Children's mental health	
Symptoms of mental illness, present and lifetime Kaufman et al (1997) ¹¹³	Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime (KSADS-PL) <i>A semi-structured diagnostic interview of current (within the last eight weeks) and past psychotic, mood, anxiety, disruptive behaviour disorder, neurodevelopmental and autistic symptoms in children. The interview is suitable for children aged 6-18 years. Parents and children are interviewed separately. Diagnoses were for research purposes only and were validated by a psychiatrist.</i>
The severity of autism spectrum symptoms Constantino and Gruber (2012) ¹¹⁴	Social Responsiveness Scale, 2 nd Edition (SRS-2) <i>Parents and teachers rated the survey with 65-items measuring autism spectrum symptoms. Higher scores indicate more severity of symptoms of autism spectrum</i>
Parent's mental health and well-being	
Diagnosis of severe mental illness or substance misuse, lifetime Wing (1990) ¹⁰²	Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1 (SCAN) <i>Semi-structured interview measuring psychopathology. We used subscales to measure symptoms of schizophrenia, mood disorders and substance misuse, present state and lifetime. Diagnoses were for research purposes only and were validated by a psychiatrist.</i>
General functioning Morosini(2000) ¹¹⁵	Personal and Social Performance Scale (PSP) <i>Semi-structured interview measuring general functioning based on four domains: socially useful activities, personal and social relationships, self-care, and disturbing/aggressive behaviour.¹</i>
Parental Stress Berry & Jones (1995) ¹¹⁶	Parental Stress Scale (PSS) <i>An 18-item questionnaire measuring primary caregivers' emotions and experiences of positive and negative aspects of parenthood.</i>

Figure 6: Primary and Secondary Outcomes (Figure 2-Paper 1)

Variable & Instrument	Descriptions
Primary outcome	
Global functioning <i>Shaffer(1987)⁹⁵</i>	Children's Global Assessment Scale (CGAS) <i>Semi-structured interview with child and their primary caregiver (separately) measuring the child's psychosocial functioning. It has a scale from 1-100 to estimate a child's lowest functioning based on their functioning at school, with their family and with their peers within the last month. Lower scores signify lower functioning. CGAS has been developed for use in psychiatric clinical samples: measuring the functional impact of mental illness symptoms. In clinical populations, it has shown good validity if used correctly¹¹⁷. Moreover, a study of a Swedish clinical sample has also shown abilities to predict for future referrals to mental health services¹¹⁸. However, the psychometric properties in children without mental illness symptoms has not been studied. We collectively rated child's lowest functioning within the last month using all available information (from home visit, child interview and parent interview).</i>
Secondary outcomes	
Emotional and behavioural symptoms <i>Achenbach & Rescorla (2001)¹¹⁹</i>	Achenbach System of Empirically Based Assessment (ASEBA). <i>Child Behavior Checklist (CBCL) and Teachers Report Form (TRF). Total score, internalizing and externalizing symptoms. higher score: more symptoms (Danish norms)</i> <i>113-items primary caregiver rated (CBCL) and teacher rated (TRF) questionnaire. Scale from 3-236. higher score: more symptoms</i> <i>We used Danish norms for comparison across age and biological sex.</i>
High absence from school <i>Data from municipalities and/or schools</i>	≥ 15% days absence from school. Data obtained from municipality or school

Figure 7. Exploratory Outcomes (Figure 2-Paper 1)

Variable, Instrument and Reference	Descriptions
Parent and Teacher-reported outcomes	
Executive functioning Behavior Rating Inventory of Executive Function (BRIEF), Gioia et al. (2000) ¹²⁰	BRIEF assesses behaviour associated with executive functioning. We used the parent- and Teacher-reported forms of the 86-item questionnaire on behaviours at home and school. It has shown good reliability ¹²⁰ . We used US norms to compute a T-score of the total problem score. A higher score signifies more problems with executive functioning.
Affective lability Children's Affective Liability Scale (CALS), Gerson et al. (1996) ¹²¹	CALS assesses affective lability in children with a 20-item questionnaire. We used the parent-report version. The questionnaire was translated into Danish and then back-translated into English by the assessment team. We asked the authors of the scale to approve the translations. However, we were not able to get approval from the authors of CALS. We derived a total score for problems with affective lability using the methods from a former study ¹²² .
Emotion regulation Emotion Regulation Checklist (ERC) Shields and Cicchetti (1997) ¹²³	ERC measures adaptive and maladaptive emotion regulation on a 24-item questionnaire. We asked parents and schoolteachers to complete the form. We used the total score. The total score serves as an indicator of children's adaptive emotion regulation, where high scores signify better adaptive emotion regulation, while lower scores signify challenges in regulating emotions. The questionnaire was translated into Danish by the assessment team and back-translated into English. The authors approved the translation of the ERC.
Strengths and difficulties with mental health Strength and Difficulties Questionnaire (SDQ) – Danish version, Obel et al. (2003) ¹²⁴	SDQ measures strengths and difficulties with children's health. We used parent- and teacher-report forms of the 25-item questionnaire. The total problem score is derived by the sum of the four negative subscales (conduct problems, peer problems, emotional problems and hyperactivity) ¹²⁴ . Higher scores signify more difficulties. We used raw scores since no norm scores for the same age were available, and data were evenly distributed across both allocation groups.
Symptoms of ADHD Attention Deficit Hyperactivity Disorder- Rating Scale (ADHD-RS), DuPaul et al. (1998) ¹²⁵	ADHD-RS is a 26-item questionnaire assessing symptoms of attention deficit hyperactivity disorder ADHD (inattention, hyperactivity and impulsivity, and oppositional and defiant symptoms. Higher scores signify more symptoms. We asked parents and teachers to answer the questionnaire. We calculated a T-score of total ADHD score based on a Danish norm sample from 2009. ¹²⁶
Sleep-related problems Interview data	Structured interviews with parents on their children's sleep-related problems. Sleep problems were measured as dichotomous outcomes (yes/no) based on four questions and scoring from 1-4. Higher scores show more sleep-related problems.

Figure 7-continued. *Exploratory Outcomes (Figure 2-Paper 1)*

Variable, Instrument and Reference	Descriptions
Child self-reported outcomes	
Social-ecological resilience Child Youth Resilience Measure (CYRM), Liebenberg et al. (2013) ¹²⁷	<i>CYRM</i> assesses how many resilience-enhancing resources are available to a child. We used the child and youth 12-item version of <i>CYRM</i> . <i>CYRM</i> has a 3-point Likert scale for children and a 5-point Likert scale for youth. Higher scores signify more resilience resources.
Self-esteem This Is Me (TIM), Suonpää et al (1989) ¹²⁸	We used the child (32 items) and youth version (72 items) of the TIM. Higher scores reflect more self-esteem, including social relations and feelings of competence. A total score was derived from the five subscales. We used norm data from a Danish population (from 2006) to compute Stanine scores based on age and sex differences ¹²⁸ .
Health-related quality of life KIDSCREEN-52 Ravens-Sieberer (2005) ¹²⁹	<i>KIDSCREEN</i> assesses health-related quality of life. Children answered the 52-item version, but we only used the total score derived from 10 items (from the KIDSCREEN-10). Higher scores indicate more well-being. We used norms of a European sample to calculate T-scores based on age and sex differences ¹³⁰ .
Childhood trauma Childhood Trauma Screener (CTS), Grabe et al. (2012) ¹³¹	<i>CTS</i> is a short 5-item questionnaire assessing childhood trauma. Higher scores indicate more reported traumatic events.

Study 2 - Data collection and generation

Focus group

We used focus group discussions with children and parents separately to collect data for part 1.

Focus group discussions can bring participants' experiences, attitudes and perceptions of a research subject to light¹³². The advantage is that we can get multiple viewpoints and experiences on the same research topic. However, especially with children, the disadvantage of focus group discussions can be that participants feel obliged to agree on the most prominent experience or opinion within the group. We tried to overcome this by only including children who already knew each other. Studies have shown that children prefer sharing thoughts, opinions and experiences with children they know rather than strangers¹⁰⁵.

Two anthropology graduate students (SKJ and KF) moderated the focus group discussions. The students were involved in the VIA Family study for their master project and had previously interviewed VIA Family researchers and team members. Apart from that, they were not involved in the trial or intervention design. They were unfamiliar with the interviewees before the sessions. Two students of psychology (student assistants from the research group) assisted in the children's focus groups, as recommended in the literature ¹⁰⁵.

We used a semi-structured discussion guide to facilitate the focus-group discussion with themes relevant to the research question (see S3 supplementary material). The interview themes explored aspects of the participants' experiences within the VIA Family program - both positive and negative. Additionally, the interviews delved into the experiences of parents and children regarding changes they attributed to involvement in the intervention.

In the focus groups of children and parent focus groups, we used icebreaker activities to the necessary degree, considering that the participants already knew each other from the support groups¹⁰⁵. The focus group method is an act of social sharing amongst the participants¹³². Therefore, it is crucial for a focus group that participants feel safe to

share their experiences and opinions¹⁰⁵. In children's focus groups, we used participatory methods, such as drawing, moving around and using picture prompts¹³³. Such activities can help some children to express themselves and engage them in the discussion^{105,133}. We provided snacks and pauses to help children concentrate. The moderators audio-recorded the discussions and transcribed the complete sessions using NVivo¹³⁴ into Microsoft Word files. Transcriptions were verbatim, including some details such as unfinished words, pauses, gesticulation, and social expressions (e.g., nodding to express agreement or laughter). We developed themes in the native language (Danish) to diminish the loss of culturally specific meanings and contexts in the data.

Setting

We conducted the focus group discussions on two weekend mornings in the off-clinic rooms of the VIA Family intervention site. The moderators facilitated discussions of children and parents in parallel sessions in separate rooms, which were familiar to the participants. The discussion lasted for approximately 1-1.5 hours, including breaks.

Study 3 - Data and measures

We used secondary data from the VIA Family trial⁹⁴. Figure 8 provides an overview of the measures used in this study. Figure 5 in Study 1 (pages 34-38) describe the measures more thoroughly.

Figure 8. Measures for subgroup analysis in Study 3 (secondary data from the VIA Family trial ⁹⁴)

Variable	Instrument	Reference
Baseline Assessment		
Demography and motivation for participation at baseline	Semi-structured interview	Interview data
Child's Behavioural and Emotional symptoms at baseline (parent-reported)	Child Behavior Checklist (CBCL). Total score, internalizing and externalizing symptoms. Higher scores, more symptoms	Achenbach (1999) ¹³⁵
Primary caregiver's diagnosis of severe mental illness or substance misuse, lifetime	Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1 (SCAN) (subscales of schizophrenia spectrum, mood disorders and substance misuse, present state and lifetime)	Wing (1990) ¹⁰²
Primary caregiver's general functioning at baseline	Personal and Social Performance Scale (PSP)	Morosini ¹¹⁵
Quality of the home environment	Home Observation for Measurement of the Environment (HOME)	Caldwell & Bradley ¹⁰⁷
Data from baseline and post-intervention assessment		
Child's Global Functioning	Children's Global Assessment Scale (CGAS)	Shaffer et al, 1983 ⁹⁵

Analyses

Study 1 - Statistical analyses

The study aimed to measure the difference in change over time between children allocated to the VIA Family group compared with children allocated to treatment as usual^{94,96}. We analysed and interpreted data blinded to the allocation group and sequence⁹⁴. Before the end of the data collection, we wrote and uploaded a statistical analysis plan attached to the trial registration at clinicaltrials.gov⁹⁶.

We used the primary outcome, global functioning (Children's Children's Global Assessment Scale, CGAS), for the power calculation of the sample size^{94,96}. With the use of a t-test, we determined that we would need a sample size of 37 children in each group to detect a significant difference of 10-point change, with a power of 0.90^{94,96}. Notably, we regard a 10-point change in the CGAS as a substantial clinical effect in our study^{94,96}. The difference of 10 points in the CGAS was based on results from a study on global functioning in 7-year-old children of parents with schizophrenia or bipolar disorder compared with children of parents not affected by these diagnoses¹³⁶. The estimated mean difference in CGAS between children of parents with schizophrenia and the control group was 9.7¹³⁶.

Due to missing data, we used an intention-to-treat (ITT) approach, where we included all children's variables regardless of their drop-out status during the trial⁹⁶. After a qualitative evaluation of the reasons for missing data, we assumed that data was missing at random (MAR). Based on the assumption of MAR, we used multiple imputations based on 100 imputations and 20 iterations until convergence⁹⁶. If we had more than 40% missing data for an outcome, we used complete case analyses¹³⁷.

Due to siblings in the sample, data were not independent⁹⁶. Therefore, we used a linear mixed model with familiarity as a random nested factor to calculate effect sizes and 95% confidence intervals for the continuous primary outcome CGAS and the secondary outcomes Child Behavior Checklist (CBCL) and Teacher Report Form (TRF)⁹⁶. A logistic

mixed effect model was used for the dichotomous secondary outcome: high absence from school⁹⁶. We included the covariates age, biological sex assigned at birth, and baseline characteristics with significant differences (children's baseline verbal memory score (immediate and recall) to adjust for differences between groups at baseline⁹⁶. We used a t-test for continuous outcomes and chi-square for binary outcomes to test for differences between allocation groups at baseline⁹⁶.

We analysed all exploratory outcomes in line with the analysis of the primary and secondary outcomes.

For all analyses, we used the statistical program R version 4.2.2^{96,138}. We used the packages 'lme4'¹³⁹ for linear mixed effect modelling, 'Zelig'¹⁴⁰ for logistic mixed effects, and 'Amelia'¹⁴¹ for multiple imputations.

We included the following predefined sensitivity analyses in the trial⁹⁶:

1. Impact of outliers (analysis with and without outliers)⁹⁶
2. Per protocol (analyses without protocol violations) ⁹⁶
3. Attendance (analyses on participants with $\geq 50\%$ attendance of intended personal meetings in treatment groups) ⁹⁶
4. Adjusting for covariates (analyses without adjustments)⁹⁶
5. For the outcome of school absenteeism, a different cut-off (10% absence) was used
6. Without familiarity as a random nested effect: CGAS change for only one child per family. In families with multiple children in the study, we used the mean change from all children in the family to define 'the child'.

We did the following post hoc sensitivity and subgroup analyses:

1. Significance of children's age for their questionnaire responses (excluding children who were not in the validated age range for the questionnaires)
2. High CGAS score at baseline (subgroup analysis excluding children with high ≥ 70 CGAS (i.e., not clinical case) score at baseline).

Study 2 – Abductive Thematic Analysis

This section outlines the procedures and data analyses of the qualitative study. We aimed to answer the following research question:

What mechanisms of change, if any, did participants experience within the intervention?

Although data for the qualitative study was gathered at the same time as the quantitative data for study 1, we analysed the qualitative data one year later to ensure blinding during quantitative data analysis. At the time of the qualitative analysis, we were therefore aware of the results from the VIA Family study (although non-published). The knowledge of the null-findings shaped our research question. Moreover, the late qualitative analysis restricted participatory approaches to the analysis. For example, we could not present participants with the analysed findings to validate them (ensure we captured their meaning correctly)¹⁰⁵.

Abductive analysis

We analysed data using the principles of abductive analysis by sociologists Iddo Tavory and Stefan Timmerman^{142,143}. In their own words, an abductive analysis is "(...) an inferential creative process of producing new hypotheses and theories based on surprising research evidence" (Timmermans and Tavory, 2012)¹⁴⁴. Qualitative analysis typically has either a hypothesis/theory-driven design (deductive) or a data-driven design (inductive)¹⁴⁵. Abductive analysis aims to combine the two approaches: constructing new theories based on gaps in existing theories and surprising findings in the empirical data¹⁴². Abductive analysis aims to find surprises in the data¹⁴⁵. *Surprising* refers to unexpected findings because they contrast our expectations of the data in the context of theory¹⁴². These surprises are the results of an abductive analysis; they highlight gaps in theory and thereby contribute to challenging and refining existing theories or contribute to new and stronger theories¹⁴³.

In this study, we aimed to explore possible mechanisms of change to understand what leads to change in the VIA Family intervention. Our theoretical knowledge was

grounded in complex intervention research, the transgenerational model of transmission, self-determination theory, and the health belief model. We integrated theory and theoretical models in the analysis to describe, explain and challenge the development of themes.

Theoretical framework: health belief model and self-determination theory

The Health Belief Model describes people's likelihood to engage in health-related behaviour to avoid a health threat (i.e., illness)¹⁴⁶. According to the model, people engage in preventive health-related behaviour if they believe that they are at risk of a severe threat¹⁴⁷. Moreover, people need to perceive more benefits than barriers when engaging in health-related behaviour¹⁴⁶. The model operationalizes these actions in four principles that determine engagement: the principle of susceptibility, the principle of severity, and the principle of barriers and benefits¹⁴⁶.

Cues to action, e.g. public campaigns and self-efficacy, can trigger engagement^{46 147}. The model acknowledges individual differences that modify the principles, e.g., demographic characteristics, psychological characteristics, and social and cultural norms and conditions⁴⁶.

The Self-Determination Theory (originally by Deci and Ryan, 2000¹⁴⁸) offers a comprehensive theoretical framework for understanding how people's basic psychological needs (need for autonomy, competence and relatedness to others) influence their motivation and well-being^{148–150}. Autonomy refers to a person's intrinsic desire for self-determination and the ability to make choices that align with one's own values and interests^{149,151}. When people engage out of a sense of autonomy, they are more self-integrated, thereby making their motivation more sustainable in the long run. The concept of competence relates to peoples' need to feel effective and capable in their actions. People are more likely to engage in behavioural change when they believe that they have the skills and capabilities to succeed. Lastly, the concept relatedness-to-others underscores the significance of social connections and relationships for a person. People engage and sustain in changed behaviour, when they feel connected, valued, and supported by peers, family or community.

Motivation, as proposed by self-determination theory, exists along a continuum, ranging from purely extrinsic to purely intrinsic¹⁴⁹. Extrinsic motivation is driven by external

factors, such as rewards or punishments, while intrinsic motivation is based on autonomy and is aligned with personal values and interests¹⁴⁹. The degree of autonomy involved plays a crucial role in determining where an individual falls on this continuum. Hence, supporting a person's autonomy is crucial to motivate them to engage in long-lasting behavioural change.

Analytical steps

We followed Timmerman and Tavory's (2022) guidelines for conducting an abductive analysis^{142,144}. The method implies multiple steps of moving back and forth between theory and data in order to find the unexpected.

First, a team of three (ADM, SC, and IG) analysed the original transcripts in the Danish language and developed the initial themes. The first round was based on open coding: developing initial codes of interest to the research question by listening to audio, reading and rereading the transcribed data ¹⁴². We followed the initial research question: “*What mechanisms of change, if any, did participants experience within the intervention?*” Second, we discussed codes in the group and grouped similar initial codes into themes. Third, ADM translated relevant quotes of the identified themes into English for further discussion in a group of four (ADM, SC, IG and GP). The team approved the translations. Next, we looked for a theme that challenged our theoretical understanding of change in prevention, i.e., in abductive terminology: a surprising finding. Here, we identified the theme of ‘need for prevention’. Emphasizing this theme, we refined the initial research question to: “*How do participants’ perceived need for support impact their experience of change?*”. Finally, we continued coding completely within this theme, i.e. focused coding¹⁴². During focused coding, we intended to discover patterns and variations of the theme, drawing on our theoretical framework. Parallely, we evaluated our theory by applying it to our data¹⁴².

Reflections on the subjectivity of the researchers

Our academic background, knowledge and personal experiences shaped this study and the questions we asked. As white female academics and mothers from developed countries specialized in mental health, high-risk populations, and prevention, we share a common belief in the importance of preventing mental illness in these groups. While

gathering, analysing and interpreting the data, we considered how our presumptions limited and strengthened this study.

Study 3 - Mixed Methods Integration and Subgroup Analyses

In Study 3, we integrated the findings of Study 2 to select a variable which could align with the identified main theme from Study 2 for a subgroup analysis. Therefore, we looked for similarities between the promising theme (qualitative) and a variable (quantitative) in the VIA Family trial data.

We chose a variable from the semi-structured interview with the child's primary caregiver from baseline assessment. The question was: "*What is your motivation to participate in the VIA Family trial?*". We grouped the answers into the following categories: 1) to help science, 2) to get support for how we function together as a family, 3) to get help with parenting/child rearing, 4) to get support or guidance in relation to the child's well-being or mental health due to a current concern, 5) to get help regarding how to talk about mental illness in our family, 6) other (including 'Don't know'), and 7) not motivated. The participants could give several answers. However, they had to prioritize them to identify the most prominent. In our study, we only used the most prominent answer.

We used the answers of a categorical variable to describe the participant's primary reasons for enrolment. The answers were grouped into the categories: A) *Contributing to Sciences* or B) *Wanting support* (see supplementary S4 for grouping of categories). We moved the variable from a categorical (non-ordered) to a dichotomized variable to understand the differences between being motivated or not, regardless of the type of need the families described.

Subgroup Analyses

After data-integration to identify a subgrouping variable, we conducted post hoc subgroup analyses. We aimed to evaluate if VIA Family was superior compared with treatment as usual for families who were motivated to participate at baseline because of

a need for support. With this analysis, we aimed to explore heterogeneity in treatment effect across subgroups based on motivation¹⁵².

For this study, we used an exploratory subgroup analysis. In contrast to confirmatory subgroup analyses, exploratory analyses aim to gather initial evidence and generate hypotheses for future exploration¹⁵². We employed exploratory subgroup analysis despite having a theory-driven hypothesis (from the mixed-methods design), as our approach was influenced by our knowledge of the null-findings from the VIA Family trial that prompted the post hoc analyses to explore additional insights. Our aim was to explore potential patterns within the subgroups and adapt to the complexity of relationships without strict pre-defined expectations.

The subgroup analyses were based on an independent research question with a corresponding null hypothesis. Consequently, we did not report statistical significance *p*-value but solely initial evidence by reporting effect sizes and 95% confidence intervals (CI)¹⁵². The subgroup analysis followed intention-to-treat (ITT) principles, encompassing all children regardless of their drop-out status. However, due to the inclusion criteria for the subgroup study, we did not impute missing data on the motivation of the participants. Consequently, we only included data from families with information on baseline motivation (*n* = 110 children).

We used multiple imputations based on 100 imputations and 20 iterations until convergence to impute missing data. We used a linear mixed model for the subgroup analyses. Due to siblings within the same family, we included a random nested factor to account for the non-independence of data (clustering effect due to familiarity). All analyses were adjusted for age at baseline and the biological sex of the child. We used R-statistics version 4.2.2¹³⁸ with the packages lme4¹³⁹ for linear mixed effect modelling and 'Amelia'¹⁴¹ for multiple imputations.

Results

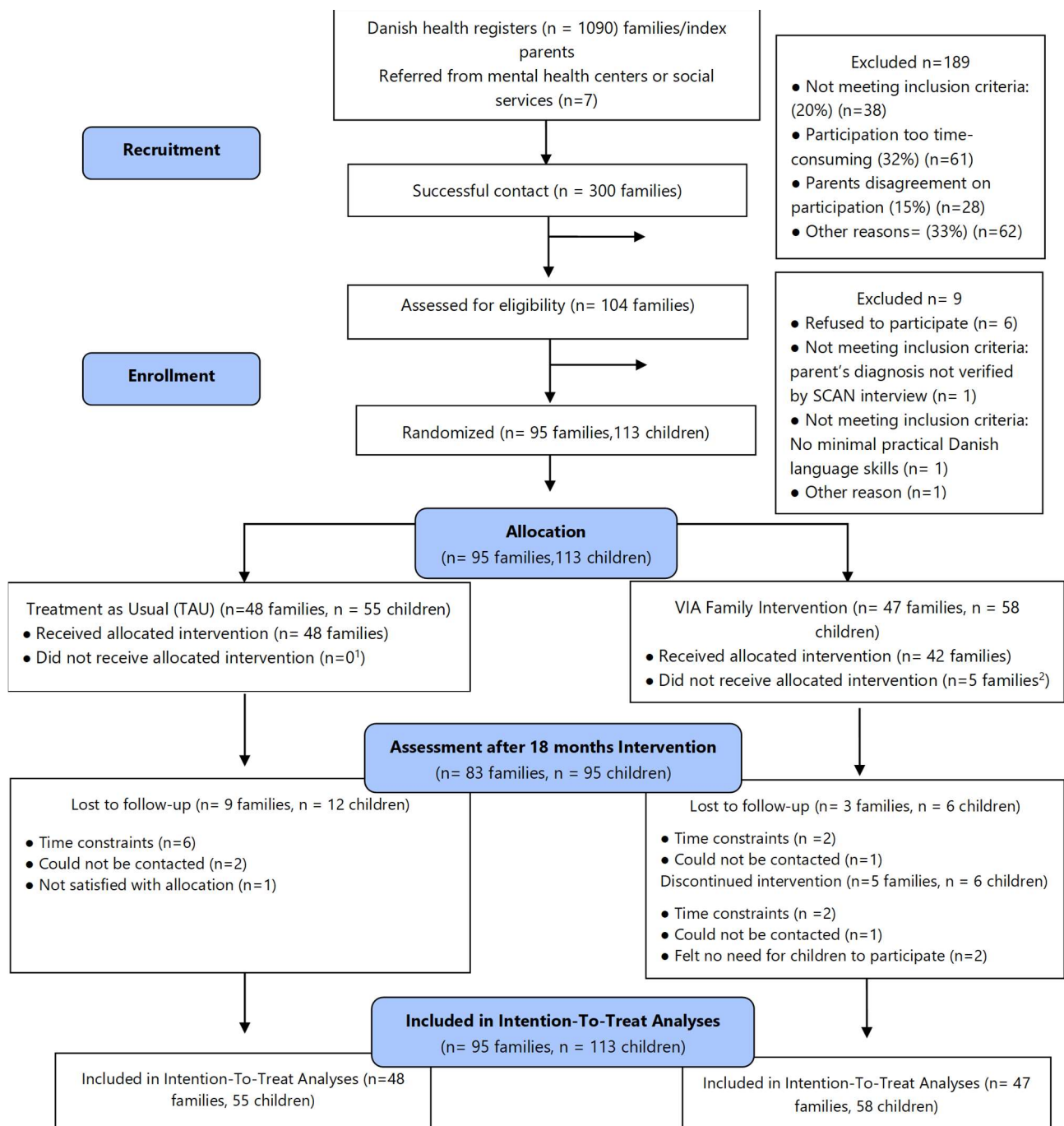
Recruitment and Flow in the VIA Family Trial

We invited 1097 index parents into the study. Out of these, we were able to get in contact with 300 families. After giving information to the families, i.e., the index parent (and sometimes the co-parent) a total of 104 families were then assessed for eligibility and 95 families with their 113 children were assessed and randomized. Finally, 48 families with 55 children were randomized to treatment as usual and 47 families with 58 children were randomized to VIA Family. At end-of-treatment, after 18 months, we assessed 83 families and their 95 children. A total of 12 families were lost to follow-up; 9 families (12 children) allocated to treatment as usual and 3 families (6 children) allocated to VIA Family.

Reasons for drop-out were diverse, nevertheless, time restrictions were the most prominent reason in both groups ($n = 9$), followed by three families being unable to contact, and one family in the treatment as usual group refused to participate due to dissatisfaction with being allocated to the treatment as usual group. All families from baseline assessment (95) were included in the intention-to-treat analyses. See Figure 9 for study flow.

All families allocated to VIA Family were assigned a case-manager, 94% of all families participated in the introductory sessions. In one family parents participated without their child. See supplementary material S5 for families' use of VIA Family intervention components and S6 for use of treatment as usual.

Figure 9. Study flow in VIA Family. Number of participants during recruitment, enrollment, allocation, baseline and post-interventions assessment (Figure 3 in Paper1)



Sample Sociodemographic and Clinical Descriptions at Baseline

VIA Family trial

At baseline, the children's mean age was 9.74 years (SD = 1.95), and 47% were girls. The mean score of children's global functioning (CGAS) was 64.67 (SD = 14.22), the mean of the estimated level of intelligence (RIST) was 101.96 (SD 13.2), and 32% of children fulfilled the criteria for a mental illness (KSADS-PL) during the preceding eight weeks (excluding elimination disorder, simple phobia, tics/tourette's syndrome) at baseline. Teachers reported high absences from school in 9% of all children. See all baseline characteristics for children in Table 1 (Table 1 – Paper 1).

The mean score of levels of support and stimulation in the home environment assessed with the HOME Inventory was 46.6 (SD = 5.9). The primary caregiver's mean score of general functioning (PSP) was 67.7 (SD = 15.5), and 71.6 % fulfilled the criteria for a severe mental illness diagnosis during the child's life.

Regarding the type of parental severe mental illness during a child's life, 12 Index-parents fulfilled the criteria for a schizophrenia spectrum disorder, 25 for bipolar disorder, and 58 for major and moderate depression. See all baseline characteristics for children's families in Table 2 (Table 1 – Paper 1).

Table 1. Sociodemographic and Clinical Descriptions of Children in the VIA Family Trial (Table 1 - **Paper 1**)

Variable	Instrument	Treatment As Usual	VIA Family	All
Children's characteristics	n	55	58	113
Biological sex, female	n (%)	28 (50.9)	25 (43.1)	53 (46.9)
Age at baseline	mean (SD)	9.70 (2.0)	9.78 (1.9)	9.74 (2.0)
Global functioning	CGAS, mean (SD)	63.78 (15.2)	65.55 (13.3)	64.67 (14.2)
Any Current Diagnosis ¹	K-SADS-PL, n (%)	21 (38.2)	15 (25.9)	36 (31.9)
Dimensional psychopathology	CBCL total problem score, T-score (Danish norms), mean (SD)	61.51(17.2)	56.59 (12.8)	59 (15.2)
≥ 15% absence from school	Data from municipalities or schools, n (%)	6 (10.9)	4 (6.9)	10 (8.9)
Neurocognition				
Estimate of general intelligence	RIST, scaled scores, mean (SD)	100.58 (12.3)	103.22 (13.9)	101.96 (13.2)
Processing speed	WISC-IV coding, scaled scores (Danish norms), mean (SD)	8.46 (2.6)	7.56 (2.9)	8 (2.8)
Visual Memory	RCFT immediate recall, T-scores (US norms), mean (SD)	46.79 (11.3)	41.18 (12.5)	43.86 (12.3)
Verbal Memory – immediate	Memory for Stories, immediate recall (TOMAL-2), scaled scores (US norms), mean (SD)	8.94 (3.0)	10.16 (2.5)	9.58 (2.7)
Verbal Memory- delayed	Memory for Stories, delayed recall (TOMAL-2) scaled scores (US norms), mean (SD)	8.41 (3.0)	9.93 (3.2)	9.19 (3.2)
General Executive Functioning	BRIEF, T-score (Danish norms), mean (SD)	52.98 (12.1)	51.73 (12.0)	52.14 (12.0)
Social responsiveness	SRS-2, raw score, mean (SD)	118.48 (13.2)	119.13 (17.4)	118.81 (15.4)

¹ Current Diagnosis within the last 8 weeks, excl. Elimination Disorder, Simple Phobia, Tics/Tourette's Syndrome

ADHD-RS Attention Deficit Hyperactivity Disorder Rating Scale¹²⁵; BRIEF Behavior Rating Inventory of Executive Function¹²⁰; CALS Children's Affective Liability Scale¹²¹; CBCL Child Behavior Checklist¹¹⁹; CGAS Children's Global Assessment Scale⁹⁵; CTS Childhood Trauma Screener¹³¹; FAD Family Assessment Device¹⁰⁸; K-SADS-PL Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime¹¹³; RCFT Rey Complex Figure Test¹¹²; RIST Reynolds Intellectual Screening Test¹⁰⁹; Social Responsiveness Scale- Version 2¹¹⁴; TOMAL-II Test of Memory and Learning, 2nd Edition¹¹⁰; WISC-IV Wechsler Intelligence Scale for Children, 4th Edition¹¹¹

Table 2 Sociodemographic descriptions of children's families (Table 1-continued - **Paper 1**)

Variable	Instrument	Treatment As Usual 48	VIA Family 47	All 95
Primary Caregiver				
SMI or/and substance misuse lifetime diagnoses ³	SCAN interview / patient journal, n (%)	34 (70.1)	34 (72.3)	68 (71.6)
General functioning (higher score better functioning)	PSP, mean (SD)	68.9 (16.7)	67.0 (14.4)	67.68(15.5)
Parental Stress (higher score more stress)	PSS, mean (SD)	40.1(10.5)	39.1 (9.7)	39.64(10.1)
Family functioning (lower score better functioning)	FAD, mean (SD)	1.9 (0.5)	1.9 (0.5)	1.89(0.49)
Currently employed or studying ⁵	Interview, n (%)	38 (79.2)	41 (87.2)	79(83.2)
Educational level				
Primary/lower secondary	n (%)	4 (8.3)	9 (19.2)	13(13.7)
Upper secondary, vocational, or short-cycle tertiary	n (%)	13 (27.1)	12 (25.5)	25(26.3)
Bachelor's degree, equivalent, or higher	n (%)	30 (62.5)	26 (55.3)	56(58.9)
Index parent's diagnosis	n	48	47	95
Lifetime ³ SZ	SCAN interview / patient journal, n (%)	6 (12.5)	6 (12.8)	12 (12.6)
Lifetime ³ BP	SCAN interview / patient journal, n (%)	12 (25.0)	13 (27.7)	25 (26.3)
Lifetime ³ rMDD	SCAN interview / patient journal, n (%)	30 (62.5)	28 (60.0)	58 (61.1)

¹ For children living 50/50 with mother and father, the HOME interview was done in both homes

²Child has only one caregiver

⁴Solely out of families with twocaregivers

³ Lifetime, i.e. during child's life (including the prenatal period)

⁴Solely out of families with two caregivers

⁵ Any form of employment, no minimum working hours, absence from work due to e.g., illness or maternity leave included as work

FAD Family Assessment Device¹⁰⁸; HOME Home Observation for Measurement of the Environment, Middle Childhood (MC) and Early Childhood (EA)¹⁰⁷; PSP Personal and Social performance Scale¹⁵³; PSS Parental Stress Scale¹¹⁶; SCAN Schedules for Clinical Assessment in Neuropsychiatry¹⁰²

Results Study 1: Differences in Change between Groups

The aim of Study 1 was to investigate the superiority of the experimental intervention, VIA Family, compared with treatment as usual.

Primary and secondary outcomes

Results of the primary outcome, change in CGAS, indicate no superiority of VIA Family over treatment as usual at post-intervention. The estimated mean change difference between VIA Family and treatment as usual at end-of-treatment was -1.2 (95% CI = -6.61 to 4.21, $p = 0.66$); after adjusting for covariates, the results remained nonsignificant (see Figure 10 and Table 3). Results of the secondary outcomes, change in CBCL and frequency of high absence from school did not favour VIA Family (see Table 3). Differences in change in CBCL total score was 0.52 (95% CI = -4.62 to 5.65, $p = 0.84$), on the internalizing subscale was -0.88 (95% CI -6.85 to 5.1, $p = 0.77$) and on the externalizing subscale was -0.08 (95% CI = -4.72 to 4.55, $p = 0.97$). We did not find a statistically significant difference in change between the groups at post-intervention on the frequency of high percentage of days absence from school (Odds Ratio (OR) = 0.30, 95% CI = 0.07 to 1.30, $p = 0.11$).

At follow-up, we obtained a 58% response rate on teachers' reports of children's well-being and emotional and behavioural symptoms at school. Due to the low response rate, we did not impute data but used complete case analyses on outcomes. We found no significant difference in the teachers' reports of change in emotional and behavioural symptoms (based on TRF). The mean change differences for the allocation group, VIA Family, was -5.43 points (CI 95% -15.87 to 5.01, $p = 0.30$) on the TRF's total score, -7.76 points (CI 95% -16.7 to 1.15, $p = 0.09$) on the subscale for internalizing symptoms, and 1.65 (CI 95% -7.25 to 10.54; $p = 0.70$) on the externalizing symptoms subscale.

Exploratory outcomes

We found no differences between the groups in change at post-intervention on ITT analyses in any of the exploratory outcomes.

Sensitivity analyses and adverse events

We found no significant differences in the a-priori-defined subgroup analyses.

Parents and children reported no adverse events associated with the VIA Family intervention recorded during and after the trial. In the treatment as usual group, one family reported drawbacks from being informed about parental mental illness risks while being allocated to treatment as usual where the support offered was not sufficient.

Figure 10. Individual changes from baseline to post-intervention on children's global functioning

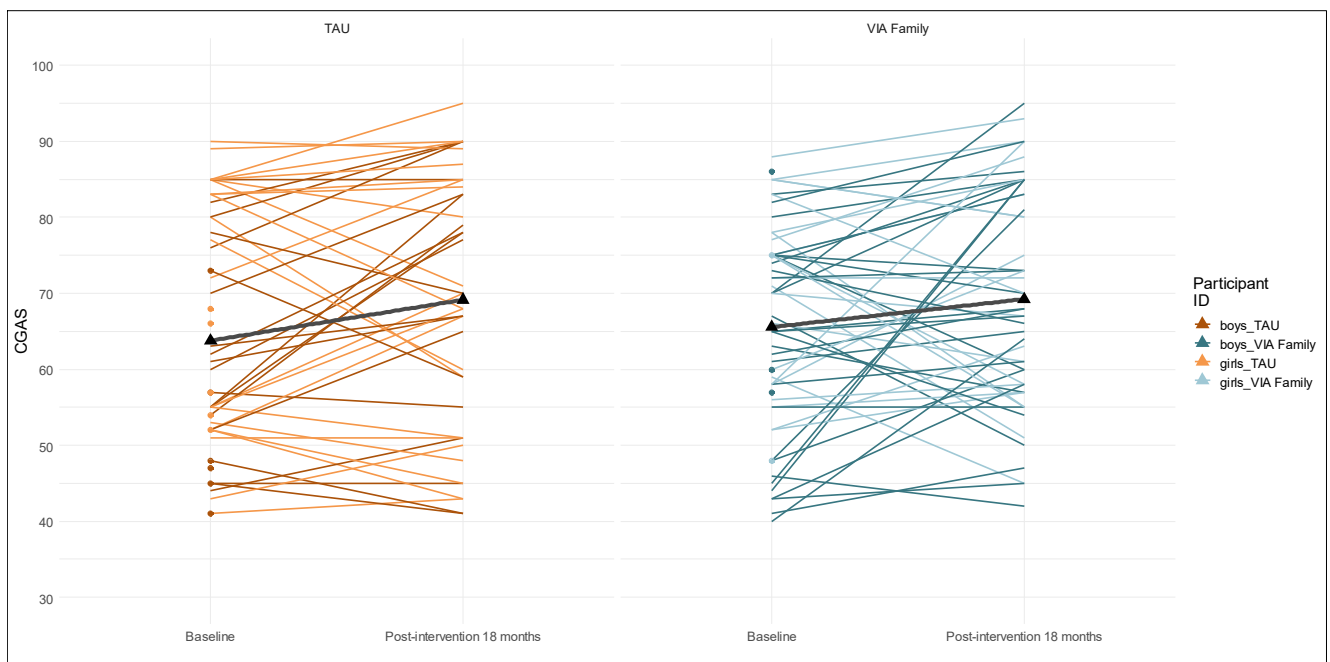


Table 3. Primary and secondary outcomes of the VIA Family trial. Change between groups at postintervention (Table 2 - Paper 1)

Outcome measures	Treatment As Usual (n= 55)		VIA Family (n=58)		Estimated between-group differences/OR on mean change from baseline to post- intervention (95% CI) for group VIA Family	p
	Baseline	Post- intervention	Baseline	Post- intervention		
Primary outcome (ITT) ¹						
CGAS, mean (SD)	63.78 (15.19)	69.14(16.76)	65.55 (13.34)	69.23(14.33)	-1.2 (-6.61;4.21)	.66
Secondary outcomes (ITT) ¹						
CBCL total, T-score, mean (SD)	61.51(17.17)	57.91(17.06)	56.59(12.75)	54.47(12.01)	0.52 (-4.62;5.65)	.84
CBCL subscale for internalizing symptoms, T-score, mean (SD)	62.11(15.52)	60.53(18.65)	56.18(9.77)	57.32(14.60)	-0.88(-6.85;5.1)	.77
CBCL, subscale for externalizing symptoms, T-score, mean (SD)	57.44(17.86)	54.49(13.49)	54.2(13.27)	51.76(11.82)	-0.08 (-4.72;4.55)	.97
≥ 15% days absence from school, n (%)	6(10.90)	7(12.73)	3(5.17)	3(5.17)	0.30(0.07;1.30) ²	.11
Teacher-report Complete-case analyses n (%) ¹	39(71)	21(38)	40(69)	25(43)		
TRF total score, T-score, mean (SD)	52.73(10.79)	57.94(18.76)	55.25(14.66)	55.33(12.05)	-5.43 (-15.87;5.01)	.30
TRF subscale for internalizing symptoms, T-score, mean (SD)	54.52(11.68)	57.16(12.40)	57.88(17.67)	53.52(8.88)	-7.76 (-16.67;1.16)	.09
TRF subscale for externalizing symptoms, T-score, mean (SD)	50.68(13.24)	53.57(20.75)	52.3(16.13)	52.71(11.60)	1.64 (-7.25;10.54)	.71

¹ Data are between-group differences on mean change (SD) adjusted for age, sex, and baseline verbal memory score (immediate and recall) unless otherwise specified.

² Data are OR for between-group differences at 18 months post-intervention adjusted for age, sex, and baseline verbal memory score (immediate and recall)

Note: CBCL: Child Behavior Checklist, T-score based on Danish norms, higher scores indicate more problems, Achenbach & Rescorla (2001)¹¹⁹; CGAS Children's Global Assessment Scale, high scores indicate better functioning, Shaffer(1987)⁹⁵

Table 4. Exploratory outcomes of the VIA Family trial. Change between groups at postintervention (Table 2 - Paper 1)

Outcome measures	Treatment As Usual (n= 55)		VIA Family (n=58)		Estimated between-group differences/OR on mean change from baseline to postintervention (95% CI) for group VIA Family	p
	Baseline	Post-intervention	Baseline	Post-intervention		
Parent-reported (ITT)						
BRIEF, T-score, mean (SD)	53.10 (12.10)	53.36(12.77)	51.20 (11.90)	50.90(11.83)	0.95 (-2.54;4.45)	.59
CALS, total raw scores, mean (SD)	10.29(11.74)	10.51(11.73)	7.32(7.29)	5.87 (6.87)	-1.09 (-4.24;1.59)	.49
ERC, total raw scores, mean (SD)	2.81(0.27)	2.83(0.27)	2.87(0.26)	2.89(0.25)	-0.01 (-0.1;0.08)	.80
SDQ total difficulty score, raw score, mean (SD)	9.65(5.90)	8.22(6.01)	7.93(5.89)	7.47(5.41)	0.94 (-0.88;2.76)	.31
ADHD-RS, T-score, mean (SD)	57.69(19.27)	54.73(17.47)	54.48(21.33)	53.77(17.60)	3.69 (-2.18;9.57)	.22
Sleep-related problems, n (%)	29(52.73)	19(34.55)	24(43.10)	22(37.93)	1.11 (0.26;4.71) ²	.80
Child self-report (ITT)						
TIM, stanine score, mean (SD)	4.23(1.49)	5.24(2.19)	4.66(1.56)	5.71(2.13)	-0.12 (-0.84;0.60)	.74
KIDSCREEN-10 (Global QoL), T-score, mean (SD)	47.19(11.76)	52.09(9.52)	52.15(9.08)	53.46(8.03)	-3.92 (-8.26;0.43)	.08
CTS, raw scores, mean (SD)	7.35(3.34)	7.39(3.50)	6.44(2.12)	6.62(2.31)	-0.23 (-0.86;0.41)	.48

Table 4 – continued. *Exploratory outcomes of the VIA Family trial. Change between groups at postintervention (Table 2 - Paper 1)*

Teacher report (CC ³) ¹ , n (%)	39(71)	21(38)	40(69)	25(43)		
BRIEF-T, T-score, mean (SD)	51.15(8.20)	56.38(15.53)	53.4(12.37)	56.7(15.23)	-4.80 (-9.10;8.14)	.90
ERC-T, total raw scores, mean (SD)	2.89(0.29)	2.85(0.27)	2.86(0.3)	2.87(0.26)	0.01 (-0.14;0.15)	.90
ADHD-RS-T, T-score mean (SD)	48.03(8.55)	55.63(20.91)	50.82(10.79)	51.59(12.72)	-3.64 (-12.5;5.18)	.40
SDQ-T total difficulty score, raw score, mean (SD)	5.85(5.01)	7.91(4.97)	6.73(5.94)	6.12(5.73)	-2.74 (-6.01;0.54)	.10

¹ Data are between-group differences on mean change (SD) adjusted for age, sex, and baseline verbal memory score (immediate and recall) unless otherwise specified.

² Data are OR for between-group differences at 18 months post-intervention adjusted for age, sex, and baseline verbal memory score (immediate and recall)

³ Complete-case analyses

Note: ADHD-RS(-T)¹²⁵: Attention Deficit Hyperactivity Disorder Rating Scale, T-score based on Danish norms, higher scores indicate more symptoms; BRIEF(-T)¹²⁰: Behavior Rating Inventory of Executive Function, T-score based on Danish norms, higher scores indicate more problems; CALS¹²¹: Children's Affective Liability Scale, higher scores indicate more affective liability, CTS¹³¹: Childhood Trauma Screener, high scores indicate more traumatic experiences, , CYRM: Child and Youth Resilience Measurement, higher scores, raw scores and comparison of percentage of total mean, higher scores indicate more resilience resources, Liebenberg et al (2013)¹²⁷; ERC(-T): Emotion Regulation Checklist¹²³, higher scores indicate better adaptive emotion regulation; SDQ(-T): Strengths and Difficulties Questionnaire¹²⁴, Higher scores indicating more difficulties with mental health, TIM: This is Me¹²⁸, higher scores indicate more self-esteem

Results Study 2: Qualitative Findings

(reported in Figure 1 – Paper 2)

This section describes the findings of the qualitative study (Study 2). We aimed to explore mechanisms of change in families participating in the VIA Family intervention. We used two different samples for the sequential mixed methods design. The sample for the qualitative study was a subsample of the VIA Family intervention group for a qualitative study.

Characteristics of participants in the qualitative sub-study – Study 2

Parents' main motivation for participation at baseline was reported as a) need for support (3 parents; 38%) and b) wanting to support science (4 parents; 50%). We did not have any information about the main motivation for participation at baseline for 1 parent (13%). Two parents and two children from the same family participated. All names were anonymized.

Qualitative findings: Perceived Need and Motivation as Mechanisms of Change

All participants, children and parents, described that the intervention led to meaningful changes for them and their families. Due to the multicomponent and flexible design of the intervention, participants' experiences of changes varied according to which components the family participated in. Nevertheless, an overall theme encompassing participants' mechanisms of change was the perceived need for support and motivation to engage. Parents' experiences of mechanisms of change differed from children's experiences. We start with exploring parents' experiences, followed by children's experiences.

A common theme across all parents' descriptions was the importance of experiencing 'a need for support' to interact with the intervention. Experiencing 'a need' acted as a

mechanism of change. In the following, we explore different aspects of how the experiences of need influenced parents' engagement and perception of change.

***'It fits perfectly'* – Need for support (Figure 1 – Paper 2)**

In the parental focus group discussions, many parents described that they participated in the trial because they sought support for their child's well-being. Peter, a father, when asked why he chose to participate in the trial, said: *"It was to support my daughter"* (Peter, father). The experience of a need for support was further enhanced if parents observed early signs of mental health problems in their child. As illustrated in the description of Charlotte:

"So, when we got this offer, we thought 'it fits perfectly', also because we had a son who had a really difficult time mentally" (Charlotte, mother)

Following the principle of susceptibility from the health belief model, Charlottes' perception of her son's ill-being engaged her in the intervention. For Charlotte, *"this offer"* (the invitation for participation in the VIA Family trial) acted as an external cue to action. Moreover, the *"offer"* enhanced her susceptibility to her son's familial high-risk status and how severely it could affect him (perceived severity). Sara, another mother, also describes that she engaged in the trial because she perceived that her daughter had a familial risk:

"I chose it [VIA Family]. I think that I really wanted to have my daughter examined because I was really afraid that she would become as sick as her father" (Sara, mother)

Peter, Charlotte, and Sara all engaged in the preventive intervention because they perceived a need for support either because they experienced that their child a) needed support, b) had signs of mental illness, or c) had a familial risk for developing a mental illness. According to the self-determination theory, their identification of a need for support was based on autonomy. Autonomy is crucial to facilitate internalized motivation. An internalized motivation, in turn, is needed for long-term changes to occur (which is the goal of preventive programs). In the above examples, all parents

internalized their motivation to engage because they experienced that their children needed support.

'We didn't have any needs' – No need for support (Figure 1 – Paper 2)

However, other parents' motivations were not internalized when they entered the study.

"We never really figured out what to get out of it (. ...) I think that if something should have changed (. ..), we would have needed guidance at a different level because that's not where our needs were, or we didn't have any needs, I don't know." (Anna, mother)

Anna did not perceive that her family needed any support from the intervention, which made her feel unengaged and without any sense of change. Despite the individually tailored approach of the intervention, the intervention did not fit with her family's needs. Consequently, she did not feel that anything had changed for them. With the terminology of self-determination theory, she describes an amotivation here. However, Anna, when allocated to the VIA Family, participated in the intervention, which suggests that she was motivated to some extent. According to the self-determination theory, her motivation was solely extrinsically, as she did not internalize the extrinsic motivation for change offered by the intervention. This lack of internalization led to her experience: *"We never really figured out what to get out of it"*.

The solely high-risk status of their children did not motivate them to engage in the intervention unless their children already showed early signs of mental illness.

'It was a need that we did not think we had.'

– Intervention changed perception of need (Figure 1 – Paper 2)

An (initial) lack of internalized motivation when entering the intervention was also experienced by other parents, such as Catherine:

"Do we really need this? Has anyone pointed out that here [in our family] we need to take action?" (Catherine, mother)

Catherine's narrative of *"has anyone pointed out..."* refers to the invitation to participate in the VIA Family trial, and "we need to act", on the other hand, refers to an extrinsic source (the research group) proposing that they need support. For Charlotte, in the previous quote, the invitation acted as an external cue to action – but not for Catherine. Her motivation to engage was not internalized, possibly because she did not perceive that she needed support despite the information that her child has a familial risk. Notably, Catherine describes that her motivation changed during the intervention. This change occurred when she, at a later point, perceived a need for support:

"At first, we didn't have any problems in our family (. ...), but then my son started first grade (. ...) The most important thing then was that 'hey, now there is something which is wrong here, and we can get help immediately.'" (Catherine, mother)

This quote highlights that when Catherine *herself* experiences a need for support, she experiences the intervention as beneficial. Motivation for participation here becomes internalized. The change from amotivation to a more internalized extrinsic motivation is enabled by a higher degree of autonomy. It was Catherine and her family who decided that *"now there is something wrong here"*, in contrast to when they were first invited to participate.

The intervention itself could also enable internalization. Some parents described that being in the intervention changed the way they were motivated to participate. Parents felt that the intervention made them aware of a need that they did not previously think they had:

"But they [VIA Family team] have fulfilled something really well, which we have talked about so much. So, it was a need that we did not think we had, but which then turned out to be super relevant" (Thomas, father)

Many parents described an internalization of motivation during the intervention. In some cases, it made them aware of a specific problem or need for support for a family member. Following HBM, the change in perception of a need for change was triggered because the intervention addressed families' beliefs about their child's high-risk status

and severity. Following self-determination theory, internalization was enabled through the support of families' autonomy – which was part of the individually tailored design of the intervention.

'If I had had that as a child' – perceived need for support enabled by parents' own unmet need (Figure 1 – Paper 2)

In all the above examples, parents felt the intervention was relevant when there was a perceived need. In these cases, the preventive intervention was used as early intervention for a concrete need they experienced.

However, in some cases, parents described motivation in the absence of a perceived need for support. Anna, for example, described that she was motivated because she had experienced parental mental illness when she was a child. Although she did not feel any current need for support, she was motivated by a previously unmet need for support growing up:

"I'm the child of a severely mentally ill mother, and there were zero offers, and I felt like ... it still affects me, and at times it also does so for my children (. ...) I think it sounds so cool to have had someone like, that the children could go and talk to [case-manager]. I mean, if I had had that as a child, my life would have looked completely different" (Anna, mother)

Anna's motivation is guided by her experiences and feelings of *"if I had had that as a child"*, i.e. by a high degree of autonomy. It is both an unmet need within herself (though in the past)) and a wish to give her children something that she herself missed as a child. Anna's unmet need for support when she was a child gave her an internalized awareness of a possible need her children may or may not have. However, Anna struggles with identifying with the support offered by the intervention as described earlier in this section: *"(. ...) that's not where our needs were, or we didn't have any needs, I don't know"*. This example illustrates the limitation of both theories: although Anna's motivation was based on autonomy (self-determination theory), and she perceived her children to have an elevated risk with high perceived benefits of the

intervention and low barriers (HBM), her motivation was not stable intrinsic or extrinsic and at times she did not “*figured out what to get out of it*”.

"It was just really nice" – Children's motivation to engage in the intervention (Figure 1 – Paper 2)

Contrary to parents, children did not discuss the concept of perceived *need* as a mechanism of change. While parents described internalizing an extrinsic motivation (self-determination theory), none of them described an intrinsic motivation to engage in the intervention (in self-determination theory, this means motivated for the joy of doing it). However, Children described an intrinsic motivation for participation. As 8-year-old Robin, for example: *"It [VIA Family] was just really nice"*. And 13-year-old Andrea describes something many children described: family-related contextual factors motivated engagement. When asked to describe and draw what VIA Family meant for them, Andrea said:

"[. ...] Bicycle rides because we usually take the bike over here. And then, romkugler [a Danish pastry], because Kirsten's bakery is just very close by, and we almost always buy romkugler. And then I also wrote 'mental illness', where I have drawn [a picture of] moving from being happy to being sad" (Andrea, child, 13 years)

Andrea describes that the preventive intervention enabled the family to engage in joint activities: riding the bike and buying pastries. Andrea associated these family activities as much with the intervention as learning about mental illness. Many children describe that they appreciated the time spent with their family before, in and after the sessions in VIA Family. Following the principles of self-determination theory, children's motivation was enhanced by spending time with their families because it supports their basic need for relatedness.

"I don't know. I can just [see a change in the family]. Almost my whole family has been down here and talked to someone, and it has just helped." (Charlie, child, 13 years)

Charlie describes that all family members were in contact with the VIA Family intervention team, which Charlie believes was a mechanism of change: *“it has just helped”*.

To sum up, the findings suggest that for children, their family's participation in the intervention served as a mechanism to feel engaged in the intervention. Contrary to parents, children were intrinsically motivated to participate. The intrinsic motivation was enabled through the activities and snacks provided by the intervention team and the fact that all family members participated.

Regarding parents, our findings suggest that recognising a need for support was a mechanism for engaging with the intervention to bring about a perceived change. Need for support could be enabled through children's signs of vulnerability, parents' susceptibility to children's elevated familial risk status, or an unmet need from parents' childhood.

Results from Study 3: Subgroup Analyses

In this section, I describe the characteristics of the subgrouped sample of Study 2 and the results from the subgroup analyses.

Characteristics of participants in subgroup analyses

In the VIA Family group, 57% of primary caregiver's main motivation was the need for support. In this subgroup, 39% fulfilled the criteria for a severe mental illness diagnosis. Their children's CGAS score mean score at baseline was 67.09 (SD = 13.21), and their mean T-score of total problems, measured with CBCL, was 55.86 (13.20).

In the treatment as usual group, 57% of the primary caregiver's main motivation was the need for support. In this subgroup, 43% fulfilled the criteria for a severe mental illness diagnosis. Their children's CGAS mean score at baseline was 65.00 (SD = 15.07), and

their mean T-score of total problems, measured with CBCL, was 56.88 (SD = 14.89). See Table 5 for sociodemographic descriptions divided by subgroup and allocation group.

Table 5. Demographic characteristics divided by allocation group and primary caregiver's main reason for study participation (Table 1 in Paper 2)

	VIA Family		Treatment As Usual	
Main reason for participation	Contributing to science	Wanting support	Contributing to science	Wanting support
All families	N=46		N=47	
Primary Caregiver, n (%)	20(43)	26(57)	20(43)	27(57)
Having a SMI diagnosis ¹	15(33)	18(39)	15(32)	20(43)
Functioning (PSP)	68.30(11.88)	66.96(15.75)	65.30(17.46)	70.26(15.28)
All children	N=56		N=54	
Children, n (%)	24 (43)	32(57)	24(44)	30(56)
Children's age at baseline in years, mean (SD)	9.5(2.1)	9.9(1.7)	9.5(2.2)	9.5(1.8)
Biological sex female, n (%)	10(42)	14(44)	11(46)	17(53)
Global functioning (CGAS), mean (SD)	64.79(13.11)	67.09(13.21)	62.38(15.47)	65.00(15.07)
Home environment (HOME), mean (SD)	47.44(4.44)	46.26(6.62)	44.67(6.70)	48.61(4.48)
Behavioural or emotional problems (CBCL), T-score, mean (SD)	56.54(10.44)	55.86(13.20)	68.17(18.39)	56.88(14.89)
¹ Diagnosis of a schizophrenia spectrum disorder, bipolar disorder, recurrent major depression during their child's life.				

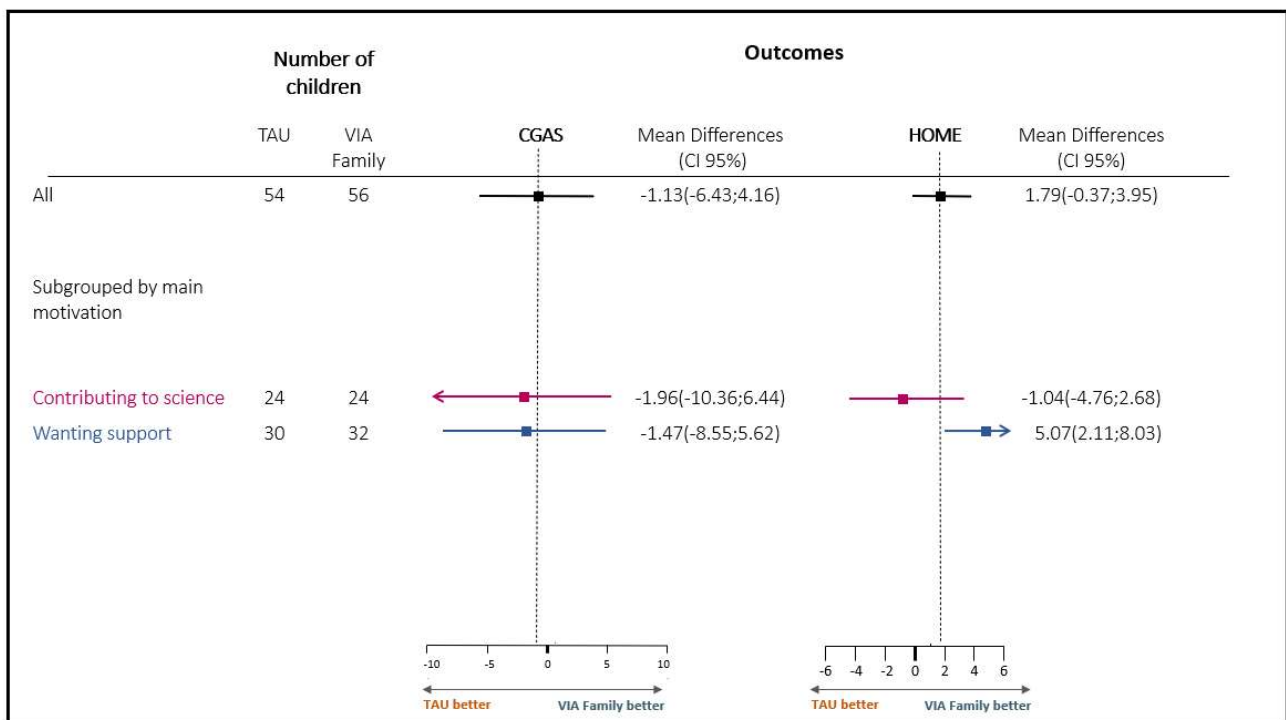
Based on the identification of a new variable from the mixed methods integration, we generated an exploratory hypothesis that children in the 'need for support' subgroup would have a higher change in CGAS (primary outcome of VIA Family) and higher increase in the levels of support and stimulation in the home environment levels of support and stimulation in the quality of home environment (HOME) from baseline to end-of-intervention compared with children in the 'contributing to science' group. We performed two post hoc subgroup analyses on secondary ITT data from the VIA Family trial.

We subgrouped data from 110 children: 46 children from the VIA Family intervention group and 47 from the treatment-as-usual group.

Results of subgroup analyses

We found no difference between changes in subgroups over time in children's global functioning (CGAS) (-1.47, 95 % CI: -8.55 to 5.62). However, we found a clinically significant difference in change over time in the quality of home environment (HOME) in favour of children in the VIA Family intervention group whose parents' main motivation was 'need for support'. The difference in HOME mean score was 5.07 (95% CI: 2.11 to 8.03). See Figure 11 for the results of the subgroup analysis.

Figure 11. Comparison of differences in mean change at post-intervention between allocation groups (Treatment as usual (TAU) and VIA Family) on CGAS and HOME, subgrouped by main motivation for study participation at baseline (Figure 2 – Paper 2)



Discussion

In this chapter, I start by summarising the main findings of each study. Next, I interpret the findings of the three studies in the context of the literature, considering each study's methodological limitations. Afterwards, I describe the strengths and limitations of the three studies' respective study designs, the use of theory, and multicomponent intervention designs. I end with concluding remarks on this thesis's aims, findings and interpretations.

Finally, I discuss ethical aspects and consider clinical implications for future preventive interventions for children with an elevated familial risk of severe mental illness.

Summary of Main Findings

This thesis aimed to explore the efficacy and mechanisms of change of the VIA Family intervention compared with treatment as usual. We conducted three studies based on a randomised clinical trial, the VIA Family trial. In Study 1, we explored the differences in change between groups at the end of the intervention. Study 2 was a qualitative study venturing into experienced mechanisms of change within a sample of families participating in the intervention. Finally, in Study 3, we investigated the effect of subgroups on the differences in change between groups at the end of the intervention.

In Study 1, contrary to our hypothesis, we did not find a superior effect of the VIA Family intervention compared with treatment as usual at the end of treatment. There were no statistically significant differences between treatment groups in change at post-intervention in the primary outcome, level of global functioning, or in the secondary outcomes, children's emotional and behavioural symptoms and absence from school. Similarly, we found no differences in change on any of the exploratory parent- or child-reported outcomes. Concerning teacher reports, there was a clinically meaningful difference in teachers' observations of children's emotional symptoms at school in

favour of the VIA Family group. However, we only performed complete case analyses on the teacher reports due to the high level of missing data.

In study 2, we explored in VIA Family intervention participating families' experiences and perceptions of mechanisms underlying change in the preventive intervention. The qualitative findings indicate that perceived needs and quality of motivation drove perceived mechanisms of change for parents and children in the VIA Family group.

In study 3, results of posthoc subgroup analyses showed a clinically meaningful improvement in children's home environment in favour of the VIA Family group, whose parent's primary motivation for study participation was 'need for support'. Notably, we found no clinically meaningful differences in children's global functioning.

To sum up, we found 1) no superiority of the VIA Family intervention compared with treatment as usual at end-of-treatment, and 2) that parents' perception of a need for support at baseline served as mechanisms of change for the families within the experimental intervention.

Interpretation of Results

Study 1: no superiority of VIA Family over treatment as usual

The null-findings of the VIA Family trial oppose our initial hypotheses and the findings from a recent meta-analysis on the effect of preventive interventions for children of parents with mental illness⁵⁰. The authors showed a significant reduction in the risk of mental disorder incidences (decrease of 47%) among children of parents with a mental illness after participation in preventive interventions⁵⁰. The effects on internalising symptoms were small but significant; however, the effects on externalising symptoms were non-significant⁵⁰. However, before comparing the results, we must assess considerable differences between our study and those included in the meta-analysis.

Firstly, contrary to our trial, the included studies of parents with severe mental illness often only assessed signs of mental illness using children's self-reports^{69,71,72}. Secondly,

only one study explored change in global functioning (Clarke et al., 2001). The authors found no significant differences between groups over time in global functioning⁶⁹. Third, the age range of children was larger. Finally, none of the included studies tested a multicomponent intervention with a flexible design, such as the VIA Family, and none of the studies included parents with a schizophrenia spectrum disorder⁵⁰.

A preventive intervention more comparable to VIA Family is the *Preventive Family Service Coordination* by Wansink and colleagues (not included in the meta-analysis)⁸¹. Similar to VIA Family, the intervention offered all families a case-management-based and multicomponent intervention for the whole family for 18 months; 99 families were included and allocated to the intervention. The results showed that the intervention was feasible and acceptable and that parents in the intervention increased significantly in parenting skills compared with the controls⁸¹. Nevertheless, the authors could not find significant group differences in children's behavioural problems (assessed with the Strengths and Difficulties Questionnaire) or any other parental outcomes (parenting stress and quality of parenting) at the end of treatment⁸¹. The authors interpreted the non-significant findings of children's outcomes with a potential delayed time effect. They hypothesize that parental change theoretically precedes children's change, and thus, children's outcomes need to be further assessed in the future⁸¹.

A potential delayed effect may also apply to the VIA Family study. The primary purpose of preventive interventions is long-term prevention. Although we could not measure a superior effect post-intervention, we cannot dismiss a sleeper effect of the intervention¹⁵⁴. Sleeper effects are latent effects of intervention components that require time before manifested¹⁵⁴. In interventions incorporating a parenting component, latent effects can emerge. This is particularly true when a parent needs time to independently apply the skills acquired in the intervention, i.e., without the practitioner's supervision. Consequently, no effect of the parenting component is measurable at a post-intervention timepoint. However, when the parent gradually feels more confident in using their newly developed skills in the unsupervised context, the effect of the component becomes measurable – resulting in a sleeper effect¹⁵⁴. Sleeper effects have been observed in parenting-based preventive interventions¹⁵⁴. Long-term follow-up studies should be conducted in family-based interventions to explore potential sleeper effects ¹⁵⁴.

Moreover, VIA Family may have led to changes that are not (yet) measurable with the outcome measures in VIA Family⁸¹. Examples of changes are increased knowledge about risk and protective factors, reduced internalised stigma, and when to seek help for early signs of vulnerability³⁷. Notably, parents with severe mental illness described those outcomes as the most important for them³⁵. Further, those types of change may result in more long-term effects as they support autonomy¹⁴⁹. Reduced internalised stigma, for example, is associated with a higher quality of life and help-seeking behaviour in adolescents with severe mental illness ^{76,155}.

Next, our sample was very diverse. We included children with very high and very low levels of global functioning and with and without mental disorders. We aimed to use the primary outcome CGAS as a proxy for the presence of risk and protective factors for children. However, CGAS was developed for clinical populations as a composite score to measure the functional impact of children's mental illness on four domains of the child's daily activities ⁹⁵. While psychopathology impacts the scoring, more external causes, e.g., having a broken leg or having no space at home to invite peers, do not^{95,117}. Subsequently, at times, it proved difficult to adequately rate functional impairment if it was caused by, e.g., parental mental illness but not children's mental health problems. Furthermore, in cases where children improved their functioning remarkably, their mental disorder restricted the extent to which the improvement in the CGAS could be rated. Hence, well-treated children with a mental illness (especially with neurodevelopmental disorders) and with many protective factors present could not improve to a 'normal level', i.e. non-clinical level¹⁵⁶.

Finally, the VIA Family trial (Study 1) had some limitations regarding the population. For example, we did not exclude parents in long-term remission of their severe mental illness. Hence, potentially, their children and partners may not have been affected by environmental risk factors of parental mental illness symptoms for many years. The potential remission may also have influenced their motivation for participation in the intervention, as described in previous studies ²⁵. Moreover, due to some of the children's young age at baseline, we did not include their description of symptoms, i.e., self-report surveys, except from the interview-based information obtained with the K-SADS-PL¹¹³.

Study 2 and 3: Need and motivation as mechanisms for change

The integrated findings of Study 2 and Study 3 indicate that participants' needs and motivation shaped their perception of change and contributed to clinically significant improvements in their home environment. Notably, it did not impact change in children's global functioning. However, changes in the home environment's levels of support and stimulation may precede improvements in the child's functioning^{81,154}.

Our findings are consistent with the literature on the association between families' perception of a need for support and their participation in preventive programs. Recent reviews highlighted that parents are more likely to participate in preventive interventions if they perceive that their child needs support^{157,158}. A lack of engagement may stem from, e.g., the absence of (visible) externalising symptoms or (less-visible) internalising symptoms¹⁵⁷. A lack of perceived need may hinder recruitment and engagement in selective interventions, especially when children may not show signs of early vulnerabilities. In the literature, various predictors of family engagement in preventive parenting programs have been described. Child mental illness has the strongest association with parental enrolment in preventive programs¹⁵⁸.

Nevertheless, despite the association between child symptoms of mental illness and *enrolment* in preventive programs, the association with *sustained* engagement in the intervention yields mixed results¹⁵⁸. Studies often operationalize engagement as drop-out status, but measuring sustained engagement in individually-tailored interventions is challenging¹⁵⁸. A definition of drop-out does not encompass a more in-depth understanding of the reasons for attrition¹⁵⁹.

Our findings suggest that selective preventive interventions can increase participants' engagement and possibly affect intervention outcomes by exploring their perception of a need for support in targeted groups for selective interventions. Encouraging engagement by addressing parents' own childhood experiences of growing up with parental mental illness may enhance engagement in the absence of a child's signs of vulnerability and parents' perceived need for support.

Limitations, Strengths and Future Directions

In this chapter, I describe the strengths, limitations, and future directions of the three studies' designs and integration of theory. Finally, I describe the strengths, limitations and future directions for family-based selective preventive interventions, such as VIA Family.

The three study designs

All three studies have both strengths and limitations in their study designs.

The main strength of Study 1 is the rigorous randomized controlled design. We conducted the trial with blinded assessments, concealed allocation sequence, a non-treatment control group, multi-informant assessments, and statistical analyses based on intention-to-treat and mixed-effect modelling blinded to the allocation group. However, even though a randomized controlled trial is the golden standard for intervention research, the design also sets some limitations. The more complex the intervention and the population get, the more challenging it is to measure an effect in a randomised controlled design¹⁶⁰.

The mixed methods design of Paper 2 has enriched the findings by combining statistical associations with in-depth understanding. Here, mixed methods provided a more comprehensive understanding of the VIA Family intervention's impact by capturing both nuanced experiences and perceptions of participants, which further guided the formulation of a new hypothesis and exploration of a statistical relationship. However, both studies also hold potential limitations.

In Study 2, the context-specific nature of qualitative design and data generation limits the generalizability of the qualitative conclusions. For example, our qualitative sample lacks ethnic diversity, with no focus group participants having an ethnic minority background, despite such diversity being present in the VIA Family trial. Notably, the qualitative sample was diverse regarding socioeconomic background, history of mental illness, and age and gender, but not regarding their religious background or ethnicity.

Moreover, we did not interview families allocated to the treatment as usual group. Consequently, we cannot definitively ascribe the mechanisms of change to the experimental intervention. Finally, although children participated vividly in the focus group discussions, their views, expressions, and understandings of mechanisms of change may be limited by their age-related verbal communication skills. Future studies could consider applying alternative methods to capture children's perspectives and voices better. Furthermore, since we analysed data almost two years after conducting the focus group discussions, we could not present participants with our findings to validate our transcripts' interpretations and translations of their discussions, i.e., ensure we captured their meaning correctly¹⁰⁵. In translating a quote, a part of the culturally specific meaning of language disappears. For this reason, we developed themes in the native language (Danish) in this study.

Lastly, in Study 3, the results of the post hoc subgroup analyses must be validated, possibly in a larger sample, to dismiss a potential false-positive finding (Type 1 error). Nonetheless, although we defined the subgroups post hoc (after the initial results of the VIA Family trial), it is a major strength that the hypothesis for the post hoc analyses was based on theory and findings from the qualitative study.

This combination of qualitative and quantitative findings results in a more robust and holistic evaluation, enriching the comprehension of complex preventive interventions⁹⁹. Future evaluations of complex preventive interventions could benefit from including qualitative methods, such as using a mixed methods design.

The application of theory

Integrating a theoretical framework into a complex intervention design has numerous advantages. It provides transferability of interventions across different contexts and fields, describes rationality behind causal pathways to inform mediator analyses, and enhances the communicability of the findings⁹⁹.

Nevertheless, the VIA Family trial design initially lacked a clear theoretical framework in, for example, the study protocol⁹⁴. The use of theory is often not mentioned explicitly in preventive intervention research for mental illness⁴⁶. However, all programs are based on a theory, although not expressly stated. Formulating a program theory can enable new conclusions and understandings of findings⁹⁹. Interpreting empirical findings draws on theoretical preconceptions of human motivation and change. Following an abductive approach, theory and empirical data can benefit from each other when used in an iterative way^{142,151}.

Several theories informed the design, analysis and interpretation of findings in this thesis. The theories of developmental psychopathology and transgenerational transmission of mental disorders inform how we assume that illness occurs and how to prevent it from occurring. While the model emphasises the role of protective and risk factors, the latter is often the most stressed and studied in empirical research. Furthermore, although social and cultural norms are appreciated to exist within the theories/models, they do not have a prominent role, which they might need to explain why families engage in preventive intervention. Stigmatisation, for example, has been shown to greatly impact resilience and vulnerability in numerous studies^{155,161–163}.

The same limitation applies to the other two theories in this thesis: self-determination theory and the health belief model. While the theories acknowledge cultural and social influences, they may not recognise the strengths of their influences on behaviour. However, self-determination theory and the health-belief model are successfully used in many fields, including preventive research. In particular, self-determination theory has shown good cultural adaptability of the association between autonomy and well-being, including mental health promotion^{164,165}.

Nevertheless, using theory to explore and explain surprises (regarding what we expected) in our data has enriched our analyses and interpretation of findings¹⁴². Theory enables us to extract surprising meaning from data, formulate surprising explanations, and, ultimately, foster the formulation of surprising hypotheses¹⁴³. Thereby, theory can strengthen the development and design of preventive interventions and the description of assumed causal relationships for statistical testing of significance.

Additionally, applying a theoretical framework enables drawing parallels to findings from other fields. For example, a study based on self-determination theory demonstrated that increasing individuals' autonomy fostered their engagement in protective behaviours during the COVID-19 pandemic, even in situations without guidance for the new behaviour¹⁶⁶. Another study showed that applying theory, such as the Health Belief Model, to inform recruitment strategies in parental preventive programs enhanced engagement¹⁵⁸.

The limitations and strengths of multicomponent complex interventions

The complexity of VIA Family's multicomponent and individually tailored design limited fidelity and efficacy assessments¹⁶⁰. With guidance from their case manager, families decided which VIA Family components they wished to engage in (see supplementary material S5 for families' use of VIA Family components). Thus, each family could engage in different components. For example, some families participated in parents' and children's support groups while others received assistance to apply for financial and social support from social services. Moreover, in some families, all family members participated, while in others, only one or two family members participated. Consequently, the intervention operated within a complex, here meaning a non-manualised, multi-component system, leading to individualised intervention trajectories. However, although the intervention team worked with the individual needs of each family, some individual needs might not have been completely met. For example, several families asked for couple counselling. Even though the individualised design is a strength of the intervention because it can be tailored to the individual needs and motivations of the family, it is a weakness for mathematical modelling^{99,167}. Despite the advancements in statistical models and study designs to assess effectiveness in complex interventions, progress to research in complex interventions is also driven by integrating theory and qualitative- and mixed methodologies^{83,99}.

Conclusion

In conclusion, we found no superior effect of the VIA Family Intervention compared with treatment as usual. Possible reasons include the intervention's brevity, a short follow-up, measurement biases, and sample heterogeneity. Furthermore, we found that participants' perceptions of need and quality of motivation serve as mechanisms that can lead to change for families engaged in the intervention. Future studies should validate the exploratory and post hoc findings. Nevertheless, addressing families' perceived need for prevention could enhance recruitment, sustain long-term changes, and guide future preventive interventions for children at familial risk of severe mental illness.

Future studies on preventive interventions can benefit from using a mixed methods design to explore effectiveness. Including theoretical frameworks in analyses enriches the interpretation and may assist in applying research findings in real-world settings.

Ethical Considerations

Selective prevention programs inform families about the increased risk of their child developing a lifetime mental illness. Noteworthy, in some interventions, children do typically not show signs of vulnerability, such as a mental illness^{47,168}. For example, in the VIA Family sample, although 32% of the children fulfilled the criteria for a mental disorder at baseline, 68% did not. Nevertheless, we informed all families, regardless of whether their child had a mental disorder or not, about the familial risk caused by the mental illness of the parent.

However, families and parents do not necessarily profit from knowledge about a statistical concept of risk¹⁶⁹. A recent paper on ethical considerations in precision psychiatry highlights how, without preparation, risk information can be difficult to understand and cope with¹⁶⁹. Moreover, knowledge about risk may also alter peoples' behaviour and thus potentially lead to other modifiable factors of risk or protection¹⁶⁹. In families with children at familial risk of mental illness, some parents may respond to risk information by engaging in resilience-enhancing behaviour. For other parents, risk

information might enhance risk factors, such as discrimination and stigmatisation, possibly also fostering self-blame and self-stigmatisation^{168,169}. Stigmatisation serves as a risk factor in the complex transmission of mental illness¹¹. However, it is also associated with various other risk factors for the development of mental illness: impaired social relationships, low self-esteem and less likelihood to seek support^{155,161,162,170}. Conversely, risk information in preventive interventions can foster stigmatisation and negatively impact factors associated with resilience. Noteworthy, contrary to precision psychiatry, the risk labelling in familiar high-risk populations is not based on an individualised screening. Risk labelling in children at familial risk comes with even greater uncertainty, and sensitivity of prediction based on familiar high risk is still weak^{169,171}.

Another ethical aspect of selective prevention is that it may foster a mental illness identity, i.e. identifying with being ill¹⁷². Selective programs often involve screening for early signs of vulnerability. In the VIA Family trial, all children went through a condensed psychiatric screening: a full diagnostic interview (K-SADS-PL¹¹³, including screening for psychotic-like symptoms) and a brief screening of neurocognitive functioning and assessing emotional and behavioural problems at home and at school. We informed all parents verbally about the outcome of the screening. Although we emphasised that the screening was for scientific purposes (and thus not comparable with a screening in a mental health centre), some parents received new information about their children's mental health. The early screening of their children may have promoted illness identification (labelling their children as 'early patients') even though they might never become patients. Sadly, illness identification is associated with self-stigma and impaired social relationships, which both are risk factors for the transgenerational transmission of mental illness¹⁷⁰.

However, qualitative studies emphasize that children and partners experience relief when informed about the mental illness of the parent^{57,65,67}. This knowledge can function as a protective factor, contributing to the development of resilience within the family and, consequently, benefiting the child¹¹.

Given the potential that prevention provides for society, the economy, and the individual family and child, ethical concerns should not hinder the development and

study of selective preventive programs^{168,169}. Nevertheless, ethical considerations should guide clinical practices for selective prevention programs.

Ethical considerations can inform and strengthen future preventive approaches, particularly in areas such as stepped-care programs, practitioner training, and anti-stigmatization campaigns.

Clinical Implications

In this last section, I discuss potential clinical implications for practice based on the results of this thesis in the context of the literature and the ethical reflections.

Support and referrals from mental health services

Clinicians in both adult mental health services and child and adolescent mental health services play a pivotal role in preventive interventions for children with an elevated familial risk¹⁷³. They can engage in conversations with their patients, who are also parents, or with the patient's families. Clinicians can inform and educate about transgenerational transmission, factors of risk and protection, and illuminate how and if the mental illness of the parents potentially affects their patients' children and family. Finally, clinicians can help families with referrals to relevant support systems if indicated. Moreover, clinicians can address and potentially reduce the stigma associated with mental illness in parents.

However, clinicians may not feel well-educated enough to do so^{169,172}. Assisting and supervising clinicians with communication about risk and protective factors and referrals to relevant support systems for families with parental severe mental illness might be one of the most important starting points for stepped-care practices in preventive programs, at least in Denmark. This also points to the importance of collaboration between professionals from different mental health services, i.e. adult mental health services and child and adolescent mental health services, as well as primary, secondary and tertiary care community care¹⁷³.

Stepped Care

Families are busy. Experiences from VIA Family showed that some families struggle to fit a family-based preventive intervention into their everyday lives. A stepped-care approach could, therefore, be promising. Families with a parent experiencing severe mental illness exhibit significant heterogeneity. For example, in the functioning of both children and parents, in the presence of risk and protective factors, and in diversity in perception of the need for support. The choice of intervention should consider the presence of factors of risk and protection in the individual family, signs of vulnerability, and family motivation. The stepped-care approach supports an individually tailored intervention design based on the family's perceived need for support and motivation¹⁷⁴.

Below are listed different levels of preventive interventions which can be included in a stepped-care approach:

1. Mental health support centres – with a subdivision in parental mental illness

The right timing for engaging in preventive intervention plays a crucial role for families with parental mental illness. However, the opportunity for preventive support depends currently on when and if the mental health centres and social services can provide support. Hence, families cannot decide on the timing for support.

A solution for this discrepancy in timing and perceived need might be a (non-psychiatric) centre for mental health promotion with a subunit specialised in families with (parental) mental illness. The centre should be in a non-clinical environment to decrease the risk of fostering stigmatisation and illness identification. Moreover, the centres should also provide universal preventive programs, like anti-stigmatisation campaigns.

Many families, especially adolescents, request online support systems^{58,175,176}. The benefits of online support are the non-stigmatising contact and support 24/7. Online support should provide relevant links to mental health support and other services that

can help families with legal, social, psychiatric, and psychological guidance. Online support for children and adolescents with mental illness has received good acceptance⁵⁸.

2. Short intervention family-based intervention

A brief intervention may be enough support for families when children show no signs of vulnerability or display vulnerability alongside numerous protective factors. Short interventions could also target families without a perceived need for support. The preventive interventions can address specific protective factors, such as parenting support or family communication about parental mental illness. Recent studies have suggested that short interventions are equally effective as longer interventions for some outcomes^{61,63}. However, changes may occur faster when children are included in the intervention⁶¹. Moreover, the results from Study 2 in this thesis demonstrate that children are motivated by their families' participation.

Given the varied activity levels of many families in their daily lives, offering brief support holds great potential.

3. Long (multi-component) family-based intervention

For families with multiple needs for support, a family-based multi-component intervention that spans over a long but flexible period, such as VIA Family, may change a potential imbalance between risk and protective factors in a positive direction. Our experiences from the VIA Family intervention show that such an intervention requires effort, flexibility, and time from the participating families, as well as perseverance and flexibility from the practitioners, and it is costly due to its long duration.

The intervention should target families where children show early signs of vulnerability, e.g., mental disorder, bullying or major academic problems or where the family's total problem load is large or complex. The level of stress for the families may increase when both children and parents are affected by a mental illness. Parents who experienced early signs of vulnerability in their child may be more engaged and prepared to participate in a long family-based intervention due to their perceived need for support.

References

1. Uher R, Pavlova B, Radua J, et al. Transdiagnostic risk of mental disorders in offspring of affected parents: a meta-analysis of family high-risk and registry studies. *World Psychiatry*. 2023;22(3):433-448. doi:10.1002/wps.21147
2. World Health Organization. World mental health report: transforming mental health for all. Published online 2022. . ISBN 978-92-4-004933-8 (electronic version) ISBN 978-92-4-004934-5 (print version)
3. Duffy A, Goodday SM, Christiansen H, et al. The well-being of children at familial risk of severe mental illness: an overlooked yet crucial prevention and early intervention opportunity. *Nat Ment Health*. 2023;1(8):534-541. doi:10.1038/s44220-023-00090-4
4. Arango C, Díaz-Caneja CM, McGorry PD, et al. Preventive strategies for mental health. *Lancet Psychiatry*. 2018;5(7):591-604. doi:10.1016/S2215-0366(18)30057-9
5. Pierce M, Abel KM, Muwonge J, et al. Prevalence of parental mental illness and association with socioeconomic adversity among children in Sweden between 2006 and 2016: a population-based cohort study. *Lancet Public Health*. 2020;5(11):e583-e591. doi:10.1016/S2468-2667(20)30202-4
6. Arias D, Saxena S, Verguet S. Quantifying the global burden of mental disorders and their economic value. *eClinicalMedicine*. 2022;54:101675. doi:10.1016/j.eclinm.2022.101675
7. Maybery D, Reupert AE. The number of parents who are patients attending adult psychiatric services. *Curr Opin Psychiatry*. 2018;31(4):358-362. doi:10.1097/YCO.0000000000000427
8. Christesen AMS, Knudsen CK, Fonager K, Johansen MN, Heuckendorff S. Prevalence of parental mental health conditions among children aged 0–16 years in Denmark: A nationwide register-based cross-sectional study. *Scand J Public Health*. 2022;50(8):1124-1132. doi:10.1177/14034948211045462
9. Ruud T, Maybery D, Reupert A, et al. Adult Mental Health Outpatients Who Have Minor Children: Prevalence of Parents, Referrals of Their Children, and Patient Characteristics. *Front Psychiatry*. 2019;10:163. doi:10.3389/fpsyt.2019.00163
10. Ungar M, Theron L. Resilience and mental health: how multisystemic processes contribute to positive outcomes. *Lancet Psychiatry*. 2020;7(5):441-448. doi:10.1016/S2215-0366(19)30434-1
11. Hosman CMH, Van Doesum KTM, Van Santvoort F. Prevention of emotional problems and psychiatric risks in children of parents with a mental illness in the Netherlands: I. The

scientific basis to a comprehensive approach. *Aust E-J Adv Ment Health*. 2009;8(3):250-263. doi:10.5172/jamh.8.3.250

12. Krantz MF, Ellersgaard D, Andersen KK, et al. Accumulation of Disadvantages Across Multiple Domains Amongst Subgroups of Children of Parents With Schizophrenia or Bipolar Disorder: Clustering Data from the Danish High Risk and Resilience Study VIA 7. *Schizophr Bull Open*. 2022;3(1):sgac010. doi:10.1093/schizbullopen/sgac010
13. Christiansen H, Reck C, Zietlow AL, et al. Children of Mentally Ill Parents at Risk Evaluation (COMPARE): design and methods of a randomized controlled multicenter study—part I. *Front Psychiatry*. 2019;10:128.
14. Smeeth D, Beck S, Karam EG, Pluess M. The role of epigenetics in psychological resilience. *Lancet Psychiatry*. 2021;8(7):620-629. doi:10.1016/S2215-0366(20)30515-0
15. Axford N, Berry V. Money Matters: Time for Prevention and Early Intervention to Address Family Economic Circumstances. *J Prev*. 2023;44(3):267-276. doi:10.1007/s10935-022-00717-9
16. Barroso NE, Mendez L, Graziano PA, Bagner DM. Parenting Stress through the Lens of Different Clinical Groups: a Systematic Review & Meta-Analysis. *J Abnorm Child Psychol*. 2018;46(3):449-461. doi:10.1007/s10802-017-0313-6
17. Gronemann FH, Jacobsen RK, Wium-Andersen MK, Jørgensen MB, Osler M, Jørgensen TSH. Association of Familial Aggregation of Major Depression With Risk of Major Depression. *JAMA Psychiatry*. Published online February 8, 2023. doi:10.1001/jamapsychiatry.2022.4965
18. Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet*. 2021;53(6):817-829. doi:10.1038/s41588-021-00857-4
19. The Brainstorm Consortium, Anttila V, Bulik-Sullivan B, et al. Analysis of shared heritability in common disorders of the brain. *Science*. 2018;360(6395):eaap8757. doi:10.1126/science.aap8757
20. Hilker R, Helenius D, Fagerlund B, et al. Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. *Biol Psychiatry*. 2018;83(6):492-498. doi:10.1016/j.biopsych.2017.08.017
21. McAdams TA, Rijdsdijk FV, Neiderhiser JM, et al. The relationship between parental depressive symptoms and offspring psychopathology: evidence from a children-of-twins study and an adoption study. *Psychol Med*. 2015;45(12):2583-2594. doi:10.1017/S0033291715000501
22. Pratt M, Zeev-Wolf M, Goldstein A, Feldman R. Exposure to early and persistent maternal depression impairs the neural basis of attachment in preadolescence. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;93:21-30. doi:10.1016/j.pnpbp.2019.03.005

23. Howard LM, Khalifeh H. Perinatal mental health: a review of progress and challenges. *World Psychiatry*. 2020;19(3):313-327. doi:10.1002/wps.20769
24. Sell M, Radicke A, Adema B, et al. Parents With Mental Illness: Parental Coping Behavior and Its Association With Children's Mental Health. *Front Psychiatry*. 2021;12:737861. doi:10.3389/fpsy.2021.737861
25. Nordsletten AE, Larsson H, Crowley JJ, Almqvist C, Lichtenstein P, Mataix-Cols D. Patterns of Nonrandom Mating Within and Across 11 Major Psychiatric Disorders. *JAMA Psychiatry*. 2016;73(4):354. doi:10.1001/jamapsychiatry.2015.3192
26. Torvik FA, Eilertsen EM, Hannigan LJ, et al. Modeling assortative mating and genetic similarities between partners, siblings, and in-laws. *Nat Commun*. 2022;13(1):1108. doi:10.1038/s41467-022-28774-y
27. Greve AN, Uher R, Als TD, et al. A nationwide cohort study of nonrandom mating in schizophrenia and bipolar disorder. *Schizophr Bull*. 2021;47(5):1342-1350.
28. Forbes MK, Rapee RM, Camberis AL, McMahon CA. Unique Associations between Childhood Temperament Characteristics and Subsequent Psychopathology Symptom Trajectories from Childhood to Early Adolescence. *J Abnorm Child Psychol*. 2017;45(6):1221-1233. doi:10.1007/s10802-016-0236-7
29. Van Loon LMA, Van De Ven MOM, Van Doesum KTM, Hosman CMH, Wittman CLM. Factors Promoting Mental Health of Adolescents Who Have a Parent with Mental Illness: A Longitudinal Study. *Child Youth Care Forum*. 2015;44(6):777-799. doi:10.1007/s10566-015-9304-3
30. Sandstrom A, Sahiti Q, Pavlova B, Uher R. Offspring of parents with schizophrenia, bipolar disorder, and depression: a review of familial high-risk and molecular genetics studies. *Psychiatr Genet*. 2019;29(5):160-169. doi:10.1097/YPG.0000000000000240
31. Ellersgaard D, Gregersen M, Ranning A, et al. Quality of life and self-esteem in 7-year-old children with familial high risk of schizophrenia or bipolar disorder: the Danish High Risk and Resilience Study-VIA 7—a population-based cohort study. *Eur Child Adolesc Psychiatry*. 2020;29(6):849-860. doi:10.1007/s00787-019-01397-3
32. Silva-Rodrigues APC, Oliveira MRE, Silva TBF, Loureiro SR. Positive Parenting of Mothers with Depression and Children's Behaviors: A Systematic Review. *Trends Psychol*. 2022;30(2):400-423. doi:10.1007/s43076-021-00105-y
33. Perera DN, Short L, Fernbacher S. There is a lot to it: Being a mother and living with a mental illness. *Adv Ment Health*. 2014;12(3):167-181. doi:10.1080/18374905.2014.11081895
34. Cheung K, Theule J. Paternal Depressive Symptoms and Parenting Behaviors: An Updated Meta-Analysis. *J Child Fam Stud*. 2019;28(3):613-626. doi:10.1007/s10826-018-01316-1

35. Harries CI, Smith DM, Gregg L, Wittkowski A. Parenting and Serious Mental Illness (SMI): A Systematic Review and Metasynthesis. *Clin Child Fam Psychol Rev*. 2023;26(2):303-342. doi:10.1007/s10567-023-00427-6
36. Calam R, Jones S, Sanders MR, Dempsey R, Sadhnani V. Parenting and the Emotional and Behavioural Adjustment of Young Children in Families with a Parent with Bipolar Disorder. *Behav Cogn Psychother*. 2012;40(4):425-437. doi:10.1017/S1352465812000094
37. Radley J, Sivarajah N, Moltrecht B, et al. A Scoping Review of Interventions Designed to Support Parents With Mental Illness That Would Be Appropriate for Parents With Psychosis. *Front Psychiatry*. 2022;12:787166. doi:10.3389/fpsyt.2021.787166
38. Krantz MF, Hjorthøj C, Brandt JM, et al. Home environment of 11-year-old children born to parents with schizophrenia or bipolar disorder – a controlled, 4-year follow-up study: The Danish High Risk and Resilience Study – VIA 11. *Psychol Med*. 2023;53(6):2563-2573. doi:10.1017/S0033291721004487
39. World Health Organization. *Social Determinants of Mental Health*. World Health Organization; 2014. Accessed October 30, 2023. <https://iris.who.int/handle/10665/112828>
40. Sullivan ADW, Forehand R, Vreeland A, Compas BE. Does Parenting Explain the Link Between Cumulative SES Risk and Child Problems in the Context of Parental Depression? *Child Psychiatry Hum Dev*. 2022;53(2):330-341. doi:10.1007/s10578-021-01130-9
41. Thorup AAE, Laursen TM, Munk-Olsen T, et al. Incidence of child and adolescent mental disorders in children aged 0-17 with familial high risk for severe mental illness - A Danish register study. *Schizophr Res*. 2018;197:298-304. doi:10.1016/j.schres.2017.11.009
42. Firth J, Siddiqi N, Koyanagi A, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry*. 2019;6(8):675-712. doi:10.1016/S2215-0366(19)30132-4
43. Renneberg CK, Brund RBK, Heuckendorff S, Bech BH, Fonager K. Children of parents with different severities of mental health conditions have higher risk of somatic morbidity: a Danish nationwide register-based cohort study. *BMC Public Health*. 2023;23(1):810. doi:10.1186/s12889-023-15714-8
44. Ranning A, Laursen T, Agerbo E, et al. School performance from primary education in the adolescent offspring of parents with schizophrenia and bipolar disorder—a national, register-based study. *Psychol Med*. 2018;48(12):1993-2000.
45. Fusar-Poli P, Correll CU, Arango C, Berk M, Patel V, Ioannidis JP. Preventive psychiatry: a blueprint for improving the mental health of young people. *World Psychiatry*. 2021;20(2):200-221. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/wps.20869>
46. Romano JL. *Prevention Psychology: Enhancing Personal and Social Well-Being*. American psychological association; 2015.
47. Hosman CMH, Jané Llopis E, Saxena S. *Prevention of Mental Disorders: Effective Interventions and Policy Options : Summary Report*. World Health Organization; 2004.

48. Reupert AE, Maybery DJ. A “snapshot” of Australian programs to support children and adolescents whose parents have a mental illness. *Psychiatr Rehabil J*. 2009;33(2):125-132. doi:10.2975/33.2.2009.125.132
49. Hafting M, Gullbrå F, Anderssen N, Rørtveit G, Smith-Sivertsen T, Malterud K. Burdened parents sharing their concerns for their children with the doctor. *The impact of trust in general practice: a qualitative study. Scand J Prim Health Care*. 2019;37(3):327-334. doi:10.1080/02813432.2019.1639907
50. Lannes A, Bui E, Arnaud C, Raynaud JP, Revet A. Preventive interventions in offspring of parents with mental illness: a systematic review and meta-analysis of randomized controlled trials. *Psychol Med*. 2021;51(14):2321-2336. doi:10.1017/S0033291721003366
51. Thanhäuser M, Lemmer G, de Girolamo G, Christiansen H. Do preventive interventions for children of mentally ill parents work? Results of a systematic review and meta-analysis. *Curr Opin Psychiatry*. 2017;30(4):283-299. doi:10.1097/YCO.0000000000000342
52. Marston N, Stavnes K, Van Loon LMA, et al. A content analysis of Intervention Key Elements and Assessments (IKEA): What’s in the black box in the interventions directed to families where a parent has a mental illness? *Child Youth Serv*. 2016;37(2):112-128. doi:10.1080/0145935X.2016.1104041
53. Bronfenbrenner U. *The Ecology of Human Development: Experiments by Nature and Design*. Harvard university press; 1979.
54. Puchol-Martínez I, Vallina Fernández Ó, Santed-Germán MA. Preventive interventions for children and adolescents of parents with mental illness: A systematic review. *Clin Psychol Psychother*. Published online March 30, 2023:cpp.2850. doi:10.1002/cpp.2850
55. Reupert AE, Maybery D. “Knowledge is Power”: Educating Children About Their Parent’s Mental Illness. *Soc Work Health Care*. 2010;49(7):630-646. doi:10.1080/00981380903364791
56. Tapias E, Coromina M, Grases N, Ochoa S. Psychological Treatments with Children of Parents with Mental Illness: A Systematic Review. *Child Youth Care Forum*. 2021;50(6):1107-1130. doi:10.1007/s10566-021-09608-2
57. Pihkala H, Sandlund M, Cederström A. Children in Beardslee’s family intervention: Relieved by understanding of parental mental illness. *Int J Soc Psychiatry*. 2012;58(6):623-628. doi:10.1177/0020764011419055
58. Villatte A, Piché G, Habib R, Gariépy J. Evaluation of a mental-health literacy and self-care website intended for young people who have a parent with a mental illness. *Adv Ment Health*. Published online October 4, 2023:1-20. doi:10.1080/18387357.2023.2264416
59. Beardslee, William, Hoke, L, Wheelok, I, Rothberg, PC, Van de Velde, P, Swatling, S. Initial findings on preventive intervention for families with parental affective disorders. *Am J Psychiatry*. 1992;149(10):1335-1340. doi:10.1176/ajp.149.10.1335

60. Solantaus T, Paavonen EJ, Toikka S, Punamäki RL. Preventive interventions in families with parental depression: children's psychosocial symptoms and prosocial behaviour. *Eur Child Adolesc Psychiatry*. 2010;19(12):883-892. doi:10.1007/s00787-010-0135-3
61. Giannakopoulos G, Solantaus T, Tzavara C, Kolaitis G. Mental health promotion and prevention interventions in families with parental depression: A randomized controlled trial. *J Affect Disord*. 2021;278:114-121. doi:10.1016/j.jad.2020.09.070
62. Nielsen SS, Mikkelsen LJ, Quaade N, et al. A study protocol for the randomized controlled trial SAFIR FAMILY TALK: a selective primary preventive intervention vs. service as usual for children of parents with mental illness. *Trials*. 2023;24(1):291. doi:10.1186/s13063-023-07256-6
63. Wirehag Nordh E, Grip K, Thorvaldsson V, Priebe G, Afzelius M, Axberg U. Preventive interventions for children of parents with depression, anxiety, or bipolar disorder: A quasi-experimental clinical trial. *Acta Paediatr*. 2023;112(1):132-142. doi:10.1111/apa.16555
64. Mulligan C, Furlong M, McGarr S, O'Connor S, McGilloway S. The Family Talk Programme in Ireland: A Qualitative Analysis of the Experiences of Families With Parental Mental Illness. *Front Psychiatry*. 2021;12:783189. doi:10.3389/fpsy.2021.783189
65. Maybery D, Goodyear M, Reupert A, et al. A mixed method evaluation of an intervention for parents with mental illness. *Clin Child Psychol Psychiatry*. 2019;24(4):717-727. doi:10.1177/1359104518822676
66. Vetri K, Piché G, Villatte A. An Evaluation of the Acceptability, Appropriateness, and Utility of a Bibliotherapy for Children of Parents With a Mental Illness. *Front Psychiatry*. 2022;13:815873. doi:10.3389/fpsy.2022.815873
67. Grové C, Melrose H, Reupert A, Maybery D, Morgan B. *When your parent has a mental illness* : children's experiences of a psycho-educational intervention. *Adv Ment Health*. 2015;13(2):127-138. doi:10.1080/18387357.2015.1063637
68. Coiro MJ, Riley A, Broitman M, Miranda J. Effects on Children of Treating Their Mothers' Depression: Results of a 12-Month Follow-Up. *Psychiatr Serv*. 2012;63(4):357-363. doi:10.1176/appi.ps.201100126
69. Clarke GN, Hornbrook M, Lynch F, et al. A randomized trial of a group cognitive intervention for preventing depression in adolescent offspring of depressed parents. *Arch Gen Psychiatry*. 2001;58(12):1127-1134.
70. Garber J, Clarke GN, Weersing VR, et al. Prevention of Depression in At-Risk Adolescents: A Randomized Controlled Trial. *JAMA*. 2009;301(21):2215. doi:10.1001/jama.2009.788
71. Compas BE, Forehand R, Keller G, et al. Randomized controlled trial of a family cognitive-behavioral preventive intervention for children of depressed parents. *J Consult Clin Psychol*. 2009;77(6):1007-1020. doi:10.1037/a0016930

72. Compas BE, Forehand R, Thigpen J, et al. Efficacy and moderators of a family group cognitive-behavioral preventive intervention for children of parents with depression. *J Consult Clin Psychol*. 2015;83(3):541-553. doi:10.1037/a0039053
73. Löchner J, Starman-Wöhrle K, Takano K, et al. *A Randomised Controlled Trial of a Cognitive-Behavioural Preventive Intervention for the Children of Parents with Depression: Short-Term Effects on Symptoms and Possible Mechanisms*. In Review; 2021. doi:10.21203/rs.3.rs-162743/v1
74. Löchner J, Platt B, Starman-Wöhrle K, et al. A randomized controlled trial of a preventive intervention for the children of parents with depression: mid-term effects, mediators and moderators. *BMC Psychiatry*. 2023;23(1):455. doi:10.1186/s12888-023-04926-2
75. Sanders MR. Triple P-Positive Parenting Program as a public health approach to strengthening parenting. *J Fam Psychol*. 2008;22(4):506-517. doi:10.1037/0893-3200.22.3.506
76. Davies G, P. Deane F, Williams V, Giles C. Barriers, facilitators and interventions to support HELP-SEEKING amongst young people living in families impacted by parental mental illness: A systematized review. *Early Interv Psychiatry*. 2022;16(5):469-480. doi:10.1111/eip.13194
77. Goodyear M, Cuff R, Maybery D, Reupert A. Champs: A peer support program for children of parents with a mental illness. *Aust E-J Adv Ment Health*. 2009;8(3):296-304. doi:10.5172/jamh.8.3.296
78. Van Santvoort F, Hosman CMH, Van Doesum KTM, Janssens JMAM. Effectiveness of preventive support groups for children of mentally ill or addicted parents: a randomized controlled trial. *Eur Child Adolesc Psychiatry*. 2014;23(6):473-484. doi:10.1007/s00787-013-0476-9
79. Wahl P, Bruland D, Bauer U, Okan O, Lenz A. What are the family needs when a parent has mental health problems? Evidence from a systematic literature review. *J Child Adolesc Psychiatr Nurs*. 2017;30(1):54-66. doi:10.1111/jcap.12171
80. Steffenak AKM, Anderzén-Carlsson A, Opheim E, Sandsdalen T. Community-based support for children who are next-of-kin for a parent experiencing illness or disability – a scoping review. *BMC Health Serv Res*. 2021;21(1):1250. doi:10.1186/s12913-021-07270-x
81. Wansink HJ, Hosman CMH, Janssens JMAM, Hoencamp E, Willems WJCT. Preventive family service coordination for parents with a mental illness in the Netherlands. *Psychiatr Rehabil J*. 2014;37(3):216-221. doi:10.1037/prj0000073
82. Wansink HJ, Janssens JMAM, Hoencamp E, Middelkoop BJC, Hosman CMH. Effects of preventive family service coordination for parents with mental illnesses and their children, a RCT. *Fam Syst Health*. 2015;33(2):110-119. doi:10.1037/fsh0000105
83. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ*. Published online September 30, 2021:n2061. doi:10.1136/bmj.n2061

84. Richards DA, Rahm Hallberg I, eds. *Complex Interventions in Health: An Overview of Research Methods*. Routledge; 2015.
85. Petticrew M. When are complex interventions “complex”? When are simple interventions “simple”? *Eur J Public Health*. 2011;21(4):397-398. doi:10.1093/eurpub/ckr084
86. Bonell C, Warren E, Melendez-Torres G. Methodological reflections on using qualitative research to explore the causal mechanisms of complex health interventions. *Evaluation*. 2022;28(2):166-181. doi:10.1177/13563890221086309
87. Taubner S, Ioannou Y, Saliba A, et al. Mediators of outcome in adolescent psychotherapy and their implications for theories and mechanisms of change: a systematic review. *Eur Child Adolesc Psychiatry*. Published online March 15, 2023. doi:10.1007/s00787-023-02186-9
88. Kazdin AE. Mediators and Mechanisms of Change in Psychotherapy Research. *Annu Rev Clin Psychol*. 2007;3(1):1-27. doi:10.1146/annurev.clinpsy.3.022806.091432
89. Bonell C, Warren E, Melendez-Torres G. Methodological reflections on using qualitative research to explore the causal mechanisms of complex health interventions. *Evaluation*. 2022;28(2):166-181. doi:10.1177/13563890221086309
90. Burchett HED, Kneale D, Blanchard L, Thomas J. When assessing generalisability, focusing on differences in population or setting alone is insufficient. *Trials*. 2020;21(1):286. doi:10.1186/s13063-020-4178-6
91. Kuckertz JM, Mitchell C, Wiggins JL. Parenting mediates the impact of maternal depression on child internalizing symptoms. *Depress Anxiety*. 2018;35(1):89-97.
92. Goodyear MJ, Allchin B, Burn M, et al. Promoting self-determination in parents with mental illness in adult mental health settings. *J Fam Nurs*. 2022;28(2):129-141.
93. Cuijpers P, Reijnders M, Huibers MJH. The Role of Common Factors in Psychotherapy Outcomes. *Annu Rev Clin Psychol*. 2019;15(1):207-231. doi:10.1146/annurev-clinpsy-050718-095424
94. Müller AD, Gjøde ICT, Eigil MS, et al. VIA Family—a family-based early intervention versus treatment as usual for familial high-risk children: a study protocol for a randomized clinical trial. *Trials*. 2019;20(1):112. doi:10.1186/s13063-019-3191-0
95. Shaffer D. A Children’s Global Assessment Scale (CGAS). *Arch Gen Psychiatry*. 1983;40(11):1228. doi:10.1001/archpsyc.1983.01790100074010
96. Müller, Anne Dorothee; Thams, Nikolaj; Gjøde, Ida C T; Hemager, Nicoline; Nordentoft, Merete; Thorup, Anne A E. Statistical Analysis Plan (SAP) for: VIA Family—a family-based early intervention versus treatment as usual for familial high-risk children. Published online May 25, 2021. https://classic.clinicaltrials.gov/ProvidedDocs/63/NCT03497663/SAP_000.pdf

97. Creswell JW, Plano Clark VL. *Designing and Conducting Mixed Methods Research*. Third edition, international student edition. Sage; 2018.
98. Drabble SJ, O’Cathain A. *Moving From Randomized Controlled Trials to Mixed Methods Intervention Evaluations*. (Hesse-Biber SN, Johnson RB, eds.). Oxford University Press; 2015. doi:10.1093/oxfordhb/9780199933624.013.26
99. Petticrew M, Rehfuess E, Noyes J, et al. Synthesizing evidence on complex interventions: how meta-analytical, qualitative, and mixed-method approaches can contribute. *J Clin Epidemiol*. 2013;66(11):1230-1243. doi:10.1016/j.jclinepi.2013.06.005
100. Sanders MR, Kirby JN, Tellegen CL, Day JJ. The Triple P-Positive Parenting Program: A systematic review and meta-analysis of a multi-level system of parenting support. *Clin Psychol Rev*. 2014;34(4):337-357. doi:10.1016/j.cpr.2014.04.003
101. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
102. Wing JK. SCAN: Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry*. 1990;47(6):589. doi:10.1001/archpsyc.1990.01810180089012
103. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7_suppl):22-25. doi:10.1177/1403494810387965
104. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(7_suppl):54-57. doi:10.1177/1403494810395825
105. Adler K, Salanterä S, Zumstein-Shaha M. Focus Group Interviews in Child, Youth, and Parent Research: An Integrative Literature Review. *Int J Qual Methods*. 2019;18:160940691988727. doi:10.1177/1609406919887274
106. Thorup AA, Hemager N, Søndergaard A, et al. The Danish High Risk and Resilience Study—VIA 11: study protocol for the first follow-up of the VIA 7 cohort— 522 children born to parents with schizophrenia spectrum disorders or bipolar disorder and controls being re-examined for the first time at age 11. *Front Psychiatry*. 2018;9:661.
107. Caldwell BM, Bradley RH. Home observation for measurement of the environment: Administration manual. *Tempe AZ Fam Hum Dyn Res Inst Ariz State Univ*. Published online 2003.
108. Epstein NB, Baldwin LM, Bishop DS. THE McMASTER FAMILY ASSESSMENT DEVICE*. *J Marital Fam Ther*. 1983;9(2):171-180. doi:10.1111/j.1752-0606.1983.tb01497.x
109. Reynolds CR, Kamphaus RW. Reynolds intellectual assessment scales (RIAS). *Lutz FL Psychol Assess Resour*. Published online 2003.

110. Reynolds CR, Voress JK. Test of Memory and Learning, 2nd Edition (TOMAL 2). Published online 2007.
111. Wechsler D. Wechsler intelligence scale for children – Fourth edition (WISC-IV). Published online 2003.
112. Meyers J, Meyers KR. *Rey Complex Figure Test and Recognition Trial*. Psychological Assessment Resources, Incorporated; 1995.
113. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980-988. doi:10.1097/00004583-199707000-00021
114. Constantino JN, Gruber CP. Social responsiveness scale: SRS-2. Published online 2012.
115. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101(4):323-329. doi:10.1111/j.1600-0447.2000.tb10933.x
116. Berry JO, Jones WH. The Parental Stress Scale: Initial Psychometric Evidence. *J Soc Pers Relatsh*. 1995;12(3):463-472. doi:10.1177/0265407595123009
117. Lundh A. *On the Children's Global Assessment Scale (CGAS)*. Karolinska institutet; 2012.
118. Lundh A, Forsman M, Serlachius E, Långström N, Lichtenstein P, Landén M. Psychosocial functioning in adolescent patients assessed with Children's Global Assessment Scale (CGAS) predicts negative outcomes from age 18: A cohort study. *Psychiatry Res*. 2016;242:295-301.
119. Achenbach TM. Manual for ASEBA school-age forms & profiles. *Univ Vt Res Cent Child Youth Fam*. Published online 2001.
120. Gioia GA, Isquith PK, Guy SC, Kenworthy L. TEST REVIEW Behavior Rating Inventory of Executive Function. *Child Neuropsychol*. 2000;6(3):235-238. doi:10.1076/chin.6.3.235.3152
121. Gerson AC, Gerring JP, Freund L, et al. The Children's Affective Lability Scale: A psychometric evaluation of reliability. *Psychiatry Res*. 1996;65(3):189-198. doi:10.1016/S0165-1781(96)02851-X
122. Zwicker A, Drobinin V, MacKenzie LE, et al. Affective lability in offspring of parents with major depressive disorder, bipolar disorder and schizophrenia. *Eur Child Adolesc Psychiatry*. 2020;29(4):445-451. doi:10.1007/s00787-019-01355-z
123. Shields A, Cicchetti D. Emotion regulation among school-age children: the development and validation of a new criterion Q-sort scale. *Dev Psychol*. 1997;33(6):906.

124. Obel C, Dalsgaard S, Stax HP, Bilenberg N. Strengths and Difficulties Questionnaire (SDQ-Dan). A new instrument for psychopathologic screening of children aged 4-16 years. *Ugeskr Læg.* 2003;165(5):462-465.
125. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. *ADHD Rating Scale—IV: Checklists, Norms, and Clinical Interpretation*. Guilford press; 1998.
126. Poulsen L, Jørgensen SL, Dalsgaard S, Bilenberg N. [Danish standardization of the attention deficit hyperactivity disorder rating scale]. *Ugeskr Laeger.* 2009;171(18):1500-1504.
127. Liebenberg L, Ungar M, LeBlanc JC. The CYRM-12: a brief measure of resilience. *Can J Public Health.* 2013;104:e131-e135.
128. Suonpää E, Kresanov K, Ouvinen-Birgerstam P, Piha J. Self-concept of Finnish children on the second grade of normal elementary school. *Acta Paedopsychiatr.* 1989;52(3):157-164.
129. Ravens-Sieberer U, Gosch A, Rajmil L, et al. KIDSCREEN-52 quality-of-life measure for children and adolescents. *Expert Rev Pharmacoecon Outcomes Res.* 2005;5(3):353-364.
130. Prof. Dr. phil. Ulrike Ravens-Sieberer. Provision of European Norm Data for Children, Adolescents, and Their Parents for Group Level Comparisons. <https://www.kidscreen.org/english/analysis/manual-appendices/>
131. Grabe H, Schulz A, Schmidt C, et al. Ein Screeninginstrument für Missbrauch und Vernachlässigung in der Kindheit: der Childhood Trauma Screener (CTS). *Psychiatr Prax.* 2012;39(03):109-115. doi:10.1055/s-0031-1298984
132. Clark CD. *In a Younger Voice: Doing Child-Centered Qualitative Research*. Oxford University Press; 2011.
133. O'Reilly M, Parker N. *Doing Mental Health Research with Children and Adolescents: A Guide to Qualitative Methods*. SAGE; 2014.
134. Jackson K, Bazeley P, Bazeley P. *Qualitative Data Analysis with NVivo*. Sage; 2019.
135. Achenbach TM. The Child Behavior Checklist and related instruments. *Use Psychol Test Treat Plan Outcomes Assess 2nd Ed*. Published online 1999:429-466.
136. Ellersgaard D, Jessica Plessen K, Richardt Jepsen J, et al. Psychopathology in 7-year-old children with familial high risk of developing schizophrenia spectrum psychosis or bipolar disorder - The Danish High Risk and Resilience Study - VIA 7, a population-based cohort study. *World Psychiatry.* 2018;17(2):210-219. doi:10.1002/wps.20527
137. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Med Res Methodol.* 2017;17(1):162. doi:10.1186/s12874-017-0442-1
138. R Core Team. A language and environment for statistical computing. Published online 2022. <https://www.R-project.org/>

139. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using **lme4**. *J Stat Softw*. 2015;67(1). doi:10.18637/jss.v067.i01
140. Imai K, King G, Lau O. Toward a Common Framework for Statistical Analysis and Development. *J Comput Graph Stat*. 2008;17(4):892-913. Accessed March 15, 2023. <http://www.jstor.org/stable/25651234>
141. Honaker J, King G, Blackwell M. **Amelia** II: A Program for Missing Data. *J Stat Softw*. 2011;45(7). doi:10.18637/jss.v045.i07
142. Timmermans S, Tavory I. *Data Analysis in Qualitative Research: Theorizing with Abductive Analysis*. University of Chicago Press; 2022.
143. Tavory I, Timmermans S. *Abductive Analysis: Theorizing Qualitative Research*. The University of Chicago Press; 2014.
144. Timmermans S, Tavory I. Theory Construction in Qualitative Research: From Grounded Theory to Abductive Analysis. *Sociol Theory*. 2012;30(3):167-186. doi:10.1177/0735275112457914
145. Thompson J. A Guide to Abductive Thematic Analysis. *Qual Rep*. Published online May 20, 2022. doi:10.46743/2160-3715/2022.5340
146. Rosenstock IM. The Health Belief Model and Preventive Health Behavior. *Health Educ Monogr*. 1974;2(4):354-386. doi:10.1177/109019817400200405
147. Green EC, Murphy EM, Gryboski K. The Health Belief Model. In: Sweeny K, Robbins ML, Cohen LM, eds. *The Wiley Encyclopedia of Health Psychology*. 1st ed. Wiley; 2020:211-214. doi:10.1002/9781119057840.ch68
148. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol*. 2000;55(1):68-78. doi:10.1037/0003-066X.55.1.68
149. Deci EL, Ryan RM, eds. *Handbook of Self-Determination Research*. Softcover edition. University of Rochester Press; 2004.
150. Ryan RM, ed. *The Oxford Handbook of Self-Determination Theory*. Oxford University Press; 2023.
151. Vansteenkiste M, Sheldon KM. There's nothing more practical than a good theory: Integrating motivational interviewing and self-determination theory. *Br J Clin Psychol*. 2006;45(1):63-82. doi:10.1348/014466505X34192
152. Rosenkranz GK. Exploratory subgroup analysis in clinical trials by model selection. *Biom J*. 2016;58(5):1217-1228. doi:10.1002/bimj.201500147
153. Michalos AC, ed. PSP Scale. In: *Encyclopedia of Quality of Life and Well-Being Research*. Springer Netherlands; 2014:5134-5134. doi:10.1007/978-94-007-0753-5_103265

154. Van Der Put CE, Assink M, Gubbels J, Boekhout Van Solinge NF. Identifying Effective Components of Child Maltreatment Interventions: A Meta-analysis. *Clin Child Fam Psychol Rev*. 2018;21(2):171-202. doi:10.1007/s10567-017-0250-5
155. Song N, Hugh-Jones S, West RM, Pickavance J, Mir G. The effectiveness of anti-stigma interventions for reducing mental health stigma in young people: A systematic review and meta-analysis. *Camb Prisms Glob Ment Health*. 2023;10:e39. doi:10.1017/gmh.2023.34
156. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC Med*. 2012;10(1):99. doi:10.1186/1741-7015-10-99
157. Houle AA, Besnard T, Bérubé A. Factors that influence parent recruitment into prevention programs in early childhood: A mixed studies systematic review. *Child Youth Serv Rev*. 2022;133:106367. doi:10.1016/j.chilcyouth.2022.106367
158. Finan SJ, Swierzbiolek B, Priest N, Warren N, Yap M. Parental engagement in preventive parenting programs for child mental health: a systematic review of predictors and strategies to increase engagement. *PeerJ*. 2018;6:e4676. doi:10.7717/peerj.4676
159. Pereira AI, Barros L. Parental Cognitions and Motivation to Engage in Psychological Interventions: A Systematic Review. *Child Psychiatry Hum Dev*. 2019;50(3):347-361. doi:10.1007/s10578-018-0852-2
160. Ginsburg LR, Hoben M, Easterbrook A, Anderson RA, Estabrooks CA, Norton PG. Fidelity is not easy! Challenges and guidelines for assessing fidelity in complex interventions. *Trials*. 2021;22(1):372. doi:10.1186/s13063-021-05322-5
161. Reupert A, Gladstone B, Helena Hine R, et al. Stigma in relation to families living with parental mental illness: An integrative review. *Int J Ment Health Nurs*. 2021;30(1):6-26. doi:10.1111/inm.12820
162. Akouri-Shan L, DeLuca JS, Pitts SC, et al. Internalized stigma mediates the relation between psychosis-risk symptoms and subjective quality of life in a help-seeking sample. *Schizophr Res*. 2022;241:298-305. doi:10.1016/j.schres.2022.02.022
163. Dobener LM, Fahrner J, Purtscheller D, Bauer A, Paul JL, Christiansen H. How Do Children of Parents With Mental Illness Experience Stigma? A Systematic Mixed Studies Review. *Front Psychiatry*. 2022;13:813519. doi:10.3389/fpsyt.2022.813519
164. Ryan RM, Deci EL. Self-Regulation and the Problem of Human Autonomy: Does Psychology Need Choice, Self-Determination, and Will? *J Pers*. 2006;74(6):1557-1586. doi:10.1111/j.1467-6494.2006.00420.x
165. Church AT, Katigbak MS, Locke KD, et al. Need Satisfaction and Well-Being: Testing Self-Determination Theory in Eight Cultures. *J Cross-Cult Psychol*. 2013;44(4):507-534. doi:10.1177/0022022112466590

166. Pietilä M, Saurio K, Martela F, Silfver M, Hankonen N. Basic psychological needs, quality of motivation, and protective behavior intentions: a nationally representative survey study. *Health Psychol Behav Med*. 2023;11(1):2257295. doi:10.1080/21642850.2023.2257295
167. Greenwood-Lee J, Hawe P, Nettel-Aguirre A, Shiell A, Marshall DA. Complex intervention modelling should capture the dynamics of adaptation. *BMC Med Res Methodol*. 2016;16(1):51, s12874-016-0149-8. doi:10.1186/s12874-016-0149-8
168. Ratheesh A, Cotton SM, Davey CG, et al. Ethical considerations in preventive interventions for bipolar disorder. *Early Interv Psychiatry*. 2017;11(2):104-112. doi:10.1111/eip.12340
169. Fusar-Poli P, Manchia M, Koutsouleris N, et al. Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. *Eur Neuropsychopharmacol*. 2022;63:17-34. doi:10.1016/j.euroneuro.2022.08.001
170. Yanos PT, DeLuca JS, Roe D, Lysaker PH. The impact of illness identity on recovery from severe mental illness: A review of the evidence. *Psychiatry Res*. 2020;288:112950. doi:10.1016/j.psychres.2020.112950
171. Zwicker A, Fullerton JM, Mullins N, et al. Polygenic Scores and Onset of Major Mood or Psychotic Disorders Among Offspring of Affected Parents. *Am J Psychiatry*. 2023;180(4):285-293. doi:10.1176/appi.ajp.20220476
172. Harzheim L, Lorke M, Woopen C, Jünger S. Health Literacy as Communicative Action—A Qualitative Study among Persons at Risk in the Context of Predictive and Preventive Medicine. *Int J Environ Res Public Health*. 2020;17(5):1718. doi:10.3390/ijerph17051718
173. Reupert A. From individuals to populations: approaches to promoting mental health and preventing mental illness. *Adv Ment Health*. 2022;20(3):181-183. doi:10.1080/18387357.2022.2143205
174. Davison J, Scott J. Should we intervene at stage 0? A qualitative study of attitudes of asymptomatic youth at increased risk of developing bipolar disorders and parents with established disease. *Early Interv Psychiatry*. 2018;12(6):1112-1119. doi:10.1111/eip.12421
175. Grové C, Reupert A, Maybery D. The Perspectives of Young People of Parents with a Mental Illness Regarding Preferred Interventions and Supports. *J Child Fam Stud*. 2016;25(10):3056-3065. doi:10.1007/s10826-016-0468-8
176. Patrick P, Reupert A, McLean L. “We Are More than Our Parents’ Mental Illness”: Narratives from Adult Children. *Int J Environ Res Public Health*. 2019;16(5):839. doi:10.3390/ijerph16050839

Paper 1

Müller, Anne D; Gjøde, Ida C T; Thams, Nikolaj; Ingversen, Sidsel; Moszkowicz, Mala; Jepsen, Jens R M; Mikkelsen, Lisbeth J; Nielsen, Signe S; Hemager, Nicoline; Nordentoft, Merete; and Thorup, Anne A E (2023) *Family-based preventive intervention for children of parents with severe mental illness: A randomized clinical trial*

Accepted for publication in JCPP-Advances

Family-based preventive intervention for children of parents with severe mental illness: A randomized clinical trial

Anne Dorothee Müller^{1,2}  | Ida Christine Tholstrup Gjøde^{1,2} | Nikolaj Thams³ | Sidsel Ingversen² | Mala Moszkowicz² | Jens Richardt Møllegaard Jepsen^{2,4} | Lisbeth Juhl Mikkelsen^{1,5} | Signe Sofie Nielsen^{5,6} | Nicoline Hemager^{2,5,6} | Merete Nordentoft^{1,5} | Anne A. E. Thorup^{1,2}

¹Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

²Child and Adolescent Mental Health Center, Research Unit, Copenhagen University Hospital – Mental Health Services CPH, Copenhagen, Denmark

³Department of Mathematical Sciences, University of Copenhagen, Copenhagen, Denmark

⁴Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark

⁵CORE – Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre Copenhagen, Copenhagen, Denmark

⁶Department of Psychology, University of Copenhagen, Copenhagen, Denmark

Correspondence

Anne Dorothee Müller, Gentofte Hospitalsvej 3A, 1.sal, 2900 Hellerup, Denmark.
Email: anne.dorothee.mueller@regionh.dk

Funding information

TrygFonden; Aase og Ejnar Danielsens fond; Region Hovedstaden, Grant/Award Number: Tværsulje; Danish Ministry of Interior and Health, Grant/Award Number: Satspulje; Municipality of Frederiksberg

Abstract

Background: Children of parents with a severe mental illness have an increased risk of developing a lifetime mental illness. We aimed to compare the effects of a preventive family-based intervention, VIA Family, with treatment as usual (TAU) on these children's global functioning.

Methods: Between 2017 and 2021, we conducted a pragmatic, rater-blinded, two-arm parallel-group superiority trial in Denmark. Families with at least one child aged 6–12 years and at least one biological parent with schizophrenia spectrum disorder, bipolar disorder, or recurrent major or moderate depression were included. We randomly allocated 95 families with their 113 children to VIA Family or TAU (ratio 1:1). VIA Family was individually tailored and based on case management. The intervention included options for psychoeducation, parental support, and treatment for emerging child psychiatric symptoms. Blinded raters assessed children and their families at baseline and after 18 months. The primary outcome was the difference in change between groups at end-of-treatment in daily global functioning measured with the Children's Global Assessment Scale. Secondary outcomes were emotional and behavioral problems and days absent from school. We analyzed data blinded to allocation.

Results: At post-intervention, differences in mean change from baseline between VIA Family and TAU were non-significant (CGAS: -1.20 , 95% CI = -6.61 ; 4.21 , $p = 0.66$), as were the differences on the secondary and exploratory outcomes.

Conclusion: Contrary to our hypothesis, we did not find a superior effect of VIA Family compared with TAU. The short follow-up period and large sample heterogeneity might explain the null findings. Therefore, a possible long-term, preventive treatment effect has yet to be explored.

KEYWORDS

affective disorders, family, parental mental illness, prevention, psychosis

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Authors. JCPP Advances published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health.

INTRODUCTION

Preventive interventions for families with parental mental illness can potentially reduce both the prevalence and the burden of mental illness. Globally, mental illness is the leading cause of disability and suicide and comes with high social and economic costs (World Health Organization, 2022). Therefore, preventive interventions could benefit society, the economy, and the individual and the relatives. There are often early indicators of emerging or increased risk of mental illness. The strongest known risk factors for a child to develop a lifetime mental illness are being born to (genetic risk) and growing up with (environmental risk) a parent with a severe mental illness (SMI) (Rasic et al., 2014), that is, schizophrenia, bipolar disorder, and recurrent major depression (Sandstrom et al., 2019). Globally, the prevalence of parents in adult psychiatric facilities ranges from 12.2% to 45.0% (Maybery & Reupert, 2018). In Denmark, 2.2% of children (0–16 years) have at least one parent who recently (past five years) received psychiatric care for SMI (Christesen et al., 2022). Children of parents with SMI have a 30% risk of developing a SMI and a 55% risk of any other mental illness (Rasic et al., 2014). Genes account for some part of the transmission of SMI (Gronemann et al., 2023; Mullins et al., 2021; The Brainstorm Consortium et al., 2018). However, the increased risk is also caused by environmental factors (Hilker et al., 2018; McAdams et al., 2015). For example, children of parents with SMI more often live in an inadequate home environment (Thorup et al., 2022) and more often experience adverse events in childhood (Brandt et al., 2022).

Early signs of vulnerability and risk are present already during childhood. For example, children of parents with SMI more often have psychiatric symptoms (Gregersen et al., 2022; Sandstrom et al., 2020), have a lower level of psychosocial functioning (Gregersen et al., 2022; Sandstrom et al., 2019), and show impaired motor and cognitive functions (Burton et al., 2017; Hemager et al., 2018; MacKenzie et al., 2020) compared with their peers without parental SMI.

Despite this increased risk, many children with a familial predisposition do not develop a lifetime mental illness, highlighting the role of resilience. Resilience is the ability to adapt competently after exposure to adverse or stressful life events (Ungar & Theron, 2020). Protective factors build and improve a child's resilience. Internal protective factors include good social skills and self-esteem (Hosman et al., 2004). External protective factors are in a child's environment, that is, in the family (e.g., positive parenting and a stimulating home environment), in the community (e.g., a supportive school/educational system), and at a more cultural and structural level (e.g., gender equality and economic wealth) (World Health Organization, 2022).

Family plays the most central role in these children's transmission and development of risk and protective factors (Raballo et al., 2021). Consequently, preventive interventions should target the whole family. A recent meta-analysis showed a significant reduction of risk for the incidence of mental illness for children of parents with a mental illness who participated in preventive interventions at the end of treatment (Combined Relative Risk = 0.53, 95% Confidence Interval (CI) 0.34–0.84) (Lannes et al., 2021). Studies

Key points

- Previous research has shown that children of parents with a SMI (schizophrenia, bipolar, and recurrent Major Depression) have a 55% risk of developing a lifetime mental illness compared with their peers. This evidence has called for research in preventive interventions targeting these children.
- In the VIA Family trial, we compared the efficacy of an 18-month-long family-based preventive intervention with TAU.
- We did not find any significant differences in change between groups at the end of treatment.
- Despite these non-significant findings, further research should explore the potential long-term clinical effects of the intervention. Future studies should consider the significant heterogeneity within the group, both for intervention and trial design.

included in the meta-analysis focused on several different treatment elements: Cognitive-behavioral therapy, psychoeducation about parental mental illness, and parenting support (Lannes et al., 2021). However, because of the significant variation of needs in families, there are no one-size-fits-all preventive interventions for these families (Van Santvoort et al., 2013). Consequently, the literature recommends family-centered interventions with individual case management (Maybery et al., 2012; Wansink et al., 2015). Nevertheless, the effectiveness of these interventions is inconclusive (Maybery et al., 2012; Wansink et al., 2015). Therefore, we developed a holistic family-based intervention, VIA Family, with a flexible approach tailored to the individual family's needs to be rigorously evaluated in a randomized design. The intervention aimed to reduce the potential impact of risk factors associated with the increased vulnerability and aimed to enhance protective factors related to resilience.

We hypothesized that a tailored and family-based intervention compared with treatment as usual (TAU) would (a) increase global functioning (primary outcome) and (b) reduce emotional and behavioral symptoms and absence from school.

METHODS

Study design

The VIA Family trial is a pragmatic, rater-blinded, randomized clinical trial in a two-arm parallel-group design located in the Capital Region of Denmark. The Danish Regional Committee for Health Research Ethics in the Capital Region of Denmark approved the ethical aspects of the study (Approval number H-17000450). The Danish Data Protection Agency approved compliance with the rules on protecting personal data. We registered the study at clinicaltrials.gov (registration number NCT03497663) and published a trial protocol before data collection ended (Müller et al., 2019).

Participants

Participants were recruited by linking data from the Danish health registers with personal data from the National Civil Registry (Pedersen, 2011) or directly from the mental health services (MHS) and social services in the Capital Region of Denmark. Eligible families had at least one child aged 6–12 years and at least one biological parent diagnosed with a SMI during the participating child's/children's life/lives (including the prenatal period). Children had to live with at least one of their biological parents within the municipalities of Frederiksberg or Copenhagen. Severe mental illness diagnoses were based on ICD-10 or ICD-8 criteria and defined as schizophrenia, bipolar disorder, or recurrent moderate or severe depression (see Appendix S1 for ICD-codes). Trained mental health workers assessed all diagnoses at baseline with the lifetime diagnostic interview Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing, 1990). A child and adolescent psychiatrist, a trained SCAN user, confirmed all diagnoses. We excluded families recently involved in an intensive family-based intervention addressing parental mental illness in the primary sector. Moreover, families were not eligible for the study if the primary caregiver's proficiency in the Danish language was insufficient to participate in the intervention or the data collection.

We gave all eligible parents written and oral information about the study, which included details about the potential risks of parental mental illness for their children. Before assessment commenced, all eligible parents gave written informed consent to their participation, and all caregiver(s) gave written informed their child's/children's participation.

Randomization and masking

Families were randomly allocated (1:1) to either VIA Family or TAU, solely stratified by parental SMI diagnosis. An intervention team member randomized the participating families using the concealed electronic system: Research Electronic Data Capture (REDCap) (Harris et al., 2009). A statistician, in collaboration with the study's primary investigator, generated the sequence and stratification of randomization. Participants were enrolled and assigned to their allocation by a member of the intervention team. All outcome assessors were blinded to allocation, sequence, and block sizes. In the case of unblinding, a different assessor interviewed the participants at follow-up. We rated clinical interviews in a team, excluding any possible unblinded assessor. It was impossible to mask participants or the intervention team due to the characteristics and duration of the treatment. Researchers were kept blinded when performing data analyses and interpreting results.

Interventions

Family-based intervention VIA Family

Families randomized to VIA Family were offered affiliation to a multidisciplinary intervention team for 18 months. We assigned all families to a case manager, who was one of four specialists in the multidisciplinary team. The team members, a social worker, a

psychologist, a nurse, and a family counselor, had competencies and experience in adult MHS, child and adolescent MHS, social services, and family-centered care. A child and adolescent psychiatrist consulted the team regularly.

The VIA Family intervention aimed to enhance modifiable protective factors and reduce modifiable risk factors. This objective was to lower the risk of developing mental illness and associated functional impairment. Therefore, a vital characteristic of the intervention was the holistic and flexible approach focusing on each family's individual needs, motivation, and risk and protective factors. The intervention contained different elements (see Figure 1). The initial sessions included the following elements: (a) family-centered lifeline, (b) mapping signs of vulnerability and resilience in the family (based on 'Signs of Safety' (Turnell et al., 2014)), and (c) family-centered psychoeducation about mental illness or emotions. Hereafter, the family decided, in collaboration with the case manager, which elements of the intervention were relevant for them and when. The additional elements of VIA Family were: (a) help and support with parenting based on the parenting program Triple P (levels 2, 4 (standard), and 5, and Stepping Stones) (Sanders et al., 2014), (b) support groups for parents, young children, and adolescents, (c) practical support or support for pedagogical topics, school attendance, leisure time activities, or social relations, and (c) optimization of the ill parent's treatment and family's lifestyle, (d) counseling and guidance regarding financial, social, or practical support offers from the municipality, and (e) assessment of the child's and/or the parent's potential mental health problems and specialized treatment. If clinically indicated, the team referred participants directly to the MHS for further assessment or treatment. Moreover, if indicated, the team would help the family transition to support systems in the public sector (e.g., the municipality) or private sector (e.g., support groups by non-governmental organizations (NGOs)).

Sessions were offered individually, in groups, or for the whole family. Parents could participate without their children and their children knowing about parental mental illness if they preferred to. A detailed description of the intervention elements can be found in the trial protocol (Müller et al., 2019) and the supporting Information (Appendix S2 & Table S1).

Treatment as usual

Families randomized to TAU were encouraged to seek relevant support in MHS, social services, and relevant NGOs.

All families, those randomized to TAU and VIA Family, received information about what kind of care for families with parental mental illness was available in the MHS in the Capital Region of Denmark, in their municipality, and the primary sector at the time of the study.

Treatment adherence, fidelity and training

We assessed fidelity of delivery, receipt and enactment of the VIA Family intervention following the recommendations by Bellg. et al. (Bellg et al., 2004). This included, for example, that all team members were trained equally in all the elements that required training (e.g., the parenting program Triple P) and weekly meetings for the team to

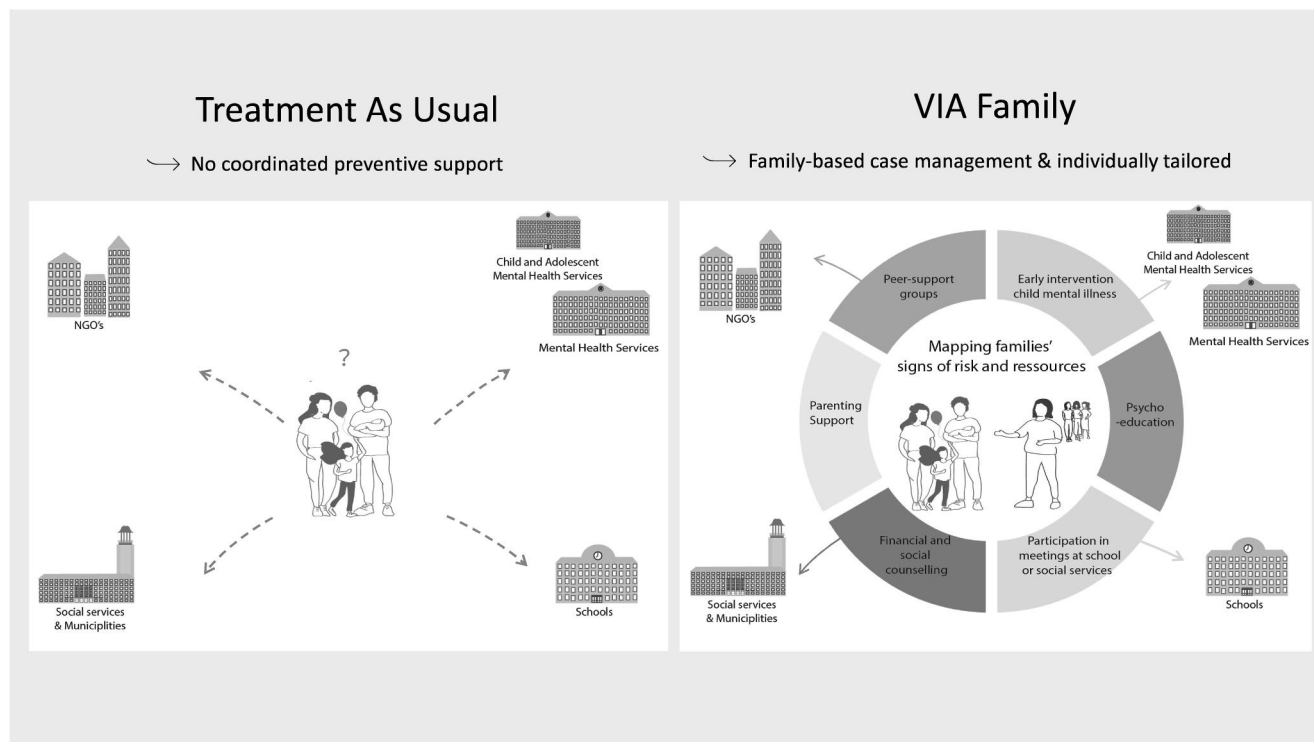


FIGURE 1 Treatment as usual (TAU) versus the tailored family-based intervention VIA Family.

discuss individual families' intervention trajectories and families' comprehension, acceptance and use of skills of the intervention. We defined adherence with intervention as a minimum of 15 contacts with the case manager and intervention team during the 18-month intervention period. Among these, at least eight meetings had to be in person, and families had to participate in the initial sessions and at least two other elements. Team members registered each contact with the enrolled families in the REDCap system (Harris et al., 2009).

We obtained information on the use of services in usual care for both groups through parents' reports and information from the municipalities on service use related to support for the family at baseline and end-of-intervention.

For feasibility, the intervention elements were pilot-tested in a small sample before the study onset (Müller et al., 2019). All four team members received regular supervision and, whenever necessary, specialized counseling by, for example, a child and adolescent psychiatrist.

Assessments and measures

Time points for data collection were at study entry (baseline) and after 18 months (post-intervention). All eligible children were included in the assessment. We assessed the biological sex and age of the participating children at baseline through their unique person identification number. At baseline, we did a brief screening of children's neurocognitive functioning. At both time points, trained psychologists interviewed children and their parents on demography, factors influencing psychosocial functioning, and mental health problems. See Figure 2 for an overview of all measures and time points.

Primary outcome

Difference in Change in Children's Global Functioning. We used children's global functioning as a proxy of protective and risk factors that are present within children's daily lives: at home, at school and with peers. We rated the children's global functioning with the Children's Global Assessment Scale (CGAS) (Shaffer, 1983) as part of the semi-structured diagnostic interview Kiddie Schedule for Affective Disorders and Schizophrenia (Present and Lifetime, K-SADS-PL) (Kaufman et al., 1997). Children's Global Assessment Scale estimates the lowest level of functioning during the preceding month based on the child's functioning at home, at school, and with peers, based on a scale from 1 to 100 (the higher the score, the better functioning). Children's Global Assessment Scale has shown moderate inter-rater reliability and good validity if used correctly in clinical samples (Lundh, 2012).

Secondary outcomes

Difference in Change in Children's Emotional and Behavioral Symptoms. We assessed children's early signs of vulnerability, defined as emotional and behavioral symptoms, with the parent- and teacher-reported questionnaires for school-aged children from the Achenbach System of Empirically Based Assessment (Achenbach, 2001). The questionnaires measure symptoms of psychopathology at home (Child Behavior Checklist, CBCL) and at school (Teacher Report Form, TRF) based on 113 questions on a 3-point Likert scale. A total score on dimensional psychopathology and scores on two subscales on internalizing and externalizing symptoms can be derived. It has shown good

Variable	Instrument	References
Assessment timepoint 0 (baseline)		
Demography and family relations	Semi-structured interview	Interview data
Neurocognitive functioning		
Estimate of general Intelligence	Reynolds Intellectual Screening Test (RIST) (Danish norms)	Reynolds & Kamphaus (2003)
Immediate and delayed verbal memory	Test of Memory and Learning (TOMAL), 2 nd Edition (Memory of Stories) (US norms)	Reynolds & Voress (2007)
Processing speed	Coding subtest from Wechsler Intelligence Scale for Children (WISC-IV), 4 th Edition (Danish norms)	Wechsler (2003)
Visuospatial memory	Rey Complex Figure Test and Recognition Trial (RCFT) (US norms)	Meyers & Meyers (1995)
Assessment timepoints 0 (baseline) and 1 (after 18 -months post-intervention)		
Primary outcome		
General functioning	Children's Global Assessment Scale (CGAS) <i>higher score better functioning</i>	Shaffer(1987)
Secondary outcomes		
Emotional and behavioral symptoms	Child Behavior Checklist (CBCL) total, internalizing, and externalizing symptoms. <i>higher score: more symptoms (Danish norms)</i>	Achenbach & Rescorla (2001)
High absence from school	≥ 15% days absence from school. Data obtained from municipality or school	Data from municipalities and/or schools
Exploratory outcomes		
Psychopathology	Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime (KSADS-PL)	Kaufman et al (1997)
Parent-reported surveys on signs of risk and resilience		
Executive functioning	Behavior Rating Inventory of Executive Function (BRIEF) <i>higher score: more problems with executive functioning</i> (Danish norms)	Gioia et al (2000)
Affective lability	Children's Affective Lability Scale (CALS) <i>higher score: more affect lability</i>	Gerson et al (1996)
Emotion regulation	Emotion Regulation Checklist (ERC) <i>higher score: better adaptive emotion regulation</i>	Shields and Cicchetti (1997)
Mental health: strengths and difficulties	Strength and Difficulties Questionnaire (SDQ) – Danish version. <i>higher score: more difficulties</i> (Danish norms)	Obel et al (2003)
Symptoms of ADHD	Attention Deficit Hyperactivity Disorder- Rating Scale (ADHD-RS), <i>higher scores: more symptoms</i>	DuPaul et al (1998)
Sleep-related problems	Structured interview with parents on sleep-related problems, <i>higher scores: more sleep-related problems</i>	Interview data
Child self-reported surveys on signs of risk and protective factors		
Social-ecological resilience	Child Youth Resilience Measure (CYRM), child and youth version, <i>higher scores: more resilience resources</i>	Liebenberg et al (2013)
Self-esteem	This Is Me (TIM), <i>higher scores: more self-esteem</i>	Suonpää et al (1989)
Health-related quality of life	KIDSCREEN-52, <i>higher scores: more well-being</i>	Ravens-Sieberer (2005)

FIGURE 2 Outcome measures for children at baseline and after 18 months post-intervention.

validity, and we used Danish norms (Henriksen J, Nielsen PF, Bilenberg N., 2012).

Difference in High Absence from School. We obtained information from the municipalities on the children's number of days absent from school 6 months before study entry and 6 months before the post-intervention assessment (i.e., after 18 months). We collected data directly from the schools in cases of children attending private schools. We focused on ≥ 15% percentage absence from school, defined as high absence by the

Ministry of Children and Education in Denmark (Børne-og Undervisningsministeriet, 2019).

Explorative outcomes

The child's primary caregiver, the schoolteacher, and the children themselves completed questionnaires at both time points (see Figure 2).

Childhood trauma	Childhood Trauma Screener (CTS) <i>higher scores: more reported traumatic events</i>	Grabe et al (2012)
Teacher-reported surveys on signs of risk and protective factors		
Emotional and behavioral symptoms	Teacher Report Form (TRF) total score, subscale for internalizing symptoms, and externalizing symptoms. <i>higher score: more symptoms</i>	Achenbach & Rescorla (2001)
Executive Functioning	Behavior Rating Inventory of Executive Function (BRIEF) <i>higher score: more problems with executive functioning</i>	Gioia et al (2000)
Emotion regulation	Emotion Regulation Checklist (ERC) <i>higher score: better adaptive emotion regulation</i>	Shields and Cicchetti (1997)
Mental health: strengths and difficulties	Strength and Difficulties Questionnaire (SDQ) – Danish version. <i>higher score: more difficulties</i> (Danish norms)	Obel et al (2003)
Symptoms of ADHD	Attention Deficit Hyperactivity Disorder- Rating Scale (ADHD-RS), <i>higher scores: more symptoms</i>	DuPaul et al (1998)

FIGURE 2 (Continued)

Procedures

In the case of more than one caregiver, caregivers decided who was the primary to give information about the child. Trained assessors rated consentingly the primary outcome CGAS. For ethical reasons and to enhance study participation, we informed all families about the outcome of the neurocognitive and diagnostic screenings. If clinically indicated, the research team would advise families to contact their general practitioner for a referral to MHS after baseline and post-intervention assessment. Due to ethical and legal principles, we always informed the municipalities if a family/child needed urgent help, irrespective of the randomization process.

Adverse events

We assessed adverse events with a questionnaire for the adults and through an interview with the children and their primary caregivers. Adverse events were defined as any undesirable physical or emotional consequences participants associated with either VIA Family or TAU. In case of adverse events in the experimental group, the principal investigators decided whether to terminate the study or the participation of an individual family.

Statistical analysis

Power calculation was based on the primary outcome CGAS. Based on a *t*-test, we calculated that a sample size of 37 children in each group would be required to detect a significant difference between groups in a change of 10 points on the CGAS with a power of 0.90 (see trial protocol (Müller et al., 2019)). A change of 10 points is considered a large clinical effect.

All analyses were based on intention-to-treat (ITT) principles that included all randomized children regardless of their drop-out status. After a qualitative assessment of reasons for drop-out, we assumed that data were missing at random. Data were imputed using multiple imputations based on 100 imputations and 20 iterations until convergence. If data were >40% missing, we did not

impute but did a complete case analysis, as suggested in the literature (Jakobsen et al., 2017). We used a linear mixed model to estimate effect sizes and test significance for the primary outcome CGAS and the secondary outcome CBCL. For school absence, we used a logistic mixed effects model. Familiarity was used as a random nested factor to account for the fact that siblings from the same family are not independent. We adjusted for age, biological sex, and baseline characteristics with significant differences (measured by a *t*-test if continuous or chi-square test if binary) between the groups by including them as covariates. Sensitivity analyses were performed for all primary and secondary outcomes. They included the following analyses: with and without outliers, per-protocol, linear regression without using familiarity as random effects (i.e., assuming independent observations), and a 10% cut-off for days absent from school.

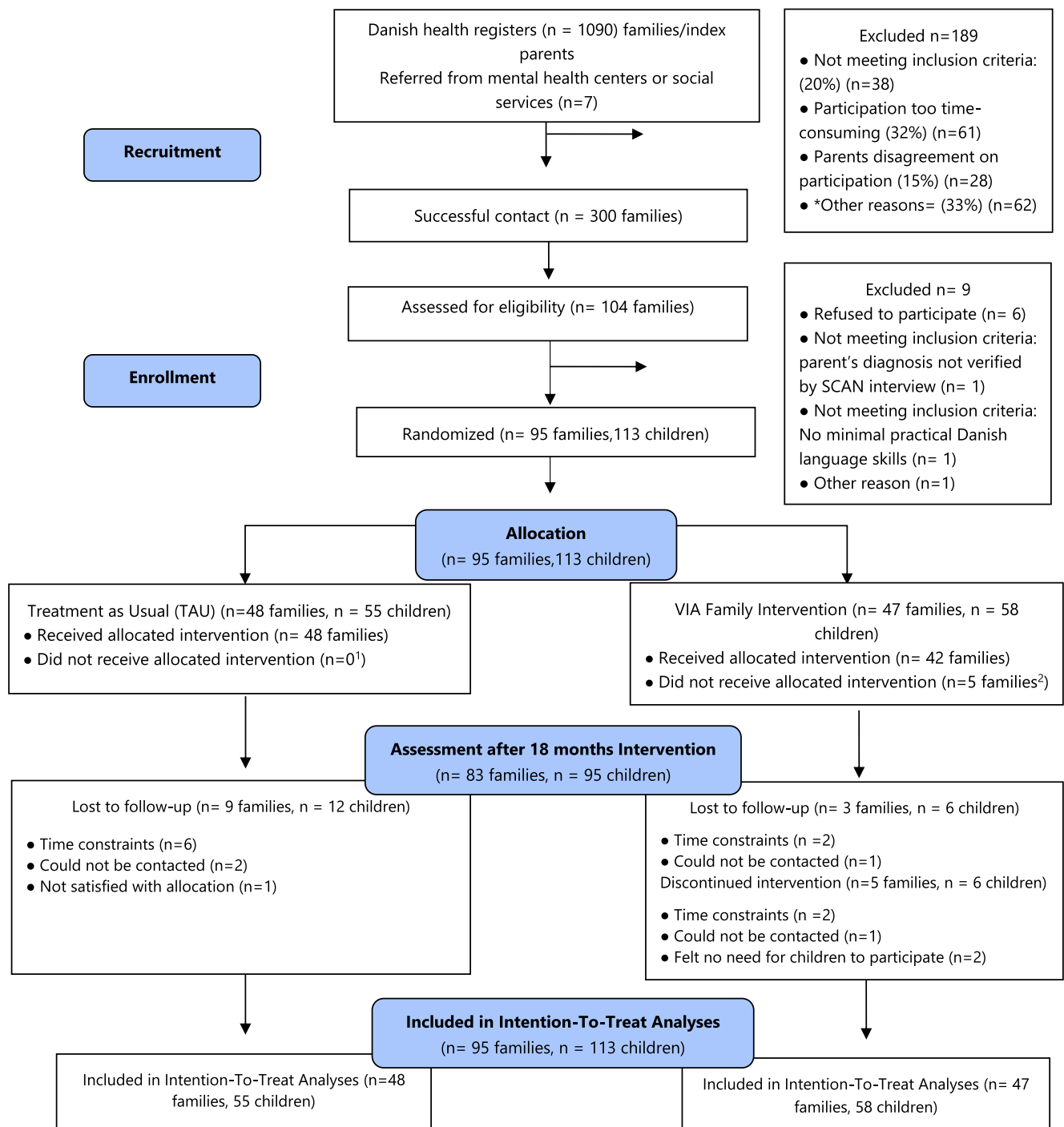
We used the statistical software R version 4.2.2 (R Core Team, 2022) for all data analyses with the packages 'lme4' (Bates et al., 2015), 'Zelig' (Imai et al., 2008), and 'Amelia' (Honaker et al., 2011).

We published a plan for the statistical analyses (SAP) before data analyses as supporting information under the clinicaltrials.gov registration. The study did not include a data monitoring committee. See supporting information for changes to the protocol (Appendix S3).

RESULTS

Between October 2017 and April 2019, we contacted 1090 eligible parents by invitation letter. Of these, 300 parents were reached by phone. The municipalities and social services referred seven families to the project. We assessed 104 families for eligibility. After screening for eligibility, nine families were ineligible; 95 families (113 children) met the inclusion criteria and were assessed. We randomized 48 families to TAU and 47 families to VIA Family. See Figure 3 for the study flow.

Children's mean age at baseline was 9.74 (SD = 1.95), 47% were girls, and the mean CGAS score was 64.67 (SD = 14.22). More children in TAU had a mental disorder, lived in a single-caregiver home, and scored lower on the verbal memory task. See Table 1 for baseline demographic and clinical characteristics of the sample.



¹ Discontinued intervention (n=0) (Treatment as usual is characterized by the combination of hospital, general practitioner, and help by the municipality. Can be from zero to many complex intervention elements.)

² Attending at least 15 sessions

FIGURE 3 Study participation: recruitment, enrollment, randomization, and post-intervention participation.

The supplementary material contains information about families' utilization of VIA Family intervention elements (Appendix, Figure S1). Moreover, it contains information on families' participation in usual care. There were no between-group differences in families' use of services in usual care, except for more parents in the VIA Family group reporting contact to a private psychologist or psychiatrist at end-of-treatment (Appendix Figure S2).

Missing data

We analyzed the data between August 2021 and October 2022. At 18 months post-intervention, 5 out of 47 families in VIA Family discontinued the intervention for the following reasons: Intervention was too time-consuming (n = 2), the family felt no need for support at the time of the study (n = 2), or they could not be contacted (n = 1). In

TABLE 1 Baseline demographic and clinical characteristics of children, their families, and parents in VIA Family and treatment as usual (TAU).

Variable	Instrument	Treatment as usual	VIA Family	All
Children's characteristics				
Biological sex, female participants ^a	n	55	58	113
Age at baseline ^a	n (%)	28 (50.9)	25 (43.1)	53 (46.9)
Global functioning ^a	Mean (SD)	9.70 (2.0)	9.78 (1.9)	9.74 (2.0)
Any current diagnosis ^{b,a}	CGAS, mean (SD)	63.78 (15.2)	65.55 (13.3)	64.67 (14.2)
Dimensional psychopathology	K-SADS-PL, n (%)	21 (38.2)	15 (25.9)	36 (31.9)
≥15% absence from school	CBCL total problem score, T-score (Danish norms), mean (SD)	61.51 (17.2)	56.59 (12.8)	59 (15.2)
	Data from municipalities or schools, n (%)	6 (10.9)	4 (6.9)	10 (8.9)
Neurocognition				
Estimate of general intelligence	RIST, scaled scores, mean (SD)	100.58 (12.3)	103.22 (13.9)	101.96 (13.2)
Processing speed	WISC-IV coding, scaled scores (Danish norms), mean (SD)	8.46 (2.6)	7.56 (2.9)	8 (2.8)
Visual memory	RCFT immediate recall, T-scores (US norms), mean (SD)	46.79 (11.3)	41.18 (12.5)	43.86 (12.3)
Verbal memory – immediate	Memory for stories, immediate recall (TOMAL-2), scaled scores (US norms), mean (SD)	8.94 (3.0)	10.16 (2.5)	9.58 (2.7)
Verbal memory- delayed	Memory for stories, delayed recall (TOMAL-2) scaled scores (US norms), mean (SD)	8.41 (3.0)	9.93 (3.2)	9.19 (3.2)
General executive functioning	BRIEF, T-score (Danish norms), mean (SD)	52.98 (12.1)	51.73 (12.0)	52.14 (12.0)
Social responsiveness	SRS-2, raw score, mean (SD)	118.48 (13.2)	119.13 (17.4)	118.81 (15.4)
Family and home characteristics				
Quality of home environment ^{c,a}	n	48	47	95
Single parent family ^d	MC-HOME/EA-HOME, mean (SD)	46.7 (5.9)	46.4 (6.1)	46.6 (5.9)
Having two parents with SMI or/and substance misuse lifetime ^e diagnoses (solely out of families with two caregivers)	parent-reported, n (%)	8 (16.7)	3 (6.4)	11 (11.6)
	SCAN interview/patient journal, n (%)	8 (16.7)	5 (10.6)	13 (13.7)
Index parent's diagnosis				
Lifetime ^e SZ ^a	n	48	47	95
Lifetime ^e BP ^a	SCAN interview/patient journal, n (%)	6 (12.5)	6 (12.8)	12 (12.6)
Lifetime ^e rMDD ^a	SCAN interview/patient journal, n (%)	12 (25.0)	13 (27.7)	25 (26.3)
Index parent with comorbid diagnosis ^e	SCAN interview/patient journal, n (%)	30 (62.5)	28 (60.0)	58 (61.1)
	SCAN interview/patient journal, n (%)	18 (37.5)	17 (36.2)	35 (36.9)

TABLE 1 (Continued)

Variable	Instrument	Treatment as usual	VIA Family	All
Primary caregiver's characteristics	n	48	47	95
SMI or/and substance misuse lifetime ^d diagnoses	SCAN interview/patient journal, n (%)	34 (70.1)	34 (72.3)	68 (71.6)
General functioning (higher score better functioning)	PSP, mean (SD)	68.9 (16.7)	67.0 (14.4)	67.68 (15.5)
Parental stress (higher score more stress)	PSS, mean (SD)	40.1 (10.5)	39.1 (9.7)	39.64 (10.1)
Family functioning (lower score better functioning)	FAD, mean (SD)	1.9 (0.5)	1.9 (0.5)	1.89 (0.49)
Employment status parents				
Currently employed or studying ^f	Interview, n (%)	38 (79.2)	41 (87.2)	79 (83.2)
Educational level parents				
Primary/lower secondary	n (%)	4 (8.3)	9 (19.2)	13 (13.7)
Upper secondary, vocational, or short-cycle tertiary	n (%)	13 (27.1)	12 (25.5)	25 (26.3)
Bachelor's degree, equivalent, or higher	n (%)	30 (62.5)	26 (55.3)	56 (58.9)
Support at baseline	n	48	47	95
Family receiving support from municipalities/MHS 6 months prior to baseline ^g	Interview/Data from municipalities, n (%)	12 (25.0)	11 (23.4)	23 (24.2)

Note: ADHD-RS Attention Deficit Hyperactivity Disorder Rating Scale (DuPaul et al., 1998); BRIEF Behavior Rating Inventory of Executive Function (Gioia et al., 2000); CALS Children's Affective Liability Scale (Gerson et al., 1996); CBCL Child Behavior Checklist (Achenbach, 2001); CGAS Children's Global Assessment Scale (Shaffer, 1983); CTS Childhood Trauma Screener (Grabe et al., 2012); FAD Family Assessment Device (Epstein et al., 1983); HOME Home Observation for Measurement of the Environment (Caldwell & Bradley, 2003); K-SADS-PL Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime (Kaufman et al., 1997); PSP Personal and Social performance Scale (In Michalos, 2014); PSS Parental Stress Scale (Berry & Jones, 1995); RCFT Rey Complex Figure Test (Meyers & Meyers, 1995); RIST Reynolds Intellectual Screening Test (Reynolds & Kamphaus, 2003); SCAN Schedules for Clinical Assessment in Neuropsychiatry (Wing, 1990); SRS-2 Social Responsiveness Scale- Version 2 (Constantino & Gruber, 2012); TOMAL-II Test of Memory and Learning, second Edition (Reynolds & Vores, 2007); WISC-IV Wechsler Intelligence Scale for Children, fourth Edition (Wechsler, 2003).

^aData are concurrently submitted for publication in Gjøde et al. (2023).

^bCurrent Diagnosis within the last 8 weeks, excl. Elimination Disorder, Simple Phobia, Tics/Tourette's Syndrome.

^cFor children living 50/50 with mother and father, the HOME interview was done in both homes.

^dChild has only one caregiver.

^eDuring child's life (including the prenatal period).

^fPersonality disorder, substance abuse, ADHD, PTSD, or eating disorder.

^gAny form of employment, no minimum working hours, absence from work due to for example, illness or maternity leave included as work.

total, 12 families were lost at the time of follow-up assessments: 9 from TAU and 3 from VIA Family. Reasons for drop-out were: one family was unsatisfied with randomization to TAU, eight families had time constraints, and three could not be contacted.

Missing data for primary and secondary outcomes were distributed as follows: CGAS included 17 missing values (12 in TAU and 5 in VIA Family), CBCL total score included 28 missing values (17 in TAU and 11 in VIA Family), and high absence from school included 21 missing values (10 in TAU and 12 in VIA Family). We had 58% of missing data in the teacher-reported surveys post-intervention.

Primary and secondary outcomes

Results from ITT analysis on the primary outcome CGAS showed no significant differences in mean change between groups over time. The estimated mean change difference between children in VIA Family and TAU from baseline to post-intervention was -1.2 (95% CI = -6.61 – 4.21 , $p = 0.66$). The results remained non-significant after adjustment for covariates. ITT analyses showed a non-significant effect on differences in mean change between the groups in the CBCL total score (0.52, 95% CI = -4.62 – 5.65 , $p = 0.84$), the internalizing (-0.88 ; 95% CI -6.85 – 5.1 , $p = 0.77$), and the externalizing subscales of the CBCL (-0.08 ; 95% CI = -4.72 – 4.55 , $p = 0.97$). Analysis of the high percentage of days absence from school showed no statistically significant difference in change between the groups (Odds Ratio (OR) = 0.30, 95% CI = 0.07–1.30, $p = 0.11$). Table 2 shows all differences in change between groups.

Exploratory outcomes

ITT analyses showed no significant differences in mean change between groups in any of the explorative outcomes: executive functioning (Behavior Rating Inventory of Executive Function, BRIEF (Gioia et al., 2000): 0.95, CI 95% -2.54 – 4.45 , $p = 0.59$), affective lability (Children's Affective Lability Scale (Gerson et al., 1996): -1.09 , CI 95% -4.24 – 1.59 , $p = 0.49$), emotion regulation (Emotion Regulation Checklist, ERC (Shields & Cicchetti, 1997): -0.01 , CI 95% -0.10 to 0.08 , $p = 0.80$), symptoms of ADHD (Attention Deficit Hyperactivity Disorder- Rating Scale, ADHD-RS (DuPaul et al., 1998): 3.69, CI 95% 2.18 – 9.57 , $p = 0.22$), mental health problems (Strength and Difficulties Questionnaire, total score, SDQ (Obel et al., 2003): 0.94, CI 95% -0.88 – 2.76 , $p = 0.31$), or parent-reported sleep-related problems (OR = 1.11, 95% CI = 0.26–4.71, $p = 0.80$). Differences in mean changes in the child-reported questionnaires addressing self-esteem (This Is Me (Suonpää et al., 1989): -0.12 , CI 95% -0.84 to 0.6 , $p = 0.74$) or quality of life KIDSCREEN-10 (Ravens-Sieberer et al., 2005) total score (-3.92 , CI 95% -8.26 – 0.43 , $p = 0.08$) were non-significant. We also did not find any significant difference in mean changes between groups in the level of child-reported trauma (Childhood Trauma Screener (Grabe et al., 2012): -0.23 , CI 95% -0.86 to 0.41 , $p = 0.48$).

Complete case analyses: Due to a high number (>40%) of missing data from teacher-reported surveys post-intervention, we only did complete case analyses on outcomes from teacher-reported questionnaires. Differences between the groups on the TRF

(Achenbach, 2001) were non-significant. TRF total score showed a mean difference change of -5.43 (CI 95% -15.87 – 5.01 , $p = 0.30$), the subscale for internalizing symptoms showed a difference of -7.76 (CI 95% -16.7 – 1.15 , $p = 0.09$), and the subscale for externalizing symptoms showed a difference of 1.65 (CI 95% -7.25 – 10.54 ; $p = 0.70$). We found no statistically significant differences in teacher-reported children's executive functioning (BRIEF (Gioia et al., 2000)) (-4.80 , CI 95% -9.10 – 8.14 , $p = 0.9$), emotion regulation (ERC (Shields & Cicchetti, 1997)) (0.01, CI 95% -0.14 – 0.15 , $p = 0.9$), symptoms of ADHD (ADHD-RS (DuPaul et al., 1998)) (-3.64 , CI 95% -12.5 – 5.18 , $p = 0.4$), or mental health difficulties (SDQ (Obel et al., 2003)) (-2.74 , CI 95% -6.01 – 0.54 , $p = 0.10$).

The sensitivity analyses did not differ from the main results of the trial. We found no significant differences between analyses with and without adjustment for age, biological sex, the child's verbal memory score, or families participating without their children ($n = 1$). Parents and children reported no adverse events associated with VIA Family intervention during and after the trial. In the TAU group, one family reported drawbacks from being informed about parental mental illness risks but receiving insufficient TAU support.

DISCUSSION

In this trial, we compared an 18-month preventive family-based intervention, VIA Family, with TAU for children of parents with SMI. There were no significant differences in changes in the primary outcome, level of global functioning, or the secondary outcomes of children's emotional and behavioral symptoms and absence from school.

These findings contradict our hypotheses and previous findings in the field (Lannes et al., 2021). Evidence from preventive trials on the effect on children's global functioning is scarce. However, similar to our findings, a previous randomized controlled trial (RCT) of a preventive group cognitive behavioral intervention for youth (aged 13–18 years) with familial high-risk for depression compared with usual care found an improvement for both groups over time, but no between-group differences in mean change (Clarke et al., 2001).

Regarding the secondary outcome, behavioral and emotional symptoms changes, our results contradict a recent meta-analysis on preventive interventions for children of parents with a mental illness (mood disorder, anxiety disorder, or substance use disorder) (Lannes et al., 2021). The meta-analysis showed a small but significant effect on internalizing symptoms but no significant between-group differences in change in externalizing symptoms. Contrary to our sample, the meta-analysis excluded children with a mental illness diagnosis at baseline. To date, there are no results from preventive intervention RCTs for parental psychosis focusing on child outcomes (Radley et al., 2022) for comparison with our results.

Possible explanations for null findings

Several factors could explain the null findings of this trial.

First, the end-of-treatment timepoint may be too early to detect the effect of a preventive intervention. A recent meta-analysis of interventions to prevent child maltreatment showed that contrary to

TABLE 2 Summary of treatment effect on participation in VIA Family compared with treatment as usual (TAU) derived by multiple imputations and complete case analyses from baseline to 18 months post-intervention.

Outcome measures	Treatment as usual (n = 55)		VIA Family (n = 58)		Estimated between-group differences/OR on mean change from baseline to postintervention (95% CI) for group VIA Family	p
	Baseline	Post-intervention	Baseline	Post-intervention		
Primary outcome (ITT) ^a						
CGAS, mean (SD)	63.78 (15.19)	69.14 (16.76)	65.55 (13.34)	69.23 (14.33)	−1.2 (−6.61; 4.21)	0.66
Secondary outcomes (ITT) ^a						
CBCL total, T-score, mean (SD)	61.51 (17.17)	57.91 (17.06)	56.59 (12.75)	54.47 (12.01)	0.52 (−4.62; 5.65)	0.84
CBCL subscale for internalizing symptoms, T-score, mean (SD)	62.11 (15.52)	60.53 (18.65)	56.18 (9.77)	57.32 (14.60)	−0.88 (−6.85; 5.1)	0.77
CBCL, subscale for externalizing symptoms, T-score, mean (SD)	57.44 (17.86)	54.49 (13.49)	54.20 (13.27)	51.76 (11.82)	−0.08 (−4.72; 4.55)	0.97
≥15% days absence from school, n (%)	6 (10.90)	7 (12.73)	3 (5.17)	3 (5.17)	0.30 (0.07; 1.30) ^b	0.11
Exploratory outcomes (ITT) ^a						
Parent-reported						
BRIEF, T-score, mean (SD)	53.10 (12.10)	53.36 (12.77)	51.20 (11.90)	50.90 (11.83)	0.95 (−2.54; 4.45)	0.59
CALS, total raw scores, mean (SD)	10.29 (11.74)	10.51 (11.73)	7.32 (7.29)	5.87 (6.87)	−1.09 (−4.24; 1.59)	0.49
ERC, total raw scores, mean (SD)	2.81 (0.27)	2.83 (0.27)	2.87 (0.26)	2.89 (0.25)	−0.01 (−0.1; 0.08)	0.80
SDQ total difficulty score, raw score, mean (SD)	9.65 (5.90)	8.22 (6.01)	7.93 (5.89)	7.47 (5.41)	0.94 (−0.88; 2.76)	0.31
ADHD-RS, T-score, mean (SD)	57.69 (19.27)	54.73 (17.47)	54.48 (21.33)	53.77 (17.60)	3.69 (−2.18; 9.57)	0.22
Sleep-related problems, n (%)	29 (52.73)	19 (34.55)	24 (43.10)	22 (37.93)	1.11 (0.26; 4.71) ^b	0.80
Child self-report						
TIM, stanine score, mean (SD)	4.23 (1.49)	5.24 (2.19)	4.66 (1.56)	5.71 (2.13)	−0.12 (−0.84; 0.60)	0.74
KIDSCREEN-10 (global QoL), T-score, mean (SD)	47.19 (11.76)	52.09 (9.52)	52.15 (9.08)	53.46 (8.03)	−3.92 (−8.26; 0.43)	0.08
CTS, raw scores, mean (SD)	7.35 (3.34)	7.39 (3.50)	6.44 (2.12)	6.62 (2.31)	−0.23 (−0.86; 0.41)	0.48
Teacher-report						
Complete-case analyses n (%) ^a	39 (71)	21 (38)	40 (69)	25 (43)		
TRF total score, T-score, mean (SD)	52.73 (10.79)	57.94 (18.76)	55.25 (14.66)	55.33 (12.05)	−5.43 (−15.87; 5.01)	0.30

(Continues)

TABLE 2 (Continued)

Outcome measures	Treatment as usual (n = 55)		VIA Family (n = 58)		Estimated between-group differences/OR on mean change from baseline to postintervention (95% CI) for group VIA Family	p
	Baseline	Post-intervention	Baseline	Post-intervention		
TRF subscale for internalizing symptoms, T-score, mean (SD)	54.52 (11.68)	57.16 (12.40)	57.88 (17.67)	53.52 (8.88)	−7.76 (−16.67; 1.16)	0.09
TRF subscale for externalizing symptoms, T-score, mean (SD)	50.68 (13.24)	53.57 (20.75)	52.3 (16.13)	52.71 (11.60)	1.64 (−7.25; 10.54)	0.71
BRIEF-T, T-score, mean (SD)	51.15 (8.20)	56.38 (15.53)	53.4 (12.37)	56.7 (15.23)	−4.80 (−9.10; 8.14)	0.90
ERC-T, total raw scores, mean (SD)	2.89 (0.29)	2.85 (0.27)	2.86 (0.3)	2.87 (0.26)	0.01 (−0.14; 0.15)	0.90
ADHD-RS-T, T-score mean (SD)	48.03 (8.55)	55.63 (20.91)	50.82 (10.79)	51.59 (12.72)	−3.64 (−12.5; 5.18)	0.40
SDQ-T total difficulty score, raw score, mean (SD)	5.85 (5.01)	7.91 (4.97)	6.73 (5.94)	6.12 (5.73)	−2.74 (−6.01; 0.54)	0.10

Note: ADHD-RS: Attention Deficit Hyperactivity Disorder Rating Scale, T-score based on Danish norms; higher scores indicate more symptoms, DuPaul et al. (1998); BRIEF: Behavior Rating Inventory of Executive Function, T-score based on Danish norms; higher scores indicate more problems, Gioia et al. (2000); CALS: Children's Affective Lability Scale, higher scores indicate more affective lability, Gerson et al. (1996); CBCL: Child Behavior Checklist, T-score based on Danish norms; higher scores indicate more problems, Achenbach et al. (2001); CGAS Children's Global Assessment Scale, high scores indicate better functioning (Shaffer, 1983), CTS: Childhood Trauma Screener, high scores indicate more traumatic experiences, Grabe et al. (2012), CYRM: Child and Youth Resilience Measurement, higher scores, raw scores and comparison of percentage of total mean, higher scores indicate more resilience resources, Liebenberg et al. (2013); ERC: Emotion Regulation Checklist, higher scores indicate better adaptive emotion regulation, Shields and Cicchetti (1997); SDQ: Strengths and Difficulties Questionnaire, Higher scores indicating more difficulties with mental health, Obel et al. (2003), TIM: This is Me (Suonpää et al., 1989), higher scores indicate more self-esteem, Gerson et al. (1996); TRF: Teachers Report Form, T-score based on Danish norms; higher scores indicate more problems, Achenbach et al. (2001).

Data are between-group differences on mean change (SD) adjusted for age, sex, and baseline verbal memory score (immediate and recall) unless otherwise specified.

Data are OR for between-group differences at 18 months post-intervention adjusted for age, sex, and baseline verbal memory score (immediate and recall).

curative interventions, preventive interventions have a larger effect at long-term follow-up compared with end-of-treatment (Van Der Put et al., 2018). The authors explain the results with a sleeper effect of preventive interventions compared with curative interventions, that is, in preventive interventions, time passes before participants apply the newly learned skills. The long-term effects of the VIA Family intervention are, therefore, yet to be explored. We are currently investigating the long-term effect of the intervention for the cohort in a 3-year post-intervention follow-up study.

Moreover, the intervention might have introduced changes in the participating families that are not measurable with the included instruments, for example, knowledge about risk and protective factors, reduced internalized stigma and when to seek help for early signs of vulnerability to mental illness. A qualitative meta-synthesis of preventive interventions for this population has identified such changes after participation in preventive interventions (Radley et al., 2022). Furthermore, a meta-synthesis determined that these particular changes were regarded as the most significant outcomes by parents with SMI (Harries et al., 2023). Especially, interventions that focused on reducing internalized stigma were associated with higher quality of life in young people (Song et al., 2023) and increased likelihood of help-seeking (Davies et al., 2022). Moreover, a mixed-methods study found discrepancies between qualitative findings of perceived effectiveness and quantitative results of efficacy (Maybery et al., 2019). We are currently preparing a mixed-methods study of VIA Family participants' perception of effectiveness.

Next, TAU might be just as good as the experimental intervention, VIA Family. However, due to the complex nature of a multi-component and individually tailored design in both interventions, it is challenging to compare the two groups (Ginsburg et al., 2021). Despite our intention to assess and ensure fidelity, the individual-tailored approaches result in individualized intervention trajectories, which interfere with fidelity assessment and ultimately may limit conclusions about effectiveness (Ginsburg et al., 2021). Furthermore, comparing the two interventions may present additional challenges: Families randomized to TAU might have received an enhanced form of TAU due to the information on potential risks and where to seek help for early signs of vulnerability that was provided to all families after baseline assessment, regardless of randomization. Previous studies have suggested that providing information about the potential risks of parental mental illness might be sufficient to encourage parents to talk with their children about parental mental illness and to seek relevant support (Maybery et al., 2019). Psychoeducation about parental mental illness has been associated with increased likelihood of help-seeking (Davies et al., 2022). This could be especially applicable to parents with socioeconomic resources like in our sample.

Lastly, we could not analyze differences in the children's school setting. Due to the lockdown of schools in Denmark because of the COVID-19 pandemic during the study period, many teachers could not report on children's functioning and well-being at school. However, a complete case analysis of teacher ratings indicated a clinically meaningful, although insignificant, difference in change in internalizing symptoms for children in the VIA Family group compared with TAU. Nevertheless, the conclusion of the results is limited due to missing data and lack of power (only 58% of teacher responses).

Strengths and limitations

The main strength of this study is the randomized controlled design with blinded assessments, concealed allocation sequence, a non-treatment control group, and intention-to-treat to account for missing data. Moreover, this is the first RCT to study an 18-month-long, family-based preventive intervention of children born to parents with SMI. Another strength is the use of multi-informants from different everyday locations of the child: parent, teacher, child, and objective participation in the experimental intervention measures.

Our study has several limitations. The small sample size does not allow for subgroup analyses. We did not include children aged younger than 6 years, which could have enabled early intervention. Moreover, for some families, parent's symptoms of SMI were in remission, which might have impacted their motivation for participation in the intervention, as described in previous studies 25.

There are some clinical implications of this trial. First, we experienced that recruitment from the MHS and the social services was difficult. The potential stigma of being a parent with a SMI prevents some families from seeking relevant support or participating in a trial (Lannes et al., 2021; Reupert et al., 2021). However, identifying the families needing support is crucial for preventive and early interventions. Mental health and social services in contact with parents with SMI should consider preventive approaches for these families. Moreover, baseline characteristics confirm the need for early identification and support for children of parents with SMI, especially for high-risk children who show early signs of vulnerability.

Future preventive studies should consider the large heterogeneity of this population. For example, including a larger sample size will allow for sub-group analyses. Moreover, depending on how many risk and protective factors are present around the child, a stepped-care intervention approach could acknowledge the large heterogeneity in this population. Nevertheless, although some children have a high level of global functioning, they are still at familial high risk and should not be excluded from preventive programs. Instead, future studies should investigate screening measures for familial high-risk children to identify who is at high risk of developing a mental illness and who is not.

In sum, despite the non-significant findings of the current study, studies on preventive interventions for mental illness are still needed to decrease the societal, economic, and personal burden of mental illness. Future studies should include a larger sample size to account for the large heterogeneity and have a longitudinal design to measure the preventive effect on the development of mental illness and related functional impairments.

AUTHOR CONTRIBUTIONS

Anne Dorothee Müller: Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Visualization; Writing – original draft; Writing – review & editing. **Ida Christine Tholstrup Gjøde:** Data curation; Funding acquisition; Investigation; Methodology; Project administration; Visualization; Writing – review & editing. **Nikolaj Thams:** Formal analysis; Methodology; Writing – review & editing. **Sidsel Ingversen:** Data curation;

Investigation; Writing – review & editing. **Mala Moszkowicz**: Data curation; Investigation; Methodology; Supervision; Writing – review & editing. **Lisbeth Juhl Mikkelsen**: Data curation; Investigation; Writing – review & editing. **Signe Sofie Nielsen**: Data curation; Investigation; Writing – review & editing. **Nicoline Hemager**: Data curation; Investigation; Methodology; Supervision; Writing – review & editing. **Merete Nordentoft**: Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing. **Anne A. E. Thorup**: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – review & editing.

ACKNOWLEDGMENTS

The authors thank all participating children, parents, and school-teachers. We also want to acknowledge the multidisciplinary team who delivered VIA Family: Kate H Jønsson, Mette S Eigil, Henriette Andreassen and (co-author) Sidsel Ingversen. A special thanks to the research team for help with data collection: Anna I Printzlau, Amalie F Kristensen, Sofie H Christensen, and Marianne Melau. Thanks to Abisha Vishnu, Johan S Kristensen, Helene K Kristensen, and Michella Heinrichsen for their help with data management and Jamal Uddin for statistical consultancy. We thank the participating municipalities – especially Merete Bonne from the municipality of Frederiksberg. The study was funded by the Danish Ministry of Interior and Health (Satspulje), TrygFonden, Capital Region in Denmark (Tværspuljen), Municipality of Frederiksberg, and Aase og Ejnar Danielsens fond. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have declared that they have no competing or potential conflicts of interest.

ETHICAL CONSIDERATIONS

The Danish Regional Committee for Health 100 Research Ethics in the Capital Region of Denmark approved the ethical aspects of the study (Approval number H-17000450).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Anne Dorothee Müller  <https://orcid.org/0000-0002-4887-6672>

REFERENCES

- Achenbach, T. M. (2001). *Manual for ASEBA school-age forms & profiles*. University of Vermont, Research Center for Children, Youth & Families.
- Achenbach, T. M., Dumenci, L., & Rescorla, L. A. (2001). *Ratings of relations between DSM-IV diagnostic categories and items of the CBCL/6-18, TRF, and YSR* (pp. 1–9). University of Vermont.
- Anttila, V., Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., Falcone, G. J., Gormley, P., Malik, R., Patsopoulos, N. A., Ripke, S., Wei, Z., Yu, D., Lee, P. H., Turley, P., Grenier-Boley, B., Chouraki, V., Kamatani, Y., & Neale, B. M. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, 360(6395), eaap8757. Retrieved March 15, 2023, from <https://www.science.org/doi/10.1126/science.aap8757>
- Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, 67(1). Retrieved March 15, 2023, from <https://doi.org/10.18637/jss.v067.i01>
- Bell, A. J., Borrelli, B., Resnick, B., Hecht, J., Minicucci, D. S., Ory, M., Ogedegbe, G., Orwig, D., Ernst, D., & Czajkowski, S. (2004). Enhancing treatment fidelity in health behavior change studies: Best practices and recommendations from the NIH behavior change Consortium. *Health Psychology*, 23(5), 443–451. Retrieved October 17, 2023, from <https://doi.org/10.1037/0278-6133.23.5.443>
- Berry, J. O., & Jones, W. H. (1995). The parental stress scale: Initial psychometric evidence. *Journal of Social and Personal Relationships*, 12(3), 463–472. Retrieved August 18, 2023, from <https://doi.org/10.1177/0265407595123009>
- Børne-og Undervisningsministeriet. (2019). Bekendtgørelse om elevers fravær fra undervisningen i folkeskolen (Vol. BEK nr 1063 af 24/10/2019. Retrieved March 9, 2023, from <https://www.retsinformation.dk/eli/lt/a/2019/1063>
- Brandt, J. M., Hemager, N., Gregersen, M., Søndergaard, A., Falkenberg Krantz, M., Ohland, J., Wilms, M., Birkehøj Rohd, S., Hjorthøj, C., Veddem, L., Bruun Knudsen, C., Krogh Andreassen, A., Greve, A., Spang, K. S., Christiani, C. A., Ellersgaard, D., Klee Burton, B., Gantriis, D. L., Bliksted, V., & Elgaard Thorup, A. A. (2022). Childhood trauma in children at familial high risk of schizophrenia or bipolar disorder: A longitudinal study. The Danish high risk and resilience study – via 7 and via 11. *British Journal of Clinical Psychology*, 61(4), 875–894. Retrieved March 12, 2023, from <https://doi.org/10.1111/bjc.12364>
- Burton, B. K., Thorup, A. A. E., Jepsen, J. R., Poulsen, G., Ellersgaard, D., Spang, K. S., Christiani, C. J., Hemager, N., Gantriis, D., Greve, A., Mors, O., Nordentoft, M., & Plessen, K. J. (2017). Impairments of motor function among children with a familial risk of schizophrenia or bipolar disorder at 7 years old in Denmark: An observational cohort study. *The Lancet Psychiatry*, 4(5), 400–408. Retrieved February 1, 2023, from [https://doi.org/10.1016/s2215-0366\(17\)30103-7](https://doi.org/10.1016/s2215-0366(17)30103-7)
- Caldwell, B. M., & Bradley, R. H. (2003). *Home observation for measurement of the environment: Administration manual*. Family & Human Dynamics Research Institute, Arizona State University.
- Christesen, A. M. S., Knudsen, C. K., Fonager, K., Johansen, M. N., & Heuckendorff, S. (2022). Prevalence of parental mental health conditions among children aged 0–16 years in Denmark: A nationwide register-based cross-sectional study. *Scandinavian Journal of Public Health*, 50(8), 1124–1132. Retrieved October 12, 2023, from <https://doi.org/10.1177/14034948211045462>
- Clarke, G. N., Hornbrook, M., Lynch, F., Polen, M., Gale, J., Beardslee, W., O'Connor, E., & Seeley, J. (2001). A randomized trial of a group cognitive intervention for preventing depression in adolescent offspring of depressed parents. *Archives of General Psychiatry*, 58(12), 1127–1134. American Medical Association. <https://doi.org/10.1001/archpsyc.58.12.1127>
- Constantino, J. N., & Gruber, C. P. (2012). *Social responsiveness scale: SRS-2*. Western psychological services Torrance, CA.
- Davies, G., Deane, P., Williams, V., & Giles, C. (2022). Barriers, facilitators and interventions to support help-seeking amongst young people living in families impacted by parental mental illness: A systematized review. *Early Intervention in Psychiatry*, 16(5), 469–480. Retrieved October 25, 2023, from <https://doi.org/10.1111/eip.13194>
- DuPaul, G. J., Power, T. J., Anastopoulos, A. D., & Reid, R. (1998). *ADHD Rating Scale–IV: Checklists, norms, and clinical interpretation*. Guilford press.
- Epstein, N. B., Baldwin, L. M., & Bishop, D. S. (1983). THE McMASTER FAMILY ASSESSMENT DEVICE*. *Journal of Marital and Family Therapy*, 9(2), 171–180. Retrieved August 18, 2023, from <https://doi.org/10.1111/j.1752-0606.1983.tb01497.x>
- Gerson, A. C., Gerring, J. P., Freund, L., Joshi, P. T., Capozzoli, J., Brady, K., & Denckla, M. B. (1996). The children's affective liability scale: A psychometric evaluation of reliability. *Psychiatry Research*, 65(3),

- 189–198. Retrieved May 10, 2023, from [https://doi.org/10.1016/s0165-1781\(96\)02851-x](https://doi.org/10.1016/s0165-1781(96)02851-x)
- Ginsburg, L. R., Hoben, M., Easterbrook, A., Anderson, R. A., Estabrooks, C. A., & Norton, P. G. (2021). Fidelity is not easy! Challenges and guidelines for assessing fidelity in complex interventions. *Trials*, 22(1), 372. Retrieved October 17, 2023, from <https://doi.org/10.1186/s13063-021-05322-5>
- Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). TEST RE-VIEW behavior rating inventory of executive function. *Child Neuropsychology*, 6(3), 235–238. Retrieved May 10, 2023, from <https://doi.org/10.1076/chin.6.3.235.3152>
- Gjorde, I. C. T., Müller, A. D., Hjorthøj, C., Hemager, N., Ingversen, S., Moszkowicz, M., Christensen, S. H., Mikkelsen, L. J., Nielsen, S. S., Melau, M., Forman, J., Nordentoft, M., & Thorup, A. E. (2023). Effects on family functioning and the home environment of an 18-month family-based preventive intervention for children of parents with severe mental illness: A randomised controlled trial. submitted.
- Grabe, H., Schulz, A., Schmidt, C., Appel, K., Driessen, M., Wingenfeld, K., Barnow, S., Spitzer, C., John, U., Berger, K., Wersching, H., & Freyberger, H. (2012). Ein Screeninginstrument für Missbrauch und Vernachlässigung in der Kindheit: Der Childhood Trauma Screener (CTS). *Psychiatrische Praxis*, 39(03), 109–115. Retrieved May 10, 2023, from <https://doi.org/10.1055/s-0031-1298984>
- Gregersen, M., Møllegaard Jepsen, J. R., Rohd, S. B., Søndergaard, A., Brandt, J. M., Ellersgaard, D., Hjorthøj, C., Ohland, J., Krantz, M. F., Wilms, M., Andreassen, A. K., Vedum, L., Knudsen, C. B., Greve, A. N., Bliksted, V., Mors, O., Clemmensen, L., Nordentoft, M., Hemager, N., & Elgaard Thorup, A. A. (2022). Developmental pathways and clinical outcomes of early childhood psychotic experiences in preadolescent children at familial high risk of schizophrenia or bipolar disorder: A prospective, longitudinal cohort study-the Danish high risk and resilience study, via 11. *American Journal of Psychiatry*, 179(9), 628–639. Am Psychiatric Assoc. <https://doi.org/10.1176/appi.ajp.21101076>
- Gronemann, F. H., Jacobsen, R. K., Wium-Andersen, M. K., Jørgensen, M. B., Osler, M., & Jørgensen, T. S. H. (2023). Association of familial aggregation of major depression with risk of major depression. *JAMA Psychiatry*, 80(4), 350. Retrieved March 20, 2023, from <https://doi.org/10.1001/jamapsychiatry.2022.4965>
- Harries, C. I., Smith, D. M., Gregg, L., & Wittkowski, A. (2023). Parenting and serious mental illness (SMI): A systematic review and meta-synthesis. *Clinical Child and Family Psychology Review*, 26(2), 303–342. Retrieved October 9, 2023, from <https://doi.org/10.1007/s10567-023-00427-6>
- Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, 42(2), 377–381. Retrieved February 12, 2023, from <https://doi.org/10.1016/j.jbi.2008.08.010>
- Hemager, N., Plessen, K. J., Thorup, A., Christiani, C., Ellersgaard, D., Spang, K. S., Burton, B. K., Gregersen, M., Søndergaard, A., Greve, A. N., Gantriis, D. L., Poulsen, G., Seidman, L. J., Mors, O., Nordentoft, M., & Jepsen, J. R. M. (2018). Assessment of neurocognitive functions in 7-year-old children at familial high risk for schizophrenia or bipolar disorder: The Danish high risk and resilience study VIA 7. *JAMA Psychiatry*, 75(8), 844. Retrieved February 1, 2023, from
- Henriksen, J., Nielsen, P. F., & Bilenberg, N. (2012). New Danish standardization of the child behaviour checklist. *New Danish standardization of the Child Behaviour Checklist*, 59(7), A4462.
- Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., Nordentoft, M., & Glenthøj, B. (2018). Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. *Biological Psychiatry*, 83(6), 492–498. Retrieved February 1, 2023, from <https://doi.org/10.1016/j.biopsych.2017.08.017>
- Honaker, J., King, G., & Blackwell, M. (2011). *Amelia II*: A program for missing data. *Journal of Statistical Software*, 45(7). Retrieved March 15, 2023, from <https://doi.org/10.18637/jss.v045.i07>
- Hosman, C. M. H., Jané Llopis, E., & Saxena, S. (2004). *Prevention of mental disorders: Effective interventions and policy options: Summary report*. World Health Organization.
- Imai, K., King, G., & Lau, O. (2008). Toward a common framework for statistical analysis and development. *Journal of Computational & Graphical Statistics*, 17(4), 892–913. [American Statistical Association, Taylor & Francis, Ltd., Institute of Mathematical Statistics, Interface Foundation of America]. Retrieved from JSTOR. <https://doi.org/10.1198/106186008x384898>
- Jakobsen, J. C., Glud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials – A practical guide with flowcharts. *BMC Medical Research Methodology*, 17(1), 162. Retrieved January 20, 2023, from <https://doi.org/10.1186/s12874-017-0442-1>
- Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(7), 980–988. Retrieved March 10, 2023, from <https://doi.org/10.1097/00004583-199707000-00021>
- Lannes, A., Bui, E., Arnaud, C., Raynaud, J.-P., & Revet, A. (2021). Preventive interventions in offspring of parents with mental illness: A systematic review and meta-analysis of randomized controlled trials. *Psychological Medicine*, 51(14), 2321–2336. Retrieved January 23, 2023, from <https://doi.org/10.1017/s0033291721003366>
- Liebenberg, L., Ungar, M., & LeBlanc, J. C. (2013). The CYRM-12: A brief measure of resilience. *Canadian Journal of Public Health*, 104(2), e131–e135. Springer. <https://doi.org/10.1007/bf03405676>
- Lundh, A. (2012). *On the children's global assessment scale (CGAS)*. Karolinska institutet.
- MacKenzie, L. E., Howes Vallis, E., Rempel, S., Zwicker, A., Drobinin, V., Pavlova, B., & Uher, R. (2020). Cognition in offspring of parents with psychotic and non-psychotic severe mental illness. *Journal of Psychiatric Research*, 130, 306–312. Retrieved February 1, 2023, from <https://doi.org/10.1016/j.jpsychires.2020.08.019>
- Maybery, D., Goodyear, M., Reupert, A., Sheen, J., Cann, W., O'Hanlon, B., & Cuff, R. (2019). A mixed method evaluation of an intervention for parents with mental illness. *Clinical Child Psychology and Psychiatry*, 24(4), 717–727. Retrieved October 25, 2023, from <https://doi.org/10.1111/1359104518822676>
- Maybery, D., & Reupert, A. E. (2018). The number of parents who are patients attending adult psychiatric services. *Current Opinion in Psychiatry*, 31(4), 358–362. Retrieved October 12, 2023, from <https://doi.org/10.1097/ycp.0000000000000427>
- Maybery, D. J., Goodyear, M. J., Reupert, A. E., & Harkness, M. K. (2012). Goal setting within family care planning: Families with complex needs. *MJA Open*, 1(Suppl 1), 37–39. Retrieved October 17, 2023, from <https://www.mja.com.au/open/2012/1/1/goal-setting-within-family-care-planning-families-complex-needs>
- McAdams, T. A., Rijdsdijk, F. V., Neiderhiser, J. M., Narusyte, J., Shaw, D. S., Natsuaki, M. N., Spotts, E. L., Ganiban, J. M., Reiss, D., Leve, L. D., Lichtenstein, P., & Eley, T. C. (2015). The relationship between parental depressive symptoms and offspring psychopathology: Evidence from a children-of-twins study and an adoption study. *Psychological Medicine*, 45(12), 2583–2594. Retrieved February 1, 2023, from <https://doi.org/10.1017/s0033291715000501>
- Meyers, J., & Meyers, K. R. (1995). *Rey complex figure test and recognition trial*. Psychological Assessment Resources, Incorporated.
- Michalos, A. C. (Ed.) (2014). *PSP scale. Encyclopedia of quality of life and well-being research* (p. 5134). Springer Netherlands. Retrieved August 18, 2023, from Retrieved from http://link.springer.com/10.1007/978-94-007-0753-5_103265
- Müller, A. D., Gjorde, I. C. T., Eigel, M. S., Busck, H., Bonne, M., Nordentoft, M., & Thorup, A. A. E. (2019). VIA Family—a family-based early intervention versus treatment as usual for familial high-risk children: A study protocol for a randomized clinical trial. *Trials*, 20(1), 112. Retrieved January 20, 2023, from <https://doi.org/10.1186/s13063-019-3191-0>

- Mullins, N., Forstner, A. J., O'Connell, K. S., Coombes, B., Coleman, J. R. I., Qiao, Z., Als, T. D., Bigdeli, T. B., Børte, S., Bryois, J., Charney, A. W., Drange, O. K., Gandal, M. J., Hagenaars, S. P., Ikeda, M., Kamitaki, N., Kim, M., Krebs, K., Panagiotaropoulou, G., & Andreassen, O. A. (2021). Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nature Genetics*, 53(6), 817–829. Retrieved March 15, 2023, from <https://doi.org/10.1038/s41588-021-00857-4>
- Obel, C., Dalsgaard, S., Stax, H.-P., & Bilenberg, N. (2003). Strengths and Difficulties Questionnaire (SDQ-Dan). A new instrument for psychopathologic screening of children aged 4–16 years. *Ugeskrift for læger*, 165(5), 462–465.
- Pedersen, C. B. (2011). The Danish Civil registration system. *Scandinavian Journal of Public Health*, 39(7_suppl), 22–25. Retrieved February 12, 2023, from <https://doi.org/10.1177/1403494810387965>
- Raballo, A., Poletti, M., & Preti, A. (2021). Applying transgenerational scientific evidence to the next wave of early identification strategies for psychopathological risk—Transdiagnostic, developmental, and personalized. *JAMA Psychiatry*, 78(10), 1067. Retrieved February 1, 2023, from <https://doi.org/10.1001/jamapsychiatry.2021.1901>
- Radley, J., Sivarajah, N., Moltrecht, B., Klampe, M.-L., Hudson, F., Delahay, R., Barlow, J., & Johns, L. C. (2022). A scoping review of interventions designed to support parents with mental illness that would be appropriate for parents with psychosis. *Frontiers in Psychiatry*, 12, 787166. Retrieved May 4, 2023, from <https://doi.org/10.3389/fpsy.2021.787166>
- Rasic, D., Hajek, T., Alda, M., & Uher, R. (2014). Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. *Schizophrenia Bulletin*, 40(1), 28–38. Retrieved January 20, 2023, from <https://doi.org/10.1093/schbul/sbt114>
- Ravens-Sieberer, U., Gosch, A., Rajmil, L., Erhart, M., Bruil, J., Duer, W., Auquier, P., Power, M., Abel, T., Czemy, L., Mazur, J., Czimbalmas, A., Tountas, Y., Hagquist, C., Kilroe, J., & Kidscreen Group, E. (2005). KIDSCREEN-52 quality-of-life measure for children and adolescents. *Expert Review of Pharmacoeconomics & Outcomes Research*, 5(3), 353–364. <https://doi.org/10.1586/14737167.5.3.353>
- R Core Team. (2022). *A language and environment for statistical computing*. R Foundation for Statistical Computing. Retrieved from <https://www.R-project.org/>
- Reupert, A., Gladstone, B., Helena Hine, R., Yates, S., McGaw, V., Charles, G., Drost, L., & Foster, K. (2021). Stigma in relation to families living with parental mental illness: An integrative review. *International Journal of Mental Health Nursing*, 30(1), 6–26. Retrieved May 9, 2023, from <https://doi.org/10.1111/inm.12820>
- Reynolds, C. R., & Kamphaus, R. W. (2003). *Reynolds intellectual assessment scales (RIAS)*. Psychological Assessment Resources.
- Reynolds, C. R., & Voress, J. K. (2007). Test of memory and learning (2nd ed.). (TOMAL 2). Austin, Texas, Pro-ed.
- Sanders, M. R., Kirby, J. N., Tellegen, C. L., & Day, J. J. (2014). The Triple P-positive parenting program: A systematic review and meta-analysis of a multi-level system of parenting support. *Clinical Psychology Review*, 34(4), 337–357. Retrieved February 12, 2023, from <https://doi.org/10.1016/j.cpr.2014.04.003>
- Sandstrom, A., MacKenzie, L., Pizzo, A., Fine, A., Rempel, S., Howard, C., Stephens, M., Patterson, V. C., Drobinin, V., Van Gestel, H., Howes Vallis, E., Zwicker, A., Propper, L., Abidi, S., Bagnell, A., Lovas, D., Cumby, J., Alda, M., Uher, R., & Pavlova, B. (2020). Observed psychopathology in offspring of parents with major depressive disorder, bipolar disorder and schizophrenia. *Psychological Medicine*, 50(6), 1050–1056. Retrieved January 23, 2023, from <https://doi.org/10.1017/S0033291719001089>
- Sandstrom, A., Sahiti, Q., Pavlova, B., & Uher, R. (2019). Offspring of parents with schizophrenia, bipolar disorder, and depression: A review of familial high-risk and molecular genetics studies. *Psychiatric Genetics*, 29(5), 160–169. Retrieved January 20, 2023, from <https://doi.org/10.1097/ypg.0000000000000240>
- Shaffer, D. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry*, 40(11), 1228. Retrieved February 12, 2023, from <http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.1983.01790100074010>
- Shields, A., & Cicchetti, D. (1997). Emotion regulation among school-age children: The development and validation of a new criterion Q-sort scale. *Developmental Psychology*, 33(6), 906–916. American Psychological Association. <https://doi.org/10.1037/0012-1649.33.6.906>
- Song, N., Hugh-Jones, S., West, R. M., Pickavance, J., & Mir, G. (2023). The effectiveness of anti-stigma interventions for reducing mental health stigma in young people: A systematic review and meta-analysis. *Cambridge Prisms: Global Mental Health*, 10, e39. Retrieved October 17, 2023, from <https://doi.org/10.1017/gmh.2023.34>
- Suonpää, E., Kresanov, K., Ouninen-Birgerstam, P., & Piha, J. (1989). Self-concept of Finnish children on the second grade of normal elementary school. *Acta Paedopsychiatrica*, 52(3), 157–164.
- Thorup, A. A. E., Gantriis, D. L., Greve, A. N., Henriksen, M. T., Zahle, K. K., Stadsgaard, H., Ellersgaard, D., Burton, B. K., Christiani, C. J., Spang, K., Hemager, N., Jepsen, J. R. M., Plessen, K. J., Nordentoft, M., Mors, O., & Bliksted, V. (2022). Exploring protective and risk factors in the home environment in high-risk families – results from the Danish high risk and resilience study—Via 7. *BMC Psychiatry*, 22(1), 100. Retrieved February 1, 2023, from <https://doi.org/10.1186/s12888-022-03733-5>
- Turnell, A., Vesterhauge-Petersen, M., & Vesterhauge-Petersen, H. (2014). *Signs of safety: Arbejdet med udsatte børn og deres familier (1. udgave)*. Hans Reitzel.
- Ungar, M., & Theron, L. (2020). Resilience and mental health: How multisystemic processes contribute to positive outcomes. *The Lancet Psychiatry*, 7(5), 441–448. Retrieved March 8, 2023, from [https://doi.org/10.1016/S2215-0366\(19\)30434-1](https://doi.org/10.1016/S2215-0366(19)30434-1)
- Van Der Put, C. E., Assink, M., Gubbels, J., & Boekhout Van Solinge, N. F. (2018). Identifying effective components of child maltreatment interventions: A meta-analysis. *Clinical Child and Family Psychology Review*, 21(2), 171–202. Retrieved October 17, 2023, from <https://doi.org/10.1007/s10567-017-0250-5>
- Van Santvoort, F., Hosman, C. M. H., Van Doesum, K. T. M., & Janssens, J. M. A. M. (2013). Children of mentally ill or addicted parents participating in preventive support groups. *International Journal of Mental Health Promotion*, 15(4), 198–213. Retrieved October 17, 2023, from <https://doi.org/10.1080/14623730.2013.851816>
- Wansink, H. J., Janssens, J. M. A. M., Hoencamp, E., Middelkoop, B. J. C., & Hosman, C. M. H. (2015). Effects of preventive family service coordination for parents with mental illnesses and their children, a RCT. *Families, Systems & Health*, 33(2), 110–119. Retrieved August 4, 2023, from <https://doi.org/10.1037/fsh0000105>
- Wechsler, D. (2003). *Wechsler intelligence scale for children – fourth edition (WISC-IV)*. The Psychological Corporation.
- Wing, J. K. (1990). Scan: Schedules for clinical assessment in Neuropsychiatry. *Archives of General Psychiatry*, 47(6), 589. Retrieved March 10, 2023, from <http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.1990.01810180089012>
- World Health Organization (2022). *World mental health report: Transforming mental health for all*. World Health Organization. Retrieved from . ISBN 978-92-4-004933-8 (electronic version) ISBN 978-92-4-004934-5 (print version)

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Müller, A. D., Gjøde, I. C. T., Thams, N., Ingversen, S., Moszkowicz, M., Jepsen, J. R. M., Mikkelsen, L. J., Nielsen, S. S., Hemager, N., Nordentoft, M., & Thorup, A. A. E. (2024). Family-based preventive intervention for children of parents with severe mental illness: A randomized clinical trial. *JCPP Advances*, e12216. <https://doi.org/10.1002/jcv.12216>

Some blank pages were omitted to accommodate the final published version of the paper

Paper 2

Müller, Anne D; Gjøde, Ida C T; Christensen, Sofie; Jørgensen, Sophie K; Fischer, Kirstine Moszkowicz, Mala; Hemager, Nicoline; Nordentoft, Merete; Piché, Geneviève; and Thorup, Anne A E (2023) *"It was a need that we did not think we had": a mixed methods study of mechanisms of change in mental illness prevention.*

Prepared for submission

Initials of Contributors to Qualitative Data Collection and Generation
(in order of appearance)

ADM= Anne Dorothee Müller

IG = Ida Gjøde

KF = Kirstine Fischer,

SKJ = Sophie K Jørgensen

SC = Sofie H Christensen

GP = Geneviève Piché

Title

"It was a need that we did not think we had": a mixed methods study of mechanisms of change in mental illness prevention

Authors

Anne Dorothee Müller^{1,2}, Ida C T Gjøde^{1,2}, Sofie H Christensen², Sophie Kiner Jørgensen², Kirstine Fischer², Mala Moszkowicz², Nicoline Hemager^{2,3,4}, Merete Nordentoft^{1,3}, Genevieve Piche^{5,6}, and Anne A E Thorup^{1,2,3}

¹ Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

² Child and Adolescent Mental Health Center, Research Unit, Copenhagen University Hospital – Mental Health Services CPH, Copenhagen, Denmark

³ CORE – Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre Copenhagen, Copenhagen, Denmark

⁴ Department of Psychology, University of Copenhagen, Copenhagen, Denmark

⁵ Department of Psychoeducation and Psychology, Université du Québec en Outaouais, Saint-Jérôme, PQ, Canada

⁶ Centre de recherche universitaire sur les jeunes et les familles (CRUJeF), Québec, Canada

Abstract

Introduction: Preventive interventions for mental illness can potentially reduce the global burden of mental illness. However, the mechanisms of change underlying the effectiveness of such interventions remain poorly understood. Understanding these mechanisms is vital for advancing prevention research and enhancing the effect and acceptance of prevention for the individual and their families.

Method: We used an exploratory sequential mixed methods design of three parts to investigate mechanisms of change in a complex, customized, multicomponent, and family-based preventive intervention for children of parents with severe mental illness, the VIA Family intervention. The effect of the intervention has previously been compared to usual care in a trial with 95 families. The current study consisted of three sequential parts. In the first part we used abductive analysis, based on the health belief model and SDT on data gathered from 4 focus group discussions with 16 children and parents participating in VIA Family. We integrated the qualitative findings to establish a variable for subgrouping the study sample. Lastly, we conducted a post hoc subgroup analysis of secondary data from the VIA family trial on the primary and secondary outcomes.

Results: Our findings indicate that participants' perception of need and motivation were vital to drive change among participants. Qualitative findings show that participants perceived *need for support* as an underlying mechanism leading to change in VIA Family. Quantitative findings indicate that families who engaged in the intervention because they at baseline were motivated by a need for support exhibited a higher increase in levels of support and stimulation in the home environment when assigned to the preventive intervention. However, there were no significant differences in children's global functioning between groups.

Discussion: Our findings highlight that families' quality of motivation and their perceived need for support to engage in prevention affects the efficacy and the perceived effectiveness of the intervention. Nonetheless, while motivation and perceived need for support potentially promote positive changes in the home environment, they may act influence global functioning of children at familial risk for mental illness.

Conclusion: The findings suggest that parent's perception of a need for support can be a significant mechanism to drive change in preventive interventions for children at familial risk for mental illness.

Introduction

Mental illness affects our society, our economy, and us and our family. Globally, the incidence of mental illness is increasing along with a request for effective preventive interventions (Fusar-Poli et al., 2021; Herrman et al., 2022; Radley et al., 2022; World Health Organization, 2022). Mental illness develops in a complex interaction of biological, psychological, and environmental risk and protective factors (World Health Organization, 2022). Children of parents with a mental illness have the highest cumulative risk of developing a mental illness (Arango et al., 2018; Krantz et al., 2022). The prevalence of parents in adult mental health services with any mental illness has been estimated to rates between 20%-39% (Maybery & Reupert, 2018). Families' vulnerabilities and needs for support are diverse and complex. Many families deal with a high level of family conflict, communication difficulties, and impaired stimulation in the home (Duffy et al., 2023; Hosman et al., 2009; Krantz et al., 2023). Moreover, protective factors such as social, financial and psychological resources are often lacking (Duffy et al., 2023). Therefore, preventive interventions for children with a familial risk propose a promising potential to promote global mental health (Fusar-Poli et al., 2021).

Preventive interventions can potentially reduce the risk of developing mental illness by 50% for children of parents with mental illness (Lannes et al., 2021). However, despite the high risk reduction, for some children, preventive interventions are not effective (Lannes et al., 2021; Puchol-Martínez et al., 2023). This lack of efficacy might be explained by the heterogeneity of the target group and their diverse and changing needs (Lannes et al., 2021). Findings from a meta-synthesis of studies of parents' perceptions and experiences of parenting programs suggest that the diversity of families' needs leads to individual pathways and outcomes in the interventions (Butler et al., 2020). To encompass the diverse needs, the design and evaluation of preventive interventions should include a high degree of complexity (Butler et al., 2020).

The preventive intervention *VIA Family* provides an example of a preventive intervention encompassing the complexity of the population and their needs (Müller et al., 2019). The intervention is family-based, multicomponent and tailored to the individual families' needs and preferences (Müller et al., 2019). Intervention components encompass parenting support, family-focused psychoeducation, social/legal support, peer support groups, and support for child mental health problems (Müller et al., 2019). The aim of the intervention is to decrease the impact of modifiable risk factors and increase protective factors for children at familial risk of severe

mental illness, i.e. recurrent major depression, bipolar disorder or schizophrenia spectrum disorder(Müller et al., 2019).

We tested the intervention in an assessor blinded randomized clinical trial in Denmark between 2017 and 2022. The trial explore the effect of VIA Family versus treatment as usual (TAU) for children at familial risk of severe mental illness(Müller et al., 2019). Eligible children were aged 6-12 years, had at least one parent diagnosed with severe mental illness, had sufficient Danish language skills, and had not participated in a family-based intervention during the preceding 6 months. At baseline, 95 families with 113 children participated.

Evaluating a complex intervention, such as VIA Family, is in itself complex(Campbell et al., 2007; Ginsburg et al., 2021; Petticrew et al., 2013). Consequently, guidelines for evaluation of complex interventions recommend applying theory and mixed methodology to explore efficacy (Petticrew et al., 2013; Skivington et al., 2021). In complex interventions a question of efficacy, therefore needs to be accompanied by a question of the context, i.e. when, how, and for whom, does it work(Skivington et al., 2021). This has led to an interest in the study of mechanisms of change(Skivington et al., 2021).

Nevertheless, the literature on mechanisms underlying change in preventive interventions enactment is scarce(Lannes et al., 2021). A previous study suggested that parental cognition, parenting behaviour, and child coping may mediate changes in prevention interventions for children at familial risk for depression(Löchner et al., 2023). Quantitative researchers have explored potential moderators like child age and gender leading to change, but evidence remains inconclusive, possibly due to population heterogeneity and intervention complexity (Argent et al., 2020; Compas et al., 2015; Lannes et al., 2021). Qualitative researchers have explored mechanisms of change as underlying contextual processes contributing to outcomes in participants' intervention enactment(Bonell et al., 2022).

Combining and integrating qualitative and quantitative approaches to understand both underlying contextual processes along with moderating and mediating factors can enhance identifying mechanisms of change in complex preventive interventions. Identifying what works for specific groups in prevention informs the design, implementation, and generalizability of complex preventive interventions(Blaisdell et al., 2023; Burchett et al., 2020). Ultimately, comprehending the mechanisms of change in mental health preventive interventions is crucial for translating research into implementation(Goodyear et al., 2022).

This current study aimed to explore mechanisms of change within the family-based preventive intervention, VIA Family, using a sequential mixed methods design (Creswell & Plano Clark, 2018). We defined mechanisms of change as ‘contextual mechanism that enact with the intervention to bring about change’ (Bonell et al., 2022; Burchett et al., 2020). The research question was:

“What are mechanisms of change in the preventive family-based intervention VIA Family?”

Methods

The current study is an exploratory sequential mixed methods study of three parts (Creswell & Plano Clark, 2018). The exploratory design is often applied to sparsely studied research fields without much available evidence to inform the creation of, e.g., a new variable to be studied (Creswell & Plano Clark, 2018). Part 1 is a qualitative study of an abductive analysis on data gathered from focus-group discussions. Part 2 builds on these findings to define a new variable for a quantitative analysis. Part 3 is a quantitative post hoc subgroup analysis based on secondary data from the VIA Family trial (Müller et al., 2019).

The following section will describe methods and results of the studies in their sequential order.

Part I: Qualitative Study

Methods

Sampling and Data Generation. The sample for the qualitative analyses was a subsample of parents and children randomized to the VIA Family intervention. Data was generated through 2 focus-group discussions with participating parents and 2 groups with participating children. We used purposive sampling; including a homogenous and small sample of only parents and children with experience from participation in several components of the intervention (Hennink & Kaiser, 2022). Due to COVID-19 social restrictions at the time of data collection, we invited only those who had been in recent (approximately within the last 4 weeks) social contact through VIA Family support groups. A total of 8 parents (3/5 parents per focus group) and their 8 children (4 children per focus group) participated. Within the parents' focus groups, 5 participants identified as female, 3 participants had a mental illness diagnosis. In one of the groups, two parents from the same family participated. Within the children's focus groups, children were aged 8 – 14 years, 5 children identified as female. In one group, two siblings from the same family participated. We pseudonymize all names in the results section.

Anthropology graduate students (KS and SFJ) moderated the focus-group discussions. They were not part of the trial or intervention and were unacquainted with the participants beforehand. The moderation was facilitated by a semi-structured theme guide exploring experiences of participation in VIA Family (see supplementary material S1 and S2). We used participatory methods, such as drawing and moving around for children and quotes for parents, to engage participants in the discussion groups (Adler et al., 2019). Focus groups discussions were held in the rooms of the off-clinic facilities of the VIA Family intervention after hours. The two moderators audio recorded the discussions and transcribed the complete sessions verbatim, with some level of details (e.g., pauses, laughter and nodding for agreement) (O'Reilly & Parker, 2014).

Data Analysis. We used thematic analysis to explore data with the principles and methods of abductive analysis by Timmerman and Tavory (2022) (Thompson, 2022; Timmermans & Tavory, 2012, 2022). Abductive analysis is an iterative analytical process where the researcher equally draws on theory and data to answer the research question with the aim to look for surprises within both (Timmermans & Tavory, 2022). We integrated theory and data to describe, explain and challenge the development of themes. In addition, based on the iterative abductive approach, we used data to explore limitations in our theories.

Our theoretical framework was based on the health-belief model (HBM) (Rosenstock, 1974) and the self-determination theory (SDT) (Ryan & Deci, 2000). HBM describes health-preventive behaviour, assuming that people engage in such actions when they perceive susceptibility and severity of a health problem, and when the benefits of the intervention outweigh the barriers (Green et al., 2020; Rosenstock, 1974). Cues to action (e.g., information campaigns) and self-efficacy can trigger engagement and reveal individual differences. In contrast, SDT emphasize that people's basic role of thrive for autonomy, competency, and relatedness influences their motivation to engage in change (Ryan, 2023; Ryan & Deci, 2000). SDT categorizes motivation on a continuum from extrinsic to intrinsic depending on the degree of autonomy involved (Vansteenkiste & Sheldon, 2006). Supporting autonomy is crucial for enhancing motivation and engagement (Ryan & Deci, 2000). Both theories acknowledge that social and cultural factors modify engagement and motivation and thus function as individual modifying factors (Green et al., 2020; Ryan, 2023).

A team of four (ADM, SC, IG and GP) analysed the focus group data. We commenced with individual open coding rounds by reading transcripts and listening to audio records. Here, we

developed initial codes aligned with our initial research question: *What mechanisms of change, if any, do participants' experience within the intervention?* In the next step, we discussed the initial codes within the group and developed a promising themes which was surprising in light of our theoretical understanding of the phenomena (Timmermans & Tavory, 2022). Next, we focused coding in our analysis to code only within the promising theme to look for patterns and variations within this theme using a modified research question: *"How does the need for change impact the experience of change?"* (Timmermans & Tavory, 2022). Finally, we evaluated our theoretical framework by applying them to our data.

Reflexivity. Our backgrounds, knowledge, and assumptions shaped this study. As white female academics and mothers from developed countries specializing in mental health, high-risk populations, and prevention, we share a common belief in the importance of preventing mental illness in these groups. Throughout data analyses and interpretation, we actively considered how our presumptions limited and strengthened this study.

Qualitative Findings

Findings of the abductive analysis of parents and children's focus group discussion are in Figure 1.

Figure 1: Findings from Qualitative Analysis

Theme	Participants Narratives	Interpretation
Parents		
<i>“It fits perfectly”</i>	<i>"It was to support my daughter (Peter, father)."</i> <i>"So, when we got this offer, we thought 'it fits perfectly', also because we had a son who had a really difficult time mentally" (Charlotte, mother)</i> <i>"I chose it [VIA Family], I think that I really wanted to have my daughter examined, because I was really afraid that she would become as sick as her father" (Sara, mother)</i>	Need for support for child Peter, Charlotte, and Sara all engaged in the preventive intervention because they perceived a need for support either because they experienced that their child a) needed support, b) had signs of mental illness, or c) had a familial risk for developing a mental illness. Their perception of a need for support was enhanced and internalized when they perceived that their child needed support for early signs of mental health problems in their child. According to SDT, their identification of a need for support was based on autonomy; this is crucial to facilitate an internalized motivation for long-term changes to occur. In the above examples According to the HBM, Charlottes’ perception of her son’s ill-being triggered engagement in the intervention. Charlotte and Sara's quotes illustrated how the invitation to participate in the VIA Family trial acted as an external cue to action and increased susceptibility to her son’s familial high-risk status and its severity.
<i>“We didn't have any needs”</i>	<i>"We never really figured out what to get out of it(. ...) I think that if something should have changed (. ...) we would have needed guidance at a different level, because that's not where our needs were, or we didn't have any needs, I don't know." (Anna, mother)</i> <i>"Do we really need this? Has anyone pointed out that here [in our family] we need to take action?" (Catherine, mother)</i>	No need for support Some parents did not feel that their family needed any support. Despite the individually tailored approach, VIA Family did not meet the family's needs in these cases. Parents felt unengaged and without any sense of change. According to the SDT, this form of motivation can be defined as solely extrinsic. For Catherine, for example, her motivation to engage was not internalized, possibly because she did not perceive that she needed support despite the information that her child has an increased familial risk for severe mental illness. In these cases, the solely familial high-risk status of their children did not motivate parents to engage in the intervention unless their children already showed early signs of mental illness.

		However, although Anna’s motivation was based on autonomy (SDT), she perceived her children to have an elevated risk with high perceived benefits of the intervention and low barriers (HBM); her motivation was not stable intrinsic or extrinsic and at times she did not “<i>figured out what to get out of it</i>”.
<i>“Hey, now there is something wrong here, and we can get help immediately “</i>	<i>"At first, we didn't have any problems in our family (. ...), but then my son started first grade (. ...) The most important thing then was that 'hey, now there is something wrong here, and we can get help immediately."</i> (Catherine, mother)	Changes in need for support However, the motivation could change during the intervention. For example, if parents perceived a need for support during the intervention, they internalized the extrinsic motivation for change and perceived the intervention as beneficial. Motivation for participation here becomes internalized. A higher degree of autonomy enables the shift from amotivation to a more internalized extrinsic motivation. This shift occurred when parents perceived they needed support but not when they got the trial invitation to participate.
<i>“It was a need that we did not think we had”</i>	<i>"But they [VIA Family team] have fulfilled something really well, which we have talked about so much. So, it was a need that we did not think we had, but which then turned out to be super relevant"</i> (Thomas, father)	The intervention changed the perception of a need for support Being in the intervention could also change parents' perception of need. Many parents described an internalization of motivation during the intervention. In some cases, it made them aware of a specific problem or need for support for a family member. Following HBM, the change in perception of a need for change was triggered by the intervention addressing families' beliefs about their child's high-risk status and severity. Following SDT, internalization was enabled through the support of families’ autonomy – which was part of the individually tailored design of the intervention.
<i>“If I had had that as a child”</i>	<i>"I'm the child of a severe mentally ill mother, and there were zero offers, and I felt like ... it still affects me, and at times it also does so for my children (. ...) I think it sounds so cool to have had someone like, that the children could go and talk to [case-manager]. I mean, if I</i>	Perceived need for support enabled by parents’ own unmet need In some cases, parents described a motivation without a perceived need for support. Anna, for example, described that she was motivated because she had experienced parental mental illness when she was a child. Although she did not feel any current support needs, she was motivated by a previously unmet need for support growing up. The unmet need from parents' childhood could act as a need for support in the present, despite the absence of signs of vulnerability in the child. Unmet need

had had that as a child, my life would have looked completely different" (Anna, mother)

for support when she was a child, gives her an internalized awareness of a possible need her children may or may not have.

Children

"Almost my whole family has been down here and talked to someone, and it has just helped."

"It [VIA Family] was just really nice"(Robin, 8 years)

"[. ...] Bicycle rides, because we usually take the bike over here. And then, romkugler [a Danish pastry], because Kirsten's bakery is just very close by, and we almost always buy romkugler. And then I also wrote 'mental illness', where I have drawn going from being happy to being sad" (Andrea, child, 13 years)

"I don't know. I can just [see a change in the family]. Almost my whole family has been down here and talked to someone, and it has just helped." (Charlie, child, 13 years)

Children's intrinsic motivation

Children described an intrinsic motivation for participation enabled by being together with the family and by the intervention itself.

The intervention offered peer-support groups with activities and snacks. All children mention that coming to VIA Family was joyful for them, i.e. in SDT terminology, the intervention enabled intrinsic motivation. The parents do not describe that.

Many of the children described that the preventive intervention enabled the family to engage in joint activities, like in this quote, riding the bike to the intervention and buying pastry after the sessions in VIA Family. Children associate these activities as much with the intervention as learning about mental illness. Many children describe that they appreciated the time spent with their family before, in and after the sessions in VIA Family. Following the principles of SDT, children's motivation was enhanced by spending time with their family because it supports their basic need for relatedness.

Part II: Mixed Methods Integration

The aim of the mixed methods integration part was to identify a variable for subgroup analysis in part III. Therefore, we operationalized the qualitative finding ‘need for support’ as ‘motivation for participation’. To do so, we used secondary data from the VIA Family trial and looked at the structured interview on participants’ demography at baseline. During this interview, all children’s primary caregivers were asked about their motivation or reason for participation. We used the primary reason they gave and dichotomized answers to either being motivated for participation a) to contribute to science or b) to receive support for a need.

Part III: Quantitative Study

Methods

Sampling and Data Collection. The sample for the quantitative analysis was a subsample of the VIA Family trial. Eligible families for the subsample were families who informed us about their reasons for participation at baseline. We used secondary data from the VIA Family trial. of measures on levels of support and stimulation in the home environment (HOME)(Caldwell & Bradley, 2003) and the children's global functioning (CGAS)(Shaffer, 1983). CGAS was the primary outcome of the VIA Family trial, and HOME was the secondary outcome(Müller et al., 2019).

Statistical Analysis. We did an exploratory post hoc subgroup analysis based on intention-to-treat (ITT) principles, where we included all participants with information on participation regardless of attrition. We imputed outcome data using multiple imputations based on 100 imputations and 20 iterations until convergence. The analyses were based on a linear mixed model with a random nested factor (effect of clustering due to familiarity) to account for data not being independent (siblings belonging to the same family). All analyses were adjusted for age at baseline and children's biological sex. We used the statistical software R version 4.2.2 for all data analyses with the packages 'lme4'(Bates et al., 2015) and 'Amelia'(Honaker et al., 2011).

Part 3: Results

We included data from 110 children and their primary caregivers in the analyses. We excluded 3 children from the analysis, with no parental data on motivation for participation.

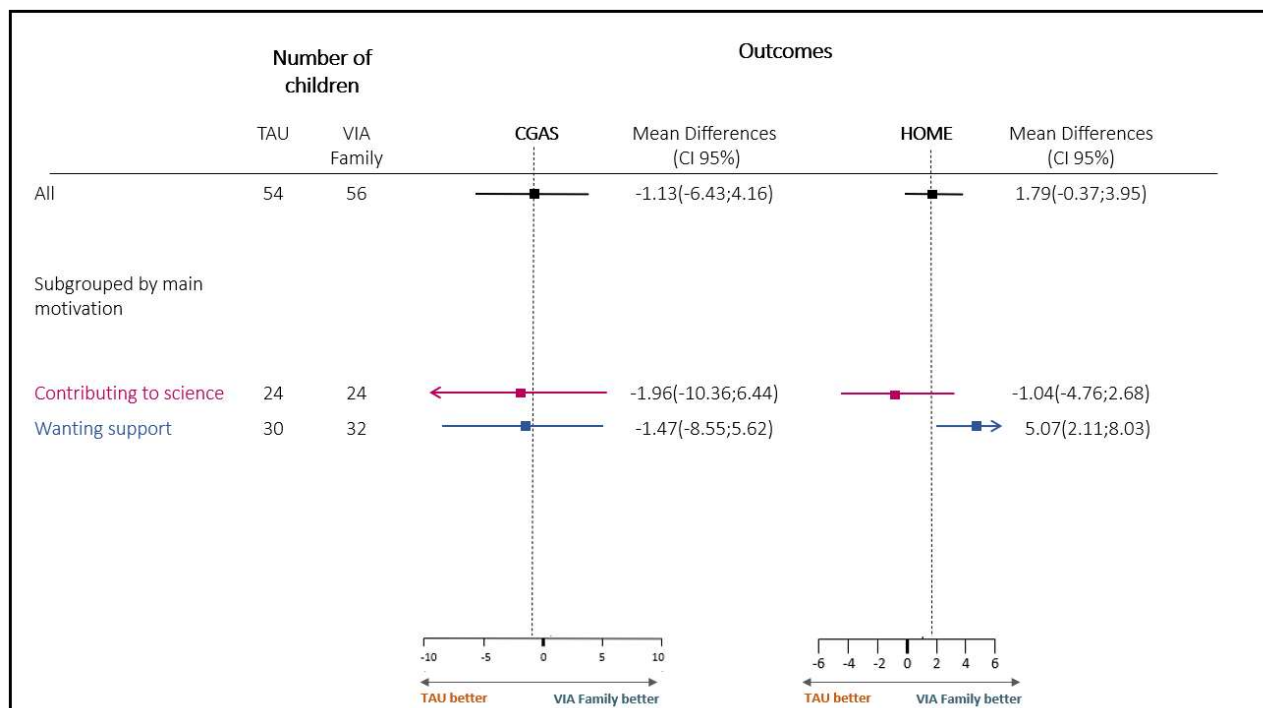
The subgroups divided by motivation showed that 48 (42.5%) primary caregivers were primarily motivated to participate in the study because they wanted to help science, and 62 (54.9%) wanted support. See Table 1 for demographic and clinical characteristics of the participating children and their parents in the subgroups for group VIA Family and TAU.

Table 1. Baseline demographic characteristics divided by intervention group and primary caregiver's main reason for study participation

Table 1 Demographic characteristics divided by allocation group and primary caregiver's main reason for study participation (Table 1 in paper 2)				
	VIA Family		Treatment As Usual	
Main reason for participation	Contributing to science	Wanting support	Contributing to science	Wanting support
All families	N=46		N=47	
Primary Caregiver, n (%)	20(43)	26(57)	20(43)	27(57)
Having a SMI diagnosis ¹	15(33)	18(39)	15(32)	20(43)
Functioning (PSP)	68.30(11.88)	66.96(15.75)	65.30(17.46)	70.26(15.28)
All children	N=56		N=54	
Children, n (%)	24 (43)	32(57)	24(44)	30(56)
Children's age at baseline in years, mean (SD)	9.5(2.1)	9.9(1.7)	9.5(2.2)	9.5(1.8)
Biological sex female, n (%)	10(42)	14(44)	11(46)	17(53)
Global functioning (CGAS), mean (SD)	64.79(13.11)	67.09(13.21)	62.38(15.47)	65.00(15.07)
Home environment (HOME), mean (SD)	47.44(4.44)	46.26(6.62)	44.67(6.70)	48.61(4.48)
Behavioural or emotional problems (CBCL), T-score, mean (SD)	56.54(10.44)	55.86(13.20)	68.17(18.39)	56.88(14.89)
¹ Diagnosis of a schizophrenia spectrum disorder, bipolar disorder, recurrent major depression during their child's life.				

Subgroup analysis of families wanting support at baseline showed no significant differences between groups at post-intervention in children's psychosocial functioning (-1.47, 95 % CI: -8.55 to 5.62). However, regarding a change in levels of support and stimulation in the home environment there was an effect for the VIA Family Intervention group with a clinically significant difference for families seeking support at baseline (5.07, 95% CI: 2.11 to 8.03) (Figure. 2).

Figure 2: Comparison between differences in mean change at post-intervention for Treatment as Usual and VIA Family on CGAS and HOME, Subgrouped by main motivation for study participation at baseline



Discussion

The aim of this study was to explore mechanisms contributing to change in a preventive mental health intervention using a sequential exploratory mixed methods design in three parts. We used data gathered from focus groups and secondary data from the VIA Family trial (Müller et al., 2019).

Findings from the qualitative study, showed that parents' own perceived *need* for intervention acted as a mechanism of change for them to engage in the intervention. For children, their families' participation acted as a mechanism of change. For the mixed-method integration part (part II) we used the theme of *need for support* to identify the variable *motivation for study participation* from baseline assessment for a subgroup analysis. Part III was a post hoc subgroup analysis on secondary data from the VIA Family trial. The subgroup analysis showed no differences in change over time in children's global functioning across subgroups. However, regarding change in levels of support and stimulation in the home environment, subgroup

analysis showed a clinically significant difference for parents' motivation at baseline in favour of the VIA Family group compared to the TAU group.

The results from the qualitative and quantitative analyses support each other. The findings that perceived need and motivation lead to experiences of change mirror the results that parents who engaged in the intervention because they wanted support had a significant increase in quality of home environment when allocated to VIA Family. However, there was no difference in change in children's global functioning for parents who wanted support at baseline. The lack of difference in change in children's daily functioning might be because motivation was not a mechanism underlying change. Conversely, changes in home environment might precede and enable change in child's functioning at a later timepoint (Van Der Put et al., 2018). This might lead to a delayed effect of the intervention on child's global functioning. We are currently exploring the long-term effects of the intervention in a follow-up trial.

Most studies that address parental engagement in preventive interventions have found similar results. A recent systematic review of qualitative, quantitative and mixed methods studies found that parents are less likely to engage in preventive interventions if they do not perceive that their child needs support (Houle et al., 2022). The authors conclude that this adds to the challenge to get families involved in preventive programs who do not perceive that their child needs support (because they, e.g., do not exhibit symptoms or the symptoms are less visible, i.e. internalized symptoms) (Houle et al., 2022). Another review summarized that despite multiple predictors of engagement in preventive parenting programs, the presence of child mental health problems had the most reliable association with enrolment (Finan et al., 2018). However, while child mental illness predicted enrolment into preventive programs, results were mixed regarding ongoing engagement (Finan et al., 2018).

None of the included studies explored a more in-depth understanding of participants' experiences of need (Finan et al., 2018). The findings of this study suggest that participants' perception of need expands from early signs of vulnerability, such as child mental health problems. The perception of need for support also includes, e.g., the parents' own experiences of unmet needs from their own childhood. Additionally, none of the studies described that the intervention itself could facilitate engagement, as indicated by our findings: *'it was a need that we did not think we had'*. Notably, it has been criticized that parental engagement in psychological interventions often is operationalized as drop-out status, which might not give an in-depth picture of engagement, which e.g., is visible in qualitative research (Pereira & Barros, 2019).

Additionally, incorporating theory such as SDT and HBM to guide enrolment strategies for preventive intervention may enhance parents' participation, as proposed in a previous review (Finan et al., 2018). Following the theoretical framework of SDT, enhancing internalized motivation through the support of autonomy can make parents maintain engagement in the preventive intervention. In contrast, ordering people with a severe mental illness into treatment (i.e. extrinsic motivation) decreases their likelihood of finding the intervention helpful (Alang & McAlpine, 2019). Applying SDT's concept of autonomy may therefore increase participants' motivation during the intervention and can keep them engaged.

Regarding children, our findings suggest that their engagement was driven by their families' participation. Family members' participation was a mechanism for change. Despite inconclusive findings in the literature in regard to the advantage of children's participation in preventive interventions, it has been suggested that their involvement might lead to faster change.

In conclusion, the results highlight the significance of parents' experience of need for support as a pivotal mechanism of change in preventive interventions for children with a familial risk of mental illness. Merely informing families about the potential familial risk of their child developing mental illness may not be a sufficient cue to action. However, addressing families' own perceived needs for support is central for enabling the long-term changes that preventive interventions for children with a familial risk seek to create.

Strengths and limitations

The qualitative part of the study has some limitations. First, the qualitative sample lacked ethnic diversity, with none of the focus group participants having an ethnic minority background, despite such diversity being present in the VIA Family trial. However, the qualitative sample was diverse in terms of socioeconomic background, history of mental illness, and age and gender. Secondly, we didn't interview families allocated to usual care (TAU), so we can't definitively attribute the observed mechanisms of change solely to the experimental intervention. Lastly, although children participated vividly in the focus group discussions, their views, expressions, and understanding of mechanisms of change may be limited by their age-related

verbal communication skills. Future studies could consider employing alternative methods to better capture children's perspectives and voices.

The post hoc subgroup analyses were exploratory. Therefore, our results need to be interpreted with caution. To rule out a possible Type 1 error, the results from the post hoc subgroup analysis must be validated, possibly in a larger sample. Nonetheless, although the subgroup analysis was defined post hoc, the hypothesis was based on a theoretical framework and the qualitative findings.

Moreover, our theoretical framework might oversimplify the factors of how and why people engage in change. Our findings suggest that the pathways of perception of need and motivation is complex, as they operate in a complex world. The theories, however, may underemphasize the role of stigma of being a parent with mental illness, parents' low functioning due to mental illness, or the complex network of a family. Especially the health belief model assumes that people make rational decisions (Green et al., 2020). However, the decision to engage in preventive interventions is not merely based on rationality, but also influenced by social stigma, feelings of guilt and shame, and the wish to protect one's child from stigma by association or the knowledge of their familial high risk status (Habib et al., 2020; Mulligan et al., 2021; Reupert et al., 2021).

Despite the limitations of the study design, the rigorous sequential mixed methods design allowed us to use the in-depth findings from the first part to generate new hypothesis and theories for an understudied field: mechanisms of change in complex preventive interventions. Despite important findings in the field of preventive intervention for high-risk groups, the research field is still understudied, partly due to financing issue for preventive compared with therapeutic interventions (Duffy et al., 2023). Furthermore, the quantitative part allowed us to not simply state these hypotheses, but also to test them quantitatively, thereby both strengthening the findings of the first part, and elaborating on them.

Furthermore, our study's strength lies in its inclusion of both parents' and children's viewpoints, enabling us to compare their differences. This approach facilitated an understanding of how their mechanisms of change mutually affected their engagement. For instance, we found that parents' perception of the need for support was influenced by their children requiring support, and family participation enhanced children's motivation to engage.

Clinical implications

Clinicians in contact with parents with a mental illness should focus on identifying signs of need for support in their patients' children. Regular assessments, screenings and evaluations families about the potential risks for their next-of-kin and potential needs for support in the family could motivate parents to engage in preventive strategies (Festen et al., 2014).

Moreover, assessing parents' and children's quality of motivation might enhance participation in preventive interventions and preventive trials. This assessment should begin during the recruitment phase, aiming to understand parents' perception of need and the quality of their motivation. If the aim of preventive interventions is to maintain behaviour over time, it is important that the intervention supports the participants' autonomy, competencies and relatedness. Nevertheless, cultural influences, such as those related to the stigma of mental illness, can hinder autonomy, and should be addressed in both universal, selective, and indicated preventive programs.

Future Directions

In light of our findings regarding the centrality of needs and motivation, a stepped care model based on the motivation and experienced need for support might be beneficial. In the stepped care model, autonomy-respecting and least intrusive programs, such as bibliotherapy and online programs for children at familial risk for mental illness, could for some families with parental mental illness be the first step to engage and develop a perception of a need that they did not think they had (Vetri et al., 2022; Villatte et al., 2023). A recent review concluded that especially online programs could increase the engagement of non-engaged parents in preventive interventions (Finan et al., 2018). Lastly, not all children at familial risk for mental illness will develop a mental illness (Uher et al., 2023). In order to target the right at risk group and motivate them to engage in preventive interventions, research in high-risk groups are essential.

Acknowledgments:

Anna Iburg Printzlau and Amalie Fabricius Kristensen for help with qualitative and quantitative data collection, Sidsel Ingversen for supervision and help with recruitment and data collection for the qualitative data, and Julie Lyng Forman for advice and support regarding statistics.

References

- Adler, K., Salanterä, S., & Zumstein-Shaha, M. (2019). Focus Group Interviews in Child, Youth, and Parent Research: An Integrative Literature Review. *International Journal of Qualitative Methods*, 18, 160940691988727. <https://doi.org/10.1177/1609406919887274>
- Alang, S. M., & McAlpine, D. D. (2019). Pathways to Mental Health Services and Perceptions about the Effectiveness of Treatment. *Society and Mental Health*, 9(3), 388–407. <https://doi.org/10.1177/2156869318802341>
- Arango, C., Díaz-Caneja, C. M., McGorry, P. D., Rapoport, J., Sommer, I. E., Vorstman, J. A., McDaid, D., Marín, O., Serrano-Drozdzowskyj, E., Freedman, R., & Carpenter, W. (2018). Preventive strategies for mental health. *The Lancet Psychiatry*, 5(7), 591–604. [https://doi.org/10.1016/S2215-0366\(18\)30057-9](https://doi.org/10.1016/S2215-0366(18)30057-9)
- Argent, S. E., Kalebic, N., Rice, F., & Taylor, P. (2020). Offspring outcomes when a parent experiences one or more major psychiatric disorder(s): A clinical review. *Evidence Based Mental Health*, 23(3), 113–121. <https://doi.org/10.1136/ebmental-2019-300123>
- Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using **lme4**. *Journal of Statistical Software*, 67(1). <https://doi.org/10.18637/jss.v067.i01>
- Blaisdell, K. N., Horn, S. R., & Fisher, P. A. (2023). Prevention Strategies: Prevention and Promotion in Child Mental Health. In J. L. Matson (Ed.), *Handbook of Clinical Child Psychology* (pp. 545–563). Springer International Publishing. https://doi.org/10.1007/978-3-031-24926-6_26
- Bonell, C., Warren, E., & Melendez-Torres, G. (2022). Methodological reflections on using qualitative research to explore the causal mechanisms of complex health interventions. *Evaluation*, 28(2), 166–181. <https://doi.org/10.1177/13563890221086309>
- Burchett, H. E. D., Kneale, D., Blanchard, L., & Thomas, J. (2020). When assessing generalisability, focusing on differences in population or setting alone is insufficient. *Trials*, 21(1), 286. <https://doi.org/10.1186/s13063-020-4178-6>
- Butler, J., Gregg, L., Calam, R., & Wittkowski, A. (2020). Parents' Perceptions and Experiences of Parenting Programmes: A Systematic Review and Metasynthesis of the Qualitative Literature. *Clinical Child and Family Psychology Review*, 23(2), 176–204. <https://doi.org/10.1007/s10567-019-00307-y>
- Caldwell, B. M., & Bradley, R. H. (2003). Home observation for measurement of the environment: Administration manual. *Tempe, AZ: Family & Human Dynamics Research Institute, Arizona State University*.
- Campbell, N. C., Murray, E., Darbyshire, J., Emery, J., Farmer, A., Griffiths, F., Guthrie, B., Lester, H., Wilson, P., & Kinmonth, A. L. (2007). Designing and evaluating complex interventions to improve health care. *BMJ*, 334(7591), 455–459. <https://doi.org/10.1136/bmj.39108.379965.BE>

- Compas, B. E., Forehand, R., Thigpen, J., Hardcastle, E., Garai, E., McKee, L., Keller, G., Dunbar, J. P., Watson, K. H., Rakow, A., Bettis, A., Reising, M., Cole, D., & Sterba, S. (2015). Efficacy and moderators of a family group cognitive-behavioral preventive intervention for children of parents with depression. *Journal of Consulting and Clinical Psychology*, 83(3), 541–553. <https://doi.org/10.1037/a0039053>
- Creswell, J. W., & Plano Clark, V. L. (2018). *Designing and conducting mixed methods research* (Third edition, international student edition). Sage.
- Duffy, A., Goodday, S. M., Christiansen, H., Patton, G., Thorup, A. A. E., Preisig, M., Vandeleur, C., Weissman, M., & De Girolamo, G. (2023). The well-being of children at familial risk of severe mental illness: An overlooked yet crucial prevention and early intervention opportunity. *Nature Mental Health*, 1(8), 534–541. <https://doi.org/10.1038/s44220-023-00090-4>
- Festen, H., Schipper, K., De Vries, S. O., Reichart, C. G., Abma, T. A., & Nauta, M. H. (2014). Parents' perceptions on offspring risk and prevention of anxiety and depression: A qualitative study. *BMC Psychology*, 2(1), 17. <https://doi.org/10.1186/2050-7283-2-17>
- Finan, S. J., Swierzbiolek, B., Priest, N., Warren, N., & Yap, M. (2018). Parental engagement in preventive parenting programs for child mental health: A systematic review of predictors and strategies to increase engagement. *PeerJ*, 6, e4676. <https://doi.org/10.7717/peerj.4676>
- Fusar-Poli, P., Correll, C. U., Arango, C., Berk, M., Patel, V., & Ioannidis, J. P. (2021). Preventive psychiatry: A blueprint for improving the mental health of young people. *World Psychiatry*, 20(2), 200–221. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/wps.20869>
- Ginsburg, L. R., Hoben, M., Easterbrook, A., Anderson, R. A., Estabrooks, C. A., & Norton, P. G. (2021). Fidelity is not easy! Challenges and guidelines for assessing fidelity in complex interventions. *Trials*, 22(1), 372. <https://doi.org/10.1186/s13063-021-05322-5>
- Goodyear, M. J., Allchin, B., Burn, M., von Doussa, H., Reupert, A., Tchernegovski, P., Sheen, J., Cuff, R., Obradovic, A., & Solantaus, T. (2022). Promoting self-determination in parents with mental illness in adult mental health settings. *Journal of Family Nursing*, 28(2), 129–141.
- Green, E. C., Murphy, E. M., & Gryboski, K. (2020). The Health Belief Model. In K. Sweeny, M. L. Robbins, & L. M. Cohen (Eds.), *The Wiley Encyclopedia of Health Psychology* (1st ed., pp. 211–214). Wiley. <https://doi.org/10.1002/9781119057840.ch68>
- Habib, R., Clément, M.-È., Milot, T., Piché, G., & Gagné, M.-H. (2020). Comment favoriser le recrutement des parents dans les programmes d'éducation parentale ? *Canadian Psychology / Psychologie Canadienne*, 61(3), 234–244. <https://doi.org/10.1037/cap0000201>
- Hennink, M., & Kaiser, B. N. (2022). Sample sizes for saturation in qualitative research: A systematic review of empirical tests. *Social Science & Medicine*, 292, 114523. <https://doi.org/10.1016/j.socscimed.2021.114523>

- Herrman, H., Patel, V., Kieling, C., Berk, M., Buchweitz, C., Cuijpers, P., Furukawa, T. A., Kessler, R. C., Kohrt, B. A., & Maj, M. (2022). Time for united action on depression: A Lancet–World Psychiatric Association Commission. *The Lancet*, 399(10328), 957–1022.
- Honaker, J., King, G., & Blackwell, M. (2011). **Amelia II**: A Program for Missing Data. *Journal of Statistical Software*, 45(7). <https://doi.org/10.18637/jss.v045.i07>
- Hosman, C. M. H., Van Doesum, K. T. M., & Van Santvoort, F. (2009). Prevention of emotional problems and psychiatric risks in children of parents with a mental illness in the Netherlands: I. The scientific basis to a comprehensive approach. *Australian E-Journal for the Advancement of Mental Health*, 8(3), 250–263. <https://doi.org/10.5172/jamh.8.3.250>
- Houle, A.-A., Besnard, T., & Bérubé, A. (2022). Factors that influence parent recruitment into prevention programs in early childhood: A mixed studies systematic review. *Children and Youth Services Review*, 133, 106367. <https://doi.org/10.1016/j.childyouth.2022.106367>
- Krantz, M. F., Ellersgaard, D., Andersen, K. K., Hemager, N., Christiani, C., Spang, K. S., Burton, B. K., Gregersen, M., Søndergaard, A., Greve, A., Gantriis, D. L., Ohland, J., Mortensen, P. B., Werge, T., Nudel, R., Wang, Y., Hougaard, D. M., Plessen, K. J., Bliksted, V., ... Nordentoft, M. (2022). Accumulation of Disadvantages Across Multiple Domains Amongst Subgroups of Children of Parents With Schizophrenia or Bipolar Disorder: Clustering Data from the Danish High Risk and Resilience Study VIA 7. *Schizophrenia Bulletin Open*, 3(1), sgac010. <https://doi.org/10.1093/schizbullopen/sgac010>
- Krantz, M. F., Hjorthøj, C., Brandt, J. M., Prøsch, Å. K., Rohd, S. B., Wilms, M., Veddem, L., Steffensen, N. L., Knudsen, C. B., Andreasen, A. K., Stadsgaard, H., Hemager, N., Burton, B. K., Gregersen, M., Søndergaard, A., Greve, A., Gantriis, D. L., Melau, M., Ohland, J., ... Nordentoft, M. (2023). Home environment of 11-year-old children born to parents with schizophrenia or bipolar disorder – a controlled, 4-year follow-up study: The Danish High Risk and Resilience Study – VIA 11. *Psychological Medicine*, 53(6), 2563–2573. <https://doi.org/10.1017/S0033291721004487>
- Lannes, A., Bui, E., Arnaud, C., Raynaud, J.-P., & Revet, A. (2021). Preventive interventions in offspring of parents with mental illness: A systematic review and meta-analysis of randomized controlled trials. *Psychological Medicine*, 51(14), 2321–2336. <https://doi.org/10.1017/S0033291721003366>
- Löchner, J., Platt, B., Starman-Wöhrle, K., Takano, K., Engelmann, L., Voggt, A., Loy, F., Bley, M., Winogradow, D., Hämmerle, S., Neumeier, E., Wermuth, I., Schmitt, K., Oort, F., & Schulte-Körne, G. (2023). A randomized controlled trial of a preventive intervention for the children of parents with depression: Mid-term effects, mediators and moderators. *BMC Psychiatry*, 23(1), 455. <https://doi.org/10.1186/s12888-023-04926-2>
- Maybery, D., & Reupert, A. E. (2018). The number of parents who are patients attending adult psychiatric services. *Current Opinion in Psychiatry*, 31(4), 358–362. <https://doi.org/10.1097/YCO.0000000000000427>
- Müller, A. D., Gjøde, I. C. T., Eigil, M. S., Busck, H., Bonne, M., Nordentoft, M., & Thorup, A. A. E. (2019). VIA Family—a family-based early intervention versus treatment as usual for

- familial high-risk children: A study protocol for a randomized clinical trial. *Trials*, 20(1), 112. <https://doi.org/10.1186/s13063-019-3191-0>
- Mulligan, C., Furlong, M., McGarr, S., O'Connor, S., & McGilloway, S. (2021). The Family Talk Programme in Ireland: A Qualitative Analysis of the Experiences of Families With Parental Mental Illness. *Frontiers in Psychiatry*, 12, 783189. <https://doi.org/10.3389/fpsy.2021.783189>
- O'Reilly, M., & Parker, N. (2014). *Doing mental health research with children and adolescents: A guide to qualitative methods*. SAGE.
- Pereira, A. I., & Barros, L. (2019). Parental Cognitions and Motivation to Engage in Psychological Interventions: A Systematic Review. *Child Psychiatry & Human Development*, 50(3), 347–361. <https://doi.org/10.1007/s10578-018-0852-2>
- Petticrew, M., Rehfuss, E., Noyes, J., Higgins, J. P. T., Mayhew, A., Pantoja, T., Shemilt, I., & Sowden, A. (2013). Synthesizing evidence on complex interventions: How meta-analytical, qualitative, and mixed-method approaches can contribute. *Journal of Clinical Epidemiology*, 66(11), 1230–1243. <https://doi.org/10.1016/j.jclinepi.2013.06.005>
- Puchol-Martínez, I., Vallina Fernández, Ó., & Santed-Germán, M. A. (2023). Preventive interventions for children and adolescents of parents with mental illness: A systematic review. *Clinical Psychology & Psychotherapy*, cpp.2850. <https://doi.org/10.1002/cpp.2850>
- Radley, J., Sivarajah, N., Moltrecht, B., Klampe, M.-L., Hudson, F., Delahay, R., Barlow, J., & Johns, L. C. (2022). A Scoping Review of Interventions Designed to Support Parents With Mental Illness That Would Be Appropriate for Parents With Psychosis. *Frontiers in Psychiatry*, 12, 787166. <https://doi.org/10.3389/fpsy.2021.787166>
- Reupert, A., Gladstone, B., Helena Hine, R., Yates, S., McGaw, V., Charles, G., Drost, L., & Foster, K. (2021). Stigma in relation to families living with parental mental illness: An integrative review. *International Journal of Mental Health Nursing*, 30(1), 6–26. <https://doi.org/10.1111/inm.12820>
- Rosenstock, I. M. (1974). The Health Belief Model and Preventive Health Behavior. *Health Education Monographs*, 2(4), 354–386. <https://doi.org/10.1177/109019817400200405>
- Ryan, R. M. (Ed.). (2023). *The Oxford handbook of self-determination theory*. Oxford University Press.
- Ryan, R. M., & Deci, E. L. (2000). Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *American Psychologist*, 55(1), 68–78. <https://doi.org/10.1037/0003-066X.55.1.68>
- Shaffer, D. (1983). A Children's Global Assessment Scale (CGAS). *Archives of General Psychiatry*, 40(11), 1228. <https://doi.org/10.1001/archpsyc.1983.01790100074010>
- Skivington, K., Matthews, L., Simpson, S. A., Craig, P., Baird, J., Blazeby, J. M., Boyd, K. A., Craig, N., French, D. P., McIntosh, E., Petticrew, M., Rycroft-Malone, J., White, M., & Moore, L. (2021). A new framework for developing and evaluating complex interventions:

Update of Medical Research Council guidance. *BMJ*, n2061.
<https://doi.org/10.1136/bmj.n2061>

Thompson, J. (2022). A Guide to Abductive Thematic Analysis. *The Qualitative Report*.
<https://doi.org/10.46743/2160-3715/2022.5340>

Timmermans, S., & Tavory, I. (2012). Theory Construction in Qualitative Research: From Grounded Theory to Abductive Analysis. *Sociological Theory*, 30(3), 167–186.
<https://doi.org/10.1177/0735275112457914>

Timmermans, S., & Tavory, I. (2022). *Data analysis in qualitative research: Theorizing with abductive analysis*. University of Chicago Press.

Uher, R., Pavlova, B., Radua, J., Provenzani, U., Najafi, S., Fortea, L., Ortuño, M., Nazarova, A., Perroud, N., Palaniyappan, L., Domschke, K., Cortese, S., Arnold, P. D., Austin, J. C., Vanyukov, M. M., Weissman, M. M., Young, A. H., Hillegers, M. H. J., Danese, A., ... Fusar-Poli, P. (2023). Transdiagnostic risk of mental disorders in offspring of affected parents: A meta-analysis of family high-risk and registry studies. *World Psychiatry*, 22(3), 433–448. <https://doi.org/10.1002/wps.21147>

Van Der Put, C. E., Assink, M., Gubbels, J., & Boekhout Van Solinge, N. F. (2018). Identifying Effective Components of Child Maltreatment Interventions: A Meta-analysis. *Clinical Child and Family Psychology Review*, 21(2), 171–202. <https://doi.org/10.1007/s10567-017-0250-5>

Vansteenkiste, M., & Sheldon, K. M. (2006). There's nothing more practical than a good theory: Integrating motivational interviewing and self-determination theory. *British Journal of Clinical Psychology*, 45(1), 63–82. <https://doi.org/10.1348/014466505X34192>

Vetri, K., Piché, G., & Villatte, A. (2022). An Evaluation of the Acceptability, Appropriateness, and Utility of a Bibliotherapy for Children of Parents With a Mental Illness. *Frontiers in Psychiatry*, 13, 815873. <https://doi.org/10.3389/fpsy.2022.815873>

Villatte, A., Piché, G., Habib, R., & Gariépy, J. (2023). Evaluation of a mental-health literacy and self-care website intended for young people who have a parent with a mental illness. *Advances in Mental Health*, 1–20. <https://doi.org/10.1080/18387357.2023.2264416>

World Health Organization. (2022). *World mental health report: Transforming mental health for all*. Geneva:World Health Organization. . ISBN 978-92-4-004933-8 (electronic version) ISBN 978-92-4-004934-5 (print version)

Supplementary Material

S1 Guide Focus Group Discussion Parents

(translated from Danish by ADM)

Agenda (30 min)

- Welcome: Information and Consent Forms
- Exercise 1: Introduction round with picture cards
- Exercise 2: My Journey through VIA Family
- Break
- Exercise 3: Draw-a-Question
- Thank you and Goodbye

Welcome: Information and Consent Forms (10:00-10:10)

Welcome, and thank you for joining us today. I am K, and along with S, I am involved with the VIA Family study as part of our anthropology thesis.

We have invited you here today because we want to hear about your experiences with being part of VIA Family. The information you share today will be used in the VIA Family Evaluation Study. To begin, I would like to pass around some consent forms. We hope you will sign them before we proceed. With these consent forms, you permit us to use the information you provided today in the evaluation. Any information you share will, of course, be anonymized.

→ *Start the recorder and go through the agenda.*

Before we start, I want to emphasize that it's entirely up to you what and how much you want to share today. If there is something you do want to talk about, that is totally ok. I would also like to mention that the purpose of today's focus group is not necessarily to paint an overly positive picture of the VIA Family. We want to hear how you have experienced being a part of it, what has worked well, and what has not worked so well.

Exercise 1: Introduction round with picture cards (10 min)

As you can see, I have placed various picture cards on the table. What I would like to start with is for each of you to look at the different cards and choose one that best describes what VIA Family has been for you and your family. Then we will go around, and you can start by stating your name and explaining why you chose the card you did.

Exercise 2: My Journey through VIA Family (35 minutes)

With the next exercise, I want to gain insight into your journey through VIA Family. In this exercise, I will ask you to reflect on your entire experience with VIA Family, from the beginning when you were recruited for the project to now, where you (almost) completed your participation. I have created seven circles on the paper, and in each circle, you should note the answer to the corresponding question as indicated on the second piece of paper I have provided. This means that in circle number 1, you write the answer to question number 1. You will have 15 minutes for the exercise, after which we will discuss what you have noted.

→ *The provided sheet*

Before: What were your initial thoughts when contacted by VIA Family?

- Why did you choose to participate?
- During:* What has been helpful for you and your family?
What has not been helpful for you and your family?
What has been particularly challenging or difficult?
- After:* How do you feel about your participation in VIA Family coming to an end?
What is the most important thing you and your family will take away from this experience?

BREAK: 10 minutes

Exercise 3: Draw-a-Question (20 minutes)

I have now placed a bowl in the middle of the table containing slips of paper with questions. The idea is for each of you to take turns drawing a question. You will begin by answering the question you draw; others can contribute with their reflections.

The Questions:

- What has made the most impression on you during the process?
- What does it mean for you to have a contact person?
- If you were to tell a friend or colleague what VIA Family is, what would you say?
- How have you experienced your meetings with the researchers and the activities you have had to do when you have been at Frederiksberg Hospital?
- Has VIA Family been able to meet the needs that you and your family have had?
- Has it changed anything in your everyday life as a family to have been a part of VIA Family?

Thank you and Goodbye (5 minutes)

- Thank you for today.
- Gift cards.
- You are always welcome to contact us if you have any questions.

S2 Guide Focus Group Discussion Children

(Translated from Danish by ADM)

Introduction: What are we doing today? (5 minutes)

Presentation of facilitator.

“Today, let us pretend we are detectives on a mission. I want to know what it was like for you as a kid in VIA Family, and since you have experienced it, I think of you as an experts. So, can you bring me onto your team and tell me more about what VIA Family is and how it has been for each of you? Are you up for it?

When we are on a mission, there are usually tasks to do. Today, we have three tasks to complete. Let me tell you the plan. I want to hear your own stories and experiences. All experiences are important, whether they are good or a bit tough. You only share what you want to. I am recording to remember all the good things you tell me.”

Agenda

- Welcome and Introduction Round
- Task 1: Puzzle
- Task 2: Plus and Minus
- Break (10 minutes)
- Task 3: Rope Activity
- Thank you, and goodbye 😊

Check-in-exercise: picture cards (10 minutes)

Goal	Material	How-to
Creating a good and safe atmosphere among the children This helps children open up in front of their peers in the focus group discussion.	Picture Card	The pictures are laid out on a table. Each child chooses one card that depicts their experience in VF (likely referring to a specific context or place). The children share their stories (cards).

Task 1: Puzzle (20 minutes)

Introduction: When on a mission, people sometimes talk about certain pieces needing to be placed in a larger puzzle. The first task is about jointly putting together a puzzle. However, the pieces are blank, so we must draw something on them.

Question: *When I say VIA Family, what comes to your mind?*

Goal	Material	How-to
To gain an understanding of how the children perceive the VIA Family.	Puzzle pieces Markers Glue	The children each receive two puzzle pieces. They draw what they associate with VF (presumably a specific context or place). During the activity, the child shares their pieces, applies glue, and attaches them to a wall or board. The task is considered completed when the puzzle has assembled all its pieces.

Assistant questions:

- When you were in VF, what did you do?
- If you had to explain VF to a friend, what would you say?
- Is it something you have participated in as a family or something you have attended individually?
- Who are the people involved in VF?
- How has it been that it has occurred here in the house?

Notes/observations:

Task 2: + and - (15 minutes)

Introduction: I would really like to understand what you think has been good and what has not been so good about being involved in VF. That is what the next task is about.

Goal	Material	How-to
To gain insight into the children's experience of being involved in VF.	Post-it Markers	The children receive three Post-its: "I think the best thing about VF has been that..." "I haven't liked that..." "When I had to go to VF, I've had a feeling of..." They write down everything they can think of, both positive and negative aspects of VF (5 minutes). Post-its are placed on the wall. Now, let's take a turn where I would like everyone to share what they have written down.

Assisting questions:

- Under 'The best...': Is it something you think you'll miss?
- Have you talked to your friends about what you've done in VF?
- Have you discussed at home what you've done in VF?

Notes/observations:

Task 3: The Rope (20 minutes)

Introduction: We are soon through with our mission, but there's one last task we need to complete. It can be challenging, so it is entirely okay if you need time to think. We need to go onto the floor.

You can stand where you feel it is right for you. It is completely okay to stand somewhere where no one else is standing.

Goal	Material	How-to
To gain an understanding of how the children have experienced VF affecting their	A rope/cord Papers with	The rope is laid out on the floor.

family's everyday life. To show diversity. To demonstrate development.	statement s. Printed paper with "Fits me very well" and "Doesn't fit me at all."	The children line up and must position themselves on the rope according to how much they agree or disagree with the statements read aloud. After the children have placed themselves on the rope, this is followed by a dialogue about why they chose to stand where they did.
--	---	---

Statements:

S2

- I can feel a difference in how we are as a family after we have been in VF.
- I talk with my parents about different things than I did before we became part of VF.
- I talk with my friends about different things than I did before we became part of VF.
- I think something in my family has gotten worse by being a part of VF.

Assisting questions:

- Has VF changed anything in your and your family's everyday life (at home, at school)?
- Is there anything you and your family have discussed/done in VF that you have used at home or school?

Notes/observations:

Conclusion (11:20-11:30)

The mission was successful! Thank you for your help and all the knowledge you shared today. You have been so awesome, and I have learned a lot. Here is a brief summary of what we have discussed.

Before we conclude, I have one last activity. Here is a wish box. You will each receive a small piece of paper with the question, "Would you wish for VF to continue?" You can write 'yes' or 'no' on the paper, and if you'd like, you can also write why you answered yes or no. Afterwards, you place your wish in the wish box. Once you've done that, we are finished for today.

Thank you and Goodbye 😊

Supplementary Material

S1 Trial Protocol

S2 Number of referrals from VIA Family to social services or mental health centres

S3 Guide for focus group discussion – Children and Parent

S4 Mixed methods grouping of categories

S5 Use of VIA Family components

S6 Use of elements in usual care

STUDY PROTOCOL

Open Access



VIA Family—a family-based early intervention versus treatment as usual for familial high-risk children: a study protocol for a randomized clinical trial

Anne D. Müller^{1*†} , Ida C. T. Gjøde^{1*†}, Mette S. Eigil¹, Helle Busck², Merete Bonne³, Merete Nordentoft^{2,4} and Anne A. E. Thorup^{1,4}

Abstract

Background: Children born to parents with a severe mental illness, like schizophrenia, bipolar disorder, or major recurrent depression, have an increased risk of developing a mental illness themselves during life. These children are also more likely to have developmental delays, cognitive disabilities, or social problems, and they may have a higher risk than the background population of experiencing adverse life events. This is due to both genetic and environmental factors, but despite the well-documented increased risk for children with a familial high risk, no family-based early intervention has been developed for them. This study aims to investigate the effect of an early intervention that focuses on reducing risk and increasing resilience for children in families where at least one parent has a severe mental illness.

Methods/design: The study is a randomized clinical trial with 100 children aged 6–12 with familial high risk. It is performed in the context of the Danish health-care system. Families will be recruited from registers or be referred from the primary sector or hospitals. The children and their parents will be assessed at baseline and thereafter randomized and allocated to either treatment as usual or VIA Family. The intervention group will be assigned to a multidisciplinary team of specialists from adult mental health services, child and adolescent mental health services, and social services. This team will provide the basic treatment elements: case management, psychoeducation for the whole family, parental training, a safety plan, and potentially an early intervention if the child has mental problems. The study period is 18 months for both groups, and all participants will be assessed at baseline and after 18 months. The primary outcome measure will be daily functioning of the child, and the secondary measures are the psychopathology of the child, days of absence from school, family functioning, child's home environment, and parental stress.

Discussion: This study is to our knowledge the first to explore the effects of a multidisciplinary team intervention that provides an intensive and flexible support to match the families' needs for children with a familial high risk for severe mental illness. The study will provide important knowledge about the potential for increasing resilience and reducing risk for children by supporting the whole family. However, a longer follow-up period may be needed.

Trial registration: ClinicalTrials.gov, [NCT03497663](https://clinicaltrials.gov/ct2/show/study/NCT03497663). Registered on 13 April 2018.

Keywords: Familial high-risk, Offspring, Schizophrenia, Bipolar disorder, Recurrent depression, Multidisciplinary, Early intervention, Child mental health, Parental training, Family-based intervention

* Correspondence: Anne.Dorothee.Mueller@regionh.dk;
Ida.Christine.Tholstrup.Gjoede@regionh.dk

[†]Anne D. Müller and Ida C. T. Gjøde contributed equally to this work.

¹Research Unit, Child and Adolescent Mental Health Center, Lersø Parkallé 107, 1 th, 2100 Copenhagen, Capital Region of Denmark, Denmark

Full list of author information is available at the end of the article



© The Author(s). 2019 **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

Background

Children born to parents with a severe mental illness (SMI), such as schizophrenia spectrum disorders, bipolar affective disorder, or major recurrent depression, are a group of familial high-risk children overlooked by the mental health service system and the social services of their municipality [1–3]. Research shows that these children are vulnerable biologically, genetically, as well as socially, and that they have an increased risk of developing a mental illness themselves [4]. More than half of them will at some point in life develop a mental illness and about one third will develop an SMI.

In the mental health service system, there is a growing awareness of the need to develop preventive strategies as an early intervention for mental illness. However, few concrete ideas have been identified and investigated. An early intervention for children with a familial high-risk of SMI could consist of providing better resources to the family, and psychoeducation and parental training—all initiatives that are supposed to strengthen the normal and healthy development of the child and prevent later mental illness. This strategy is widely recommended in the international literature [5, 6].

High-risk studies and early risk factors

Over recent decades, several familial high-risk studies, i.e., cohort studies of individuals born to parents with SMI, have been conducted. These studies have documented that the increased risk of developing mental illness is caused by complex interactions between genetic and environmental factors [7–9]. This has especially been shown for schizophrenia [10–13], but also for affective disorders, i.e., bipolar disorder [14, 15], and major recurrent depression [16]. There is growing evidence that on a group level, these three diagnostically different disorders have a considerable phenomenological, biological, and genetic overlap [4, 17]. Research has also shown that children born to parents with an SMI more often display a series of the early signs of mental vulnerability or delayed or disturbed development during childhood [18–20]. These signs are understood as early risk factors for the development of a mental illness later in life. Prenatal risk factors include infections during pregnancy, unwanted pregnancy, stress and trauma during pregnancy, and obstetric complications [5, 21]. Examples of risk factors during childhood are different kinds of childhood traumas such as child neglect, physical abuse, emotional abuse, sexual abuse, and bullying [22]—all of which may have a serious, negative impact on child development [5, 23]. Moreover, there are a number of social early risk factors, such as having a mother diagnosed with schizophrenia, which may increase the risk of living in a dysfunctional family [23], with a single parent [24] or a parent with poor parenting skills [25], or in poor

socioeconomic conditions [26]. It is important to mention that some children of parents with an SMI will not be influenced by these risk factors, while others will be affected by several.

Neurodevelopmental perspective

Studies have shown that familial high-risk children born to parents with an SMI are vulnerable in several aspects [27–31]. Familial high-risk children are more likely to have unspecific mental health problems like anxiety, autism spectrum symptoms, or subtle psychosis-like symptoms called psychotic-like experiences, such as brief or transient hallucinations or delusion-like convictions. They may also show delayed motor or language development or cognitive disabilities, like attention deficits or problems with working memory or impulse control [10, 27, 32–34]. Furthermore, behavioral patterns, like poor emotional regulation (i.e., the ability to regulate and adapt emotions and impulses to the given situation) [35], affective control [36], or social adaptation, may also be affected in familial high-risk children [5, 19].

This increased mental vulnerability of the children is best understood from a neurodevelopmental perspective, which is to say that the child's normal developmental process is influenced by interacting aspects of genetic disposition and environmental factors broadly speaking, including, for example, insufficient parental support and stimulation, increased risk of childhood trauma, unstable living conditions, and poor social status [7, 23].

Mental illness can, thus, be understood as neurodevelopmental deviations that start very early in life and are influenced by risk factors as well as resilience factors throughout the individual's life [21, 37, 38].

Parental perspective

Parents with an SMI often lack resources in several aspects of life—material, financial, psychological, or social. It can, for some, be a very demanding task to provide their children with the necessary level and amount of support, care, and stimulation [39]. Further, they may not always have the energy or overview to navigate the complicated public health system and social services, so that the provision of help or support may be uncoordinated or random. The level of conflicts and disagreement in the families may be high and access to resilience-providing factors, like sound social relations or leisure activities, may be limited. Some children are overinvolved in their parent's symptoms, such as delusions, hallucinations, or negative and depressive symptoms, which sometimes leads to over-responsible children, also called young carers, i.e., children doing tasks that should be done by an adult [40]. All these factors may increase the child's risk of developing a mental illness later in life [41, 42].

However, it is important also to mention that parents who, at some time in their life, have suffered from an SMI can do very well in terms of parenting, especially if relevant and specialized support is available [43].

Early preventive interventions

This evidence has led to increased interest in investigating the potential of intervening at an early stage, i.e., before the child is diagnosed with a mental illness for the first time or before the problems get too big and complex. This is widely recommended in the international research literature but has been tested systematically only in a very few instances and not before in Denmark [5, 6]. The hypothesis is that by providing a very early intervention it will be possible to protect the most vulnerable individuals against the known risk factors (e.g., childhood trauma or some of the consequences of cognitive disabilities) and strengthen the individual's resilience by enhancing protective factors (e.g., social relations or recreational activities). This very early intervention will inhibit or diminish the cascade effect, which is seen when several risk factors over time influence an individual's development. This may be true not only for individuals who are born with familial high-risk but for people in general [44–47].

International studies on early preventive interventions

There are a few papers investigating the overall effect of an early, preventive approach, but in general effect sizes are small and there is still a lack of knowledge of many aspects [47, 48]. The Canadian study Families Overcoming Risks and Building Opportunities for Well-Being (FORBOW) led by Prof. Uher aims at providing an intervention in the form of cognitive therapy and psychoeducation for families with an SMI of any kind, but no results are available yet [29]. The idea is that the intervention is “low-burden, low-risk,” i.e., not risky for the participants, as, for example, medication could be, and it is directed against a concrete and currently existing problem or situation that it seems relevant to alleviate or solve for the family here and now. Other initiatives [5] emphasize the importance of parental skills training and support, psychoeducation, reducing the effects of cognitive disabilities, and providing practical, financial, and legal assistance.

Development of intervention and pilot testing

Based on the above mentioned evidence from the existing literature combined with clinical experience from the Danish High-Risk and Resilience Study VIA 7 [31, 49] (conducted by the last author) and results from qualitative studies including focus group interviews by our own research group, we have proposed a model for a specialized intervention for this specific group of children. Based on this model, a manual for

the intervention was developed and pilot tested by the intervention team in the pilot phase of the study. The pilot study consists of two volunteer families, who were included 5 months prior to the start of the study period and who agreed to give feedback to the team during the 18 months of the intervention.

Methods/design

This paper was written in line with the explanation and elaborations relating to the guidance for protocols of clinical trials in the 2013 SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials). The SPIRIT figure (schedule of enrolment, interventions, and assessments; Fig. 2), SPIRIT checklist (Additional file 1), and the World Health Organization Trial Registration Data Set (Additional file 2) were used.

Trial design

The VIA Family study is a two-armed parallel-group randomized clinical trial testing for superiority of the VIA Family group. The treatment allocation ratio is 1:1, stratified exclusively by diagnostic group. The allocation will be executed in a preset concealed block size order.

Objectives

The main objective of the trial is to test the VIA Family intervention against treatment as usual (TAU). Currently, there is no specific treatment or support for familial high-risk children born to parents with an SMI in Denmark.

Research question and hypothesis

The research question for this project is

- to investigate the effect of VIA Family, a multidisciplinary and family-based intervention for children born to a parent with an SMI, with a series of preset outcome measures

The hypothesis is that by providing such children and their families with an integrated, multidisciplinary, specialized, non-stigmatizing, and family-based intervention, it will be possible

- to improve the child's daily functioning, including a reduction in the number of days absent from school
- to reduce the magnitude of the child's mental problems and symptoms of psychopathology
- to improve the general functioning of the family
- to relieve the total burden experienced by family members and increase well-being

Over a longer perspective (5–10 years), we hypothesize that VIA Family will:

- reduce the prevalence and severity of mental illness among the children
- enable parents to develop sufficient parenting skills to reduce the possibility that their children will be referred to institutional upbringing or foster care

Participants, interventions, and outcomes

Study setting

The VIA Family study is a close collaboration between the Child and Adolescent Mental Health Center, Capital Region of Denmark, the Adult Mental Health Center Copenhagen, Capital Region of Denmark, and the local social services. Families are recruited from the municipalities of Frederiksberg and Copenhagen. The intervention sessions are held in a single center in Copenhagen in a building away from all hospitals and in a different location from the research team doing the assessment at baseline and follow-up.

Eligibility criteria

The inclusion criteria are:

1. Families in the Frederiksberg or Copenhagen municipalities who have at least one child aged 6–12. Families living in Frederiksberg are prioritized. Further, at least one of the parents must have a diagnosis of an SMI, which is defined as schizophrenia spectrum disorder (ICD-10 codes F20, F21, F22, or F25, or ICD-8 codes 295, 297, 298.29, 298.39, 298.89, 298.99, or 301.83), bipolar affective disorder (ICD-10 codes F30 or F31 or ICD-8 codes 296.19 or 296.39), or recurrent

moderate or severe depression (ICD-10 codes F 33.1, F33.2, or F 33.3 or ICD-8 codes: 296.0, 298.0 or 300.4). The diagnoses will be confirmed by the diagnostic interview Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [50] at baseline.

2. For those recruited from the register sample, the parent with an SMI diagnosis must have had at least one in- or outpatient contact with the mental health system within the lifetime of the child.

The exclusion criteria are:

1. Parents who do not speak and understand enough Danish to be able to give informed consent for their own participation and for the child's participation.
2. If all family members are currently engaged in an intensive family intervention program addressing parental functioning and child development.

Criteria for discontinuing the intervention

If a family withdraws informed consent, they will be excluded from the study. All participants will still be asked to participate in the follow-up interviews.

VIA Family intervention

The families, who by randomization are assigned to a VIA Family team, are offered contact with a specialized multidisciplinary team. This team's competences include knowledge and experience of the mental health system and municipality social services, allowing them to achieve a high degree of cross sectional synergy to meet the families'

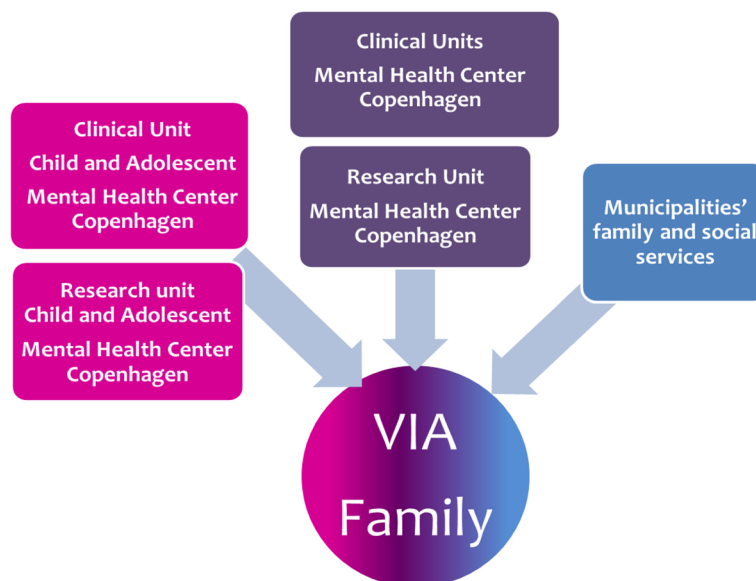


Fig. 1 Model for multidisciplinary resources in the team

needs as much as possible (Fig. 1). A team consists of five members:

- a child and adolescent psychiatrist or physician who has experience with providing child and adolescent mental health services
- a psychologist who has experience with providing child and adolescent mental health services
- a nurse with clinical experiences from adult mental health services
- a social worker who has worked with families in the municipality
- a family counsellor or family therapist who has worked with children in the municipality

The trial is a pragmatic trial, since we know that the target families' needs and problems are very diverse and will vary over time. During the first two meetings, two team members will collaborate with the family in trying to uncover what kind of problems or unmet needs the child or the family may experience. In co-operation with the family, a problem-solving plan will be produced that focuses on the issues that the family has described. VIA Family is based on a series of basic elements and a number of additional options can be included if they are suitable for the family's subjective preferences.

The basic elements in VIA Family are:

- *Case manager.* A case manager will be designated for the whole family. They will be easily accessible and can offer home visits if relevant. The case manager can help to coordinate appointments, will participate in meetings, and will give information and advice concerning possible support from the municipality. The case manager is generally available for the family for questions, worries, or problems of any kind and will guide the family to the right resources if the problem is outside the capacity of the VIA Family team. The case manager will stay in touch with the family when the family is not actively working with the team, e.g., by sending text messages or making phone calls.
- *Psychoeducation.* This focuses on what it is like to be part of a family where one of the parents has an SMI. This may also be relevant for those children who do not live with the ill parent. The case manager (often together with another team member) will provide a specialized psychoeducational course that is based on the family's current situation and relevant aspects of the parent's illness status. The course consists of approximately 6–8 sessions, which include all family members. There is a planning phase of 1–3 sessions with the parents followed by 1–3

sessions where the children are present. The course ends with an evaluation session with the parents, which includes considering the next issue for the family to work with. The team has written and collected relevant Danish-language material including books and films that can be used.

- *Parental training and support for the parenting role.* The parents are offered parental training based on the evidence-based Positive Parenting Program (Triple P) [51–53], with intensity and content according to their specific needs. Triple P is a multilevel program, meaning that the intensity, content, and administration of the program can be adapted to each family's specific situation. It starts at a less intensive, general level and can then be unfolded to a more intensive level if needed or if needs change. There are highly specific modules for specific target groups and families and for specific problems.
- *Safety plan and mapping the social network and the social resources of the family.* The safety plan can be used by any family member in an unexpected situation or an acute crisis, e.g., if the family's plans and routines are not being followed due to the ill parent's sudden need for psychiatric first aid or hospitalization. The safety plan addresses issues such as who the family members can contact, what to tell the children, and who should take care of them in an acute crisis. It can include resources from the municipality, possibly as a strategy to prevent an acute situation. For the ill parent, meetings about the parent's mental state can be arranged within a short time (e.g., if there are early signs of exacerbation). Supportive meetings for the other parent are also provided, since being the closest relative can be demanding.

Other additional treatment options offered by the VIA Family team

If needed, the team can offer the following treatment elements facilitated by the case manager:

- *Specialized treatment for the child's (transient or sub-threshold) mental problems or disturbances.* This can include anxiety, obsessive–compulsive disorder, tics, or attention problems. The child and adolescent psychologist and the child and adolescent psychiatrist in the team can provide cognitive therapy or psychoeducation according to Danish national guidelines for treatment (from the Danish Ministry of Health), and also specific cognitive therapy, e.g., for children who have had psychotic-like experiences.
- *Treatment groups for children, parents, and relatives.* The children will be offered a group course of 6–10

meetings with 6–8 other children in a similar situation. Together with a group therapist, they will have the opportunity to talk openly about their thoughts, experiences, and worries, and they can ask questions and listen to the other children's coping strategies. The parents can simultaneously participate in groups for relatives and parents with a mental illness (parent café), where presentations about relevant topics and networking between the participants will be the main content. Treatment groups are either facilitated by the VIA Family team or by an external partner, to whom the families will be directly referred, if they prefer.

- *Counselling and guidance regarding financial, social, or practical support from the municipality.* This may make it possible for the child to attend some kind of leisure activity, like sports, the scouts, or music. The financial support may pay any extra costs due to child-related problems (e.g., washing and nappies for a child with enuresis, which is very common). The social support may be a supportive adult who can build an independent relationship with the child while also giving the parent a break. The case manager will assist the family in the application process, maybe assisted by the social worker in the team. The municipality will make the final decision regarding any request for support.
- *Information about or supervision by institutions and schools.* This may be about the parent's mental illness or possible mental problems that the child might have, if the parents agree.
- *Optimization of the ill parent's treatment and lifestyle.* This will be done in close collaboration with the Adult Mental Health Center. Dialogues focusing on the parenting role in relation to a recovery process could be offered by the case manager.
- *Fast track to mental health services.* The Adult Mental Health Center at Frederiksberg will offer all families in the VIA Family group a fast track for acute psychiatric assessments, which the case manager can refer to whenever relevant. The Child and Adolescent Mental Health Center will also offer a fast track for any acute child psychiatric situation and will provide supervision for more complicated cases concerning the child's mental health problems or any detected need for further examination and diagnosing.
- *Other help.* Whenever possible, the team will also try to help and assist the family with other matters that are relevant for their well-being and everyday functioning. It can help them to find the right resources needed to solve a problem.

The sequence of engaging in the various elements is: introduction (1–2 sessions), life line and history with

both parents (2–4 sessions), psychoeducational course (6–8 sessions), Triple P (3–10 sessions), and groups for both children and parents (8 sessions), followed by a flexible period of up to 16 months of intervention with individual or family meetings, evaluation, termination, and transition to TAU.

The VIA Family team is not based in a hospital. The building has a very non-clinical atmosphere, which is family and child friendly. It can accommodate meetings and confidential conversations and it has a room for group sessions and educational courses. The surroundings are suitable for families with small children too. A small selection of psychoeducational literature, books, and folders are available for free.

Monitoring intervention fidelity

To ensure treatment fidelity, intervention team members are all trained and supervised in treatment delivery and the intervention is regularly monitored by the principal investigators of the study group.

The VIA Family intervention is a specialized intervention consisting of different treatment elements, which are offered to all families. Each family will receive an individual package containing different elements and doses of the intervention. To measure treatment fidelity, the intervention team will register every single element of treatment given to a family for later analyses (e.g., how many hours of psychoeducation and which members of the family participated, number of contacts, number of meetings etc.) in the data entry system Research Electronic Data Capture (REDCap) [54]. To ensure some degree of consistency for the VIA Family intervention and to differentiate the experimental treatment from TAU, some criteria for minimum participation in the VIA Family group have been defined: (1) a minimum of 15 contacts with the case manager (at least two contacts with personal attendance), (2) at least one session of psychoeducation, (3) one session to map the safety plan for the family, and (4) one session to address parental training.

Treatment as usual

The families who by randomization are assigned to TAU will continue to receive the same kind of help and support as they did before entering the study. TAU is defined as any kind of help and support focusing on high-risk children and parental mental illness. At present, the municipalities and the mental health services do not offer any kind of family-focused intervention addressing parental mental illness that can be compared to the VIA Family program. Moreover, the VIA Family team will work only with the families randomized to VIA Family, thus contamination from TAU to the VIA Family intervention will be very limited. We expect a variation in TAU, as some of the

families who are invited to participate will not be involved with the municipality or the mental health system, while other families are.

After the baseline assessment and before randomization, all families (TAU and VIA Family) will receive a brief phone call offering a standardized guide to the psychosocial help and support for high-risk children and their families available within the municipalities (Additional file 3). All families will also be offered verbal feedback on their child's performance and mental health status after the assessment has been completed.

The families in the VIA Family intervention group will have access to the same help and support available within the municipalities and mental health services as the TAU group, hence TAU is common for both groups. However, we expect a difference in the usage of TAU, because the case manager in the VIA Family intervention group will help the families to access the relevant services in the community. Moreover, some of the services available within TAU and the intervention (e.g., child support groups) have limited capacity and access for participation within TAU but are offered to all families in the VIA Family group. Data on each child's service use and on municipality involvement and support for the whole family will be registered for both groups using information from the municipality and by asking the families at baseline and at the 9- and 18-month follow-ups.

During the trial, all forms of intervention and concomitant care are allowed except for participation in any kind of ongoing and intensive family intervention program addressing parental functioning and child development involving all family members.

Outcomes

All outcome measures are listed in Fig. 2 for the 18-month follow up. The children can later be traced uniquely in the Danish registers, and information on e.g., the need for supportive efforts, placement out of home, and termination of elementary schooling can be investigated.

The selection of assessment instruments for the intervention outcomes is based upon results from the Danish High Risk and Resilience Study VIA 7 (conducted by the last author [49]), and focus group interviews conducted prior to the study with parents with schizophrenia and bipolar disorder who participated in the VIA 7 study. The same study confirmed that the instruments are relevant and acceptable for families to complete.

Primary outcome The primary outcome is the change in the estimate of the child's general functioning, as measured by the current score on the Children's Global Assessment Scale (CGAS) [55]. It is an estimate of the child's

lowest level of functioning within the previous month. CGAS will be measured at baseline and after 18 months of the intervention. CGAS is a scale from 1 to 100 (the higher score, the better the function), which is included in the diagnostic interview Kiddie Schedule for Affective Disorders and Schizophrenia (Present and Lifetime; K-SADS-PL) [56]. The K-SADS-PL interview is done separately with the parent and the child, and covers all kinds of mental or psychiatric problems that a child can have. It also concerns the child's daily level of functioning in the family, in school, and during leisure time, which is the basis of setting the CGAS score. CGAS is often used in research and considers all available information. It has been shown to have high validity and acceptable interrater reliability [57]. It is a dimensional and detailed measurement that accommodates that a given diagnosis (e.g., attention deficit hyperactivity disorder) may have a very different impact on the functioning of different children. The CGAS score will be rated by a group of trained and blinded clinicians with experience in child and adolescent mental health services and experience and training in the use of CGAS.

Secondary outcomes for the child

- *Change in extent of psychopathology.* Psychopathology is measured by the Child Behavior Checklist (CBCL) [58] after 18 months. The CBCL is a questionnaire with 113 items that is given to the parent. A score of 0 indicates that the child almost never displays the behavior (e.g., being impulsive), a 1 indicates that the behavior is sometimes present, and 2 that the behavior is observed often or always. A maximum (but not realistic score) is 226. Clinical cases, such as e.g., autism or attention deficit hyperactivity disorder, score approximately 60 on the CBCL scale. If the parents agree, the child's main teacher/pedagogue will also be asked to fill in the Teachers Report Form (same questions as the CBCL). The CBCL is very well validated and is widely used. It has the advantage of being dimensional and has been shown to have very good correlations with clinical diagnoses in numerous studies (<http://www.aseba.org/ordering/reliabilityvalidity.html>). Danish norms are available [59, 60].
- *Change in number of days absent from school within the last 6 months.* This is an objective proxy measure for the child's well-being and family function. It assumes that children in families with poor functioning have a higher frequency of absence from school due to lack of support and structure in everyday routines, or due to more frequent somatic complaints resulting in the child staying home from school. It is mandatory for schools to report to the

	Enrolment	Allocation	Follow-up	
TIMEPOINT	Baseline		9 months	18 months
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
VIA Family Team Intervention				
Treatment as Usual				
CHILD ASSESSMENTS:				
Child's Level of General Functioning CGAS [*]	X			X
Days absent from school ¹	X			X
Psychopathology K-SADS-PL incl. psychosis-like symptoms ^{**}	X			X
Anamnestic information ^{**}	X			X
Neurocognitive screening ²	X			X
Testers Observation Form TOF ^{3a}	X			X
Questionnaires Child as respondent:				
This is me, KIDS-Screen, CYRM, CTS, MACA, PANOC	X			X
Questionnaires Primary Caregiver as respondent:				
CBCL ⁴ , ERC, CALS, ADHD-RS, SDQ, BRIEF	X			X
SRS	X			
Questionnaires Teacher as respondent:				
TRF ⁵ , ERC, ADHD-RS, SDQ, BRIEF	X			X
SRS	X			
PARENT AND FAMILY ASSESSMENTS:				
FMSS	X			X
Psychopathology SCAN ^{**}	X			X
Psychopathology in years of child's life LifeChart ^{**}	X			X
Parents Level of General Functioning PSP ^{**}	X			X
HOME ^{**}	X			X
Sociodemographic and anamnestic information ^{**}	X			X
Questionnaires				
Adverse life events, parental stress and social provision ACES, PSS, SPS	X			X
Family Functioning FAD	X			X
Parenting Functioning PAFAS, PS	X			X
Other instruments				
Client Satisfaction Questionnaire				X
TAU-SR ^{***}	X		X	X
Adverse events ^{**}				X
Qualitative interviews				X

Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Schedule of enrolment, interventions, and assessments (SPIRIT Figure). *Clinical rating, **semi-structured interview, ***self-report on use of treatment and intervention facilities in private and public institutions (by any family member) ¹ Days of absence from school (registry, parents report, and teachers report). ² Neurocognitive tests: RIST; Wechsler Intelligence Scale for Children, 4th Edition (Coding); Rey Complex Figure Test and Recognition Trial; and Test of Memory and Learning, 2nd Edition (Memory of Stories). ³ Clinical Rating: TOF is in ASEBA. ⁴ CBCL is in ASEBA. ⁵ TRF is in ASEBA. ACES Adverse Childhood Experiences, ADHD-RS Attention Deficit Hyperactivity Disorder Rating Scale, ASEBA Achenbach System of Empirically Based Assessment, BRIEF Behavior Rating Inventory of Executive Function, CALS Children's Affective Liability Scale, CBCL Child Behavior Checklist, CGAS Children's Global Assessment Scale, CTS Childhood Trauma Screener, CYRM Child and Youth Resilience Measurement, ERC Emotion Regulation Checklist, FAD Family Assessment Device, FMSS Five-Minute Speech Sample, HOME Home Observation for Measurement of the Environment, K-SADS-PL Kiddie Schedule for Affective Disorders and Schizophrenia: Present and Lifetime, MACA Multidimensional Assessment of Caring Activities Checklist, PAFAS Parenting and Family Adjustment Scale, PANOC Positive and Negative Outcomes of Caring Questionnaire, PS Parenting Scale, PSP Personal and Social Performance Scale, PSS Parental Stress Scale, RIST Reynolds Intellectual Screening Test, SCAN Schedules for Clinical Assessment in Neuropsychiatry, SDQ Strengths and Difficulties Questionnaire, SPS Social Provision Scale, SRS Social Responsiveness Scale, TAU-SR Treatment as Usual Self Report, TOF Test Observation Forms

municipality days of absence for all pupils. Data will be collected for the 18 months of the intervention and changes will be analyzed.

Secondary outcomes for the family

- *Evaluation of family functioning.* This is assessed with the Family Assessment Device (FAD) [61]. FAD is a thorough questionnaire with 60 items based on a comprehensive sociological theory about the different functions of a family. It is completed by the parents or the actual caregivers in the family. It will be used at baseline and after 18 months.
- *Level of stimulation and support in the home.* This is evaluated by the Home Observation for Measurement of the Environment (HOME) [62], which is a semi-structured interview that can be done only in the home with both the child and the parent present. HOME is a continuous scale A score under the predefined cut-off indicates that there may be problems in the family.
- *Secondary outcome FAD.* In a previous study with a similar psychiatric population, the FAD general functioning score was normally distributed with SD = 0.51 (scale: 1–4, mean: 2.27) [66]. If the true difference between the mean of the VIA Family group and the mean in the TAU group at the 18-month follow-up is 0.4, we will need to study 35 families in each treatment group. Therefore, we need a total of 70 families to be able to reject the null hypothesis that the population means of the VIA Family and TAU groups are equal with probability (power) 0.90. The probability of a type I error associated with this test of this null hypothesis is 0.05.

Sample size

We used G*Power to calculate the sample size and power of the study [63, 64]. We assumed that the treatment and control groups were equal in size with the same standard deviation (SD). The SD for the sample size calculation was obtained from previous studies [30] and from a cross-national reliability study [65].

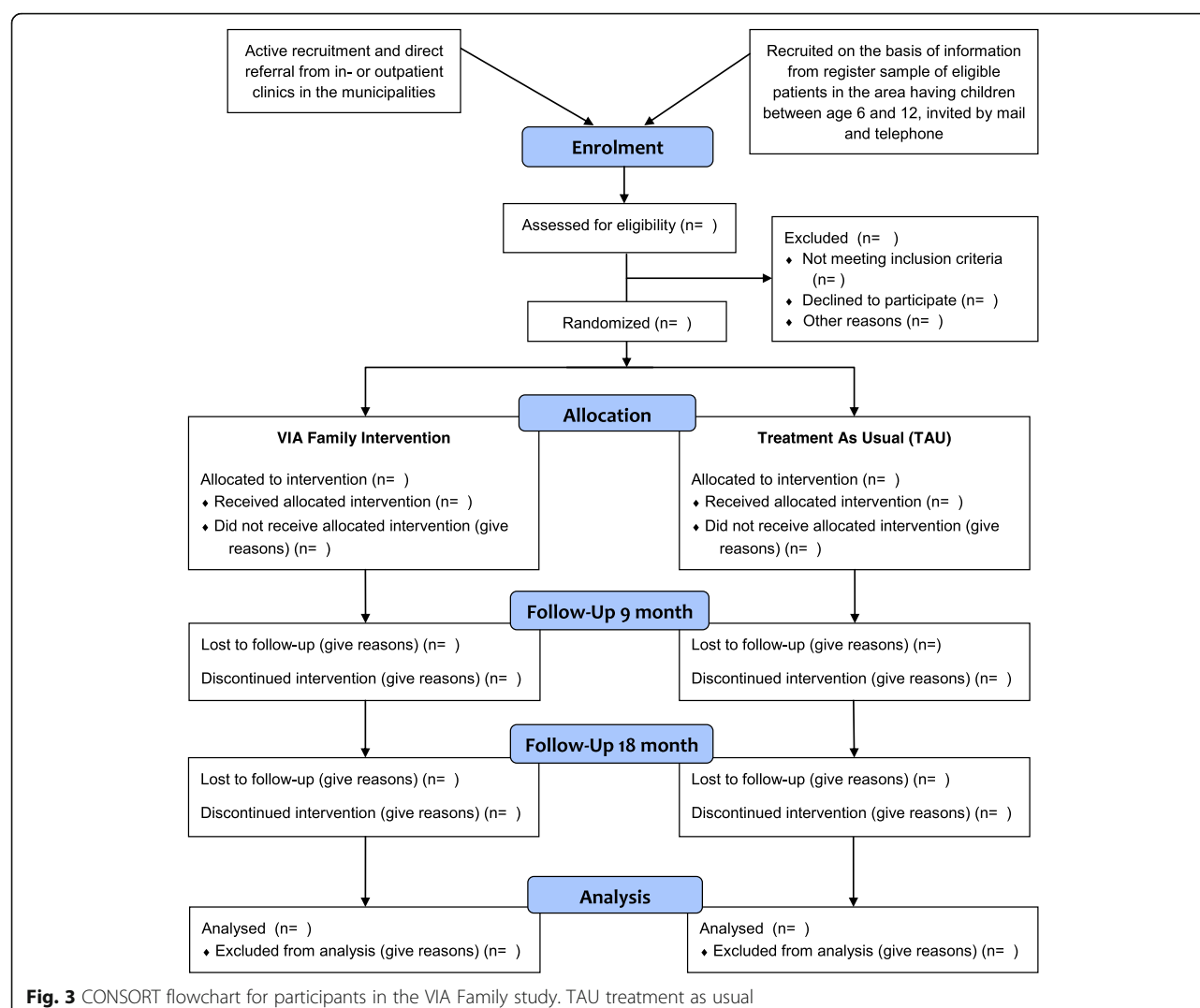
- *Primary outcome CGAS.* If the intervention results in an increase of the CGAS score of 10 points (e.g., from 55 to 65, SD = 13), which is a realistic estimate, we will have a high effect size. Power calculations show that by including 37 children in each group, we will be able to measure a difference of 10 points on the CGAS score between the two groups with a power of 0.90.
- *Secondary outcome CBCL.* If the intervention reduces the total problem score on CBCL by 10

points (from 28 to 18, SD = 15), which will be clinically very relevant and realistic, we will have an effect size of 0.66. Power calculations show that with 37 in each group, we will be able to detect a difference between the two groups of 10 points in the CBCL with a power of 0.80.

Recruitment

Method for recruitment in the study A list of eligible participants will be drawn from the Danish Psychiatric Central Register and the Central Person Register and will, together with those referred directly from the in- or outpatient clinics in the Mental Health Center of Copenhagen, form the group of potential participants. At least 100 families will be invited to participate (Fig. 3). Data from the Danish registries show that a sufficient number of participants can be found within the catchment area of the trial, and that recruiting 100 families is realistic even if some potential participants decline.

Eligible parents and families will receive a letter and an e-mail in their personal inbox, which is used for public communications of all kinds in Denmark. They will receive a folder briefly describing the project and an invitation to participate in the study. After the initial mail, the research team will invite all families by phone to an information meeting about the study. Moreover, parents who



fit the inclusion criteria can be directly referred to the study from in- or outpatient clinics in the municipalities.

If there are children in the family who are not aged between 6 and 12, they are included in the activities of the intervention, but the assessment prior to randomization and at follow-up will involve only children within the defined age group at baseline.

Procedure for recruitment and enrollment if parents do not live together The ill parent does not need to live with the other parent or with the child if the child lives in the municipalities of Frederiksberg or Copenhagen. In these cases and when the parents share custody of the child, the first step is to ask the ill parent for permission to invite the child and the other parent. Both parents do not need to participate, but if there has been a divorce or legal separation with shared custody of the child, both

parents need to give their informed consent for the child's participation in the project.

Allocation

Randomization is carried out by a member of the intervention team situated away from the research assessors. The team member assigns participants to interventions. The allocation concealment mechanism is performed by a computer algorithm saved in REDCap [54]. The randomization process cannot be influenced by the person who makes the randomization or any other person. The randomization sequence is set in a preset concealed block size order with an allocation ratio 1:1. The randomization is stratified solely by diagnostic group.

Blinding

Outcome assessors, data analysts, and researchers will be blinded throughout the study, including during the

statistical analysis. In addition, researchers are blinded to block size and frequencies. It is not possible to blind the participants nor those providing the intervention. The VIA Family intervention takes place at a site away from the assessors, data analysts, and researchers, which combined with the minimal interaction and communication between the intervention team and the assessors, aims to minimize the risk of unblinding. If unblinding occurs during the study, it will be registered and another assessor will perform the outcome assessment at the follow-up for the family whose treatment allocation has been revealed.

In theory, no circumstances should necessitate unblinding of the assessors or researchers, since all relevant information and clinical evaluations will be available to the research manager (AAET) and members of the intervention team, who can intervene in an emergency.

Data collection, management, and analysis

Data collection methods

Families are assessed with a range of diagnostic interviews, neurocognitive tests, interviews, and questionnaires at baseline and at the 18-month follow-up (Fig. 2 and Table 1). The assessment at baseline takes approximately 8 h in total for a family of two adults and one child. The 9-month follow-up consists of a mid-phase telephone call by an independent research assistant. This contact seeks to decrease the risk of attrition from the study. Data will be collected from all participants independently of compliance to treatment.

To ensure the high quality of data, all assessors are certified in administering K-SADS-PL, SCAN, and HOME and perform regular co-ratings of videotaped interviews. Furthermore, assessors are trained in administering the Personal and Social Performance Scale (PSP) [67], and the CGAS and ratings are done in an expert group setting. Only trained clinical psychologists administer the neurocognitive tests. All diagnoses are confirmed at clinical conferences with a child and adolescent psychiatrist being present.

Data management

All data, including all personal information about potential and enrolled participants, are entered directly into the data entry system REDCap [54] by the assessors on site, except for a few neurocognitive tests that can only be made on paper. Self-report surveys for adults are either answered electronically on site or at home and in rare cases on paper if need be (e.g., by families who do not have access to the internet at home and wish to fill out the surveys at home). The surveys answered on paper are entered into the data entry system REDCap using double data entry.

All surveys for children are read out to the child. The reasons are (1) to ensure standard procedures are used, (2) to minimize the risk of variance between assessors' judgement of children's ability to read for themselves, and (3) to avoid having surveys read to younger children and not to older ones.

Range checks for data values have been implemented in the data entry systems in REDCap.

Statistical methods

All tests will be two-tailed. The primary outcome analysis will be by intention to treat. Multiple imputations will be used to handle missing data (if any). The imputations will be based on a linear regression model with 100 imputations and 20 iterations. Pooled analyses will subsequently be used for our analysis. In the imputation model, we will select possible variables if they are independent predictors of the outcome or predictors of missing values ($P < 0.05$ in a univariable model). Analysis of covariance (ANCOVA or MANOVA as appropriate) will be used to calculate any significant results between the two groups, using the baseline value and the sex of the child as stratification variables.

All distributions of continuous outcome variables will be assessed for normality using a visual inspection of histograms with a normal probability curve and Q–Q plots. If a variable is not normally distributed, the variable will be transformed (e.g., log or square root), and if unsuccessful, a non-parametric test (e.g., the Wilcoxon–Mann–Whitney test) will be used.

For dichotomous outcomes, we will perform multiple logistic regressions with TAU as the reference and stratification variables as covariates after having imputed missing values (if any) using a logistic regression model. If the experimental groups are not significantly correlated to the outcome ($P > 0.05$), no further analyses will be performed. If we find a significant correlation, a model that is equivalent to the approach for continuous variables will be used.

Sensitivity analyses will include an analysis of complete cases, removal of outliers (defined as standardized residuals greater than 3 standard deviations), a per protocol analysis defining participants not having a single contact as violating the protocol, and a second per protocol analysis including only participants attending at least 50% of intended personal meetings in the VIA Family group. The second per protocol analysis is likely to cause severe selection bias, as the VIA Family group would include the participants with the highest level of motivation. Therefore, it is considered meaningful to report only negative results from this analysis.

Monitoring

The study does not have a data monitoring committee. All study participants randomized to VIA Family are

Table 1 Test battery

Instrument Name	Domain	Child	Parent	Teacher
CGAS [55]	Daily functioning	x	x	
HOME [62]*	Home environment, level of stimulation, and support	x	x	
K-SADS-PL, including psychosis-like symptoms [56]	Diagnostic screening and psychopathology	x	x	
FMSS [72]	Parent–child relationship		x	
RIST [73]	General intelligence	x		
Coding from WISC-IV [74]	Processing speed	x		
RCFT [75]	Visual memory	x		
TOMAL-II: Memory for Stories [76]	Verbal memory	x		
This is me [77]	Self esteem	x		
Kids-Screen [78]	Quality of life	x		
CTS [79]	Childhood trauma	x		
CYRM [80]	Resilience	x		
MACA-YC18 + PANOC-YC20 [81]	Over-responsibility and caretaking	x		
CALS [82]	Affective lability		x	
CBCL [58]	Psychopathology		x	
TRF [83]	Psychopathology			x
BRIEF [84]	Executive functioning		x	x
ADHD-RS [85]	Attention		x	x
SDQ [86]	Daily functioning and psychopathology		x	x
SRS-2 [87]	Social cognition		x	x
ERC [88]	Emotion regulation		x	x
FAD [61]	Family functioning		x	
PSS [89]	Parental level of stress		x	
PAFAS [90]	Parental and family functioning		x	
Parenting Scale [91]	Parenting style		x	
SPS [92]	Social network, adult		x	
ACES [93]	Adverse life events, adult		x	
PSP [94]	Daily functioning, adult		x	
Anamnesis	Socioeconomic status, developmental milestones, adverse life events, school, and family relations		x	
SCAN interview, including LifeChart [50]	Psychopathology in adults and course of illness in relation to child's age		x	
Absence from school, child			x	x
CSQ [95]	Client satisfaction	x	x	
TOF [96]	Psychopathology: clinical rating after 60 min. of neuropsychological testing	x		

ACES Adverse Childhood Experiences, ADHD-RS Attention Deficit Hyperactivity Disorder Rating Scale, BRIEF Behavior Rating Inventory of Executive Function, CALS Children's Affective Lability Scale, CBCL Child Behavior Checklist, CGAS Children's Global Assessment Scale, CSQ Client Satisfaction Questionnaire, CTS Childhood Trauma Screener, CYRM Child and Youth Resilience Measurement, ERC Emotion Regulation Checklist, FAD Family Assessment Device, FMSS Five-Minute Speech Sample, HOME Home Observation for Measurement of the Environment, K-SADS-PL Kiddie Schedule for Affective Disorders and Schizophrenia (Present and Lifetime), MACA-YC18 Multidimensional Assessment of Caring Activities Checklist for Young Carers 18 items, PAFAS Parenting and Family Adjustment Scale, PANOC-YC20 Positive and Negative Outcomes of Caring Questionnaire for Young Carers 20 items, PSP Personal and Social performance Scale, PSS Parental Stress Scale, RCFT Rey Complex Figure Test, RIST Reynolds Intellectual Screening Test, SCAN Schedules for Clinical Assessment in Neuropsychiatry, SDQ Strengths and Difficulties Questionnaire, SPS Social Provision Scale, SRS Social Responsiveness Scale, TOF Test Observation Form, TOMAL-II Test of Memory and Learning, 2nd Edition, TRF Teachers Report Form, WISC-IV Wechsler Intelligence Scale for Children, 4th Edition

*) For children living 50/50 with mother and father, the HOME interview will be made in both homes

monitored for harmful events by the intervention team or, in cases of hospitalization, by their general practitioner or a doctor from the Mental Health Center. If

necessary, the principal investigator will make the final decision to terminate the trial. All study participants will be asked to report voluntarily all adverse events or other

unintended effects of the trial at the 9-month and 18-month follow-ups. The study will be audited weekly by the principal investigator group, who are not involved in the day-to-day work of the study and are independent of the sponsors.

Discussion

There is an urgent need for visionary strategies and preventive interventions in mental health services. Currently, we do not have a specific approach for preventing mental illness in children who are born with a well-documented familial-based increased risk. The VIA Family study is an innovative study attempting to investigate the effects of an early, family-based, flexible, and multidisciplinary intervention for families with children who are known to have a significantly increased risk for developing a mental illness later in life. Further, evidence from qualitative studies and experience from large clinical studies show that these families often struggle with everyday problems to a much greater extent than other families [5].

The intervention to be tested, VIA Family, is based on both evidence from the existing literature and on the very first results from another Danish study, the Danish High-risk and Resilience Study VIA 7 [49], as well as on clinical experience and information from focus group interviews with mentally ill parents and their co-parents. Evidence from the literature has demonstrated that the vulnerability of these children is detectable at a very early age [10, 19]. Research and clinical experience have documented the increased risk of trauma, adverse life experiences, and sub-optimal living conditions, including problems with parenting for the children, all factors that we know increase the risk of later mental illness [22]. Qualitative analyses confirm that a multidisciplinary approach and close collaboration between different units and sectors are essential and needed to meet these families' unmet needs [68]. In this way, the prevention will help to solve problems that exist here and now.

One of the theories behind the project is developmental traumatology, which focuses on the severe impact that any childhood trauma and adverse life events may have on a child's brain and mental development, their cognitive and social functioning, their stress regulation and reward mechanism etc. [69]. If we can reduce the total load of these environmental risk factors and stimulate potential resilience mechanisms, then hopefully we can reduce each child's risk of falling ill or experiencing other negative life events.

We have also investigated the large body of literature on resilience and how this can be strengthened in children. Factors like secure attachments, a social network, being part of a community, having positive experiences, and

finding meaning in life are mentioned as crucial factors for individuals with a high degree of resilience [70, 71].

Strengths

The intervention being offered to the families is very intensive and flexible, and this should increase our chances of getting conclusive results. It lasts for 18 months and aims to meet almost any kind of problem that the families may struggle with. It is more intensive than those in most other studies [36]. Moreover, 18 months is quite a long intervention period. The intervention does not focus on illness and disabilities but more on everyday life in a non-stigmatizing way and is, thus, expected to be acceptable for most families. That the intervention is more intensive and comprehensive than those in other studies may be experienced in a negative way by some. However, each element has been chosen based on qualitative interviews and very recent results from a Danish cohort study [30, 31]. No treatment elements will be introduced before the family approve them and find them relevant and motivating.

By using comprehensive Danish registries, we will be able to follow these children in the future and have long term follow-up results, since some outcomes may be in the distant future. The assessment battery is comprehensive and covers several areas of interest with validated tests. For many of the tests we have Danish norms.

The target groups of people with schizophrenia, bipolar disorder, or major depression were chosen because evidence of the genetic impact in these disorders is well documented. However, from the child's perspective, the diagnoses may not matter very much. Instead, it is the impact on the parent that is relevant. Parents with diagnoses other than those included in our study may have similar problems or behavior, e.g., negative symptoms, like anhedonia, lack of energy, restlessness, and anxiety. If the results of our study are positive, the next step will be to include families where one of the parents has other serious mental problems, e.g., parents with personality disorders or with multiple diagnoses or complex co-morbidities including substance abuse, to test the generalizability.

Limitations

We intend to include 100 families in the study, which, based on the power calculation of our primary outcomes, is a sufficient number of participants for the study to show an effect of the intervention. However, it may be that the intervention is effective at a lower although still clinically relevant level, which would need a larger sample size to be detected.

Moreover, the study design is limited by the absence of data from the pilot phase of the study, which could have contributed to the design and feasibility assessment

of the intervention. Although experience from the pilot testing of the intervention and the instruments for assessment, as well as the feedback from the pilot families, were included in the intervention and overall study design, this knowledge cannot contribute to the study of its feasibility. Hence, this trial will provide data that can be used as pilot data for the development of a revised version of the intervention manual and for future studies in this field.

Also, we include children from three different diagnostic categories, although we believe from research evidence that the children born to parents with schizophrenia are the most vulnerable of the three. From the child's point of view, the diagnosis of the parent may not mean much in terms of how the family is functioning on a daily level, although the genetic impact may be milder for those born to parents with affective disorders. In particular, recruitment of families where one of the parents is suffering from schizophrenia may be the most troublesome.

Another challenge in all intervention studies is how to avoid attrition, especially from the control group. We hope that the initial feedback from the researchers, the 9-month status contact, and the emphasis on the importance of participating in research will keep the families in the study.

The intensive intervention may sound positive, but we should be aware that this could also be experienced as overwhelming or over-involving for some participants. Due to this study's pragmatic and flexible approach, we will not be able to identify which of the treatment elements was the most effectual. Further, it may be a problem that 18 months of intervention is too short for the relevant differences to be recognizable.

Trial status

The current protocol is Version 4, December 2018. Recruitment will take place from September 2017 to March 2019.

Additional files

Additional file 1: Completed SPIRIT checklist. (DOC 127 kb)

Additional file 3: World Health Organization Trial Registration Data Set. (DOCX 21 kb)

Additional file 2: Guide for all study participants on psychosocial help and support. (DOCX 24 kb)

Abbreviations

ACES: Adverse Childhood Experiences; ADHD-RS: Attention Deficit Hyperactivity Disorder Rating Scale; ASEBA: Achenbach System of Empirically Based Assessment; BRIEF: Behavior Rating Inventory of Executive Function; CALS: Children's Affective Liability Scale; CBCL: Child Behavior Checklist; CGAS: Children's Global Assessment Scale; CSQ: Client Satisfaction Questionnaire; CTS: Childhood Trauma Screener; CYRM: Child and Youth Resilience Measurement; ERC: Emotion Regulation Checklist; FAD: Family Assessment Device; FMSS: Five-Minute Speech Sample; FORBOW: Families Overcoming Risks and Building Opportunities for Well-Being; HOME: Home Observation for Measurement of the Environment; K-SADS-PL: Kiddie Schedule for

Affective Disorders and Schizophrenia: Present and Lifetime; MACA: Multidimensional Assessment of Caring Activities Checklist; PAFAS: Parenting and Family Adjustment Scale; PANOC: Positive and Negative Outcomes of Caring Questionnaire; PS: Parenting Scale; PSP: Personal and Social Performance Scale; PSS: Parental Stress Scale; RCFT: Rey Complex Figure Test; REDCap: Research Electronic Data Capture; RIST: Reynolds Intellectual Screening Test; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SD: Standard deviation; SDQ: Strengths and Difficulties Questionnaire; SMI: Severe mental illness; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SPS: Social Provision Scale; SRS: Social Responsiveness Scale; TAU: Treatment as usual; TAU-SR: Treatment as Usual Self Report; TOF: Test Observation Form; TOMAL-II: Test of Memory and Learning, 2nd Edition; TRF: Teachers Report Form; Triple P: Positive Parenting Program; WISC-IV: Wechsler Intelligence Scale for Children, 4th Edition

Acknowledgements

Henriette I. C. Andreasen, Sidsel Ingversen, and Kate H. Jønsson are members of the intervention team and developed the specific elements of the treatment offered. Sofie H. Christensen developed the material for the families, conducted the qualitative research, and will make the 9-month telephone contacts with all participants, among many other tasks. Marianne Melau will contribute to data collection. Jens R. M. Jepsen assisted us with the cognitive battery. Mala Moszkowicz will participate in conferences with clinical experience and supervision. C. Felix Müller and Lasse Böhling helped us with data management. Anna I. Printzlau is in charge of coordinating all data from questionnaires. Mette Rubæk assisted with setting up the database. Jamal Uddin was responsible for all statistical aspects. We thank all the families who are and will be involved in the study for their positive participation.

Funding

The research part of the project is funded by the Danish non-profit foundation TrygFonden while the intervention part is funded by a grant from the Danish government through the Danish Ministry of Health (Satspuljen) and the Municipality of Frederiksberg, Denmark.

Availability of data and materials

Not applicable.

Protocol amendments

All changes to this protocol will be sent for approval to the Regional Committee on Health Research Ethics (DNVK), and all changes will be communicated to sponsors and other relevant parties.

Dissemination policy

All trial results will be communicated to health-care professionals, the public, and other relevant groups, independently of the outcomes. No later than 3 years after the assessment of the last family at the 18-month follow-up, we will deliver a completely deidentified data set to an appropriate data archive for sharing purposes.

Authors' contributions

AAET obtained funding for the study, designed the VIA Family intervention, designed the trial, and drafted the manuscript. ADM and ICTG contributed to the design of the trial and equally to writing this manuscript. MSE contributed to the design of the VIA Family intervention and helped to draft the manuscript. HB contributed to the design of the VIA Family intervention and contributed to the design of the trial. MB contributed to the design of the trial. MN contributed to the design of the trial and helped to draft the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study has been approved by the Regional Committee on Health Research Ethics (DNVK) for the Capital Region of Denmark (H-17000450). The research team will obtain oral and written informed consent to participate in the study from all adult participants before enrolment. Each child's guardians will give consent for the child to participate (i.e., if custody is shared, both parents need to give their informed consent). Guardians will also be asked to consent to the researchers' contacting the child's teacher to obtain information from the child's school.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

¹Research Unit, Child and Adolescent Mental Health Center, Lersø Parkallé 107, 1 th, 2100 Copenhagen, Capital Region of Denmark, Denmark. ²Mental Health Center, Copenhagen, Capital Region of Denmark, Denmark.

³Municipality of Frederiksberg, Family Department, Copenhagen, Denmark.

⁴University of Copenhagen, Institute for Clinical Medicine, Faculty of Health Science, Copenhagen, Capital Region of Denmark, Denmark.

Received: 2 May 2018 Accepted: 10 January 2019

Published online: 08 February 2019

References

- Hinden BR, Biebel K, Nicholson J, Mehnert L. The Invisible Children's Project: key ingredients of an intervention for parents with mental illness. *J Behav Health Serv Res*. 2005;32(4):393–408.
- Gladstone BM, Boydell KM, Seeman MV, McKeever PD. Children's experiences of parental mental illness: a literature review. *Early Interv Psychiatry*. 2011;5(4):271–89.
- Socialstyrelsen So. Koncept for systematisk inddragelse af pårørende. Digital ISBN: 978–87–93052–97-0; 2014.
- Rasic D, Hajek T, Alda M, Uher R. Risk of Mental Illness in Offspring of Parents With Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Meta-Analysis of Family High-Risk Studies. *Schizophr Bull*. 2014; 40:28–38.
- Liu CH, Keshavan MS, Tronick E, Seidman LJ. Perinatal Risks and Childhood Premorbid Indicators of Later Psychosis: Next Steps for Early Psychosocial Interventions. *Schizophr Bull*. 2015;41(4):801–16.
- Seidman LJ, Nordentoft M. New Targets for Prevention of Schizophrenia: Is It Time for Interventions in the Premorbid Phase? *Schizophr Bull*. 2015; 41(4):795–800.
- Walder DJ, Faraone SV, Glatt SJ, Tsuang MT, Seidman LJ. Genetic liability, prenatal health, stress and family environment: risk factors in the Harvard Adolescent Family High Risk for schizophrenia study. *Schizophr Res*. 2014; 157(1–3):142–8.
- Uher R. Gene-environment interactions in common mental disorders: an update and strategy for a genome-wide search. *Soc Psychiatry Psychiatr Epidemiol*. 2014;49(1):3–14.
- van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med*. 2009;39(2):179–95.
- Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lonnqvist JK. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophr Res*. 2003;60(2–3):239–58.
- Thaker G, Adami H, Moran M, Lahti A, Cassidy S. Psychiatric illnesses in families of subjects with schizophrenia-spectrum personality disorders: high morbidity risks for unspecified functional psychoses and schizophrenia. *Am J Psychiatry*. 1993;150(1):66–71.
- Cannon TD, Mednick SA. The schizophrenia high-risk project in Copenhagen: three decades of progress. *Acta Psychiatr Scand Suppl*. 1993;370:33–47.
- Johnstone EC, Lawrie SM, Cosway R. What does the Edinburgh high-risk study tell us about schizophrenia? *Am J Med Genet*. 2002;114(8):906–12.
- Zappitelli MC, Bordin IA, Hatch JP, Caetano SC, Zunta-Soares G, Olvera RL, et al. Lifetime psychopathology among the offspring of Bipolar I parents. *Clinics (Sao Paulo)*. 2011;66(5):725–30.
- Bora E, Pantelis C. Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls. *Schizophr Bull*. 2015;41(5):1095–104.
- Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdelli H. Offspring of depressed parents: 20 years later. *Am J Psychiatry*. 2006; 163(6):1001–8.
- Pearlson GD. Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. *Annu Rev Clin Psychol*. 2015;11:251–81.
- Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: a meta-analytic review. *Clin Child Fam Psychol Rev*. 2011;14(1):1–27.
- Hameed MA, Lewis AJ. Offspring of Parents with Schizophrenia: A Systematic Review of Developmental Features Across Childhood. *Harv Rev Psychiatry*. 2016;24(2):104–17.
- Sanchez-Gistau V, Romero S, Moreno D, de la Serna E, Baeza I, Sugranyes G, et al. Psychiatric disorders in child and adolescent offspring of patients with schizophrenia and bipolar disorder: A controlled study. *Schizophr Res*. 2015; 168(1–2):197–203.
- Laurens KR, Luo L, Matheson SL, Carr VJ, Raudino A, Harris F, et al. Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses. *BMC Psychiatry*. 2015;15:205.
- Varese F, Smeets F, Drukker M, Lieveer R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull*. 2012;38(4):661–71.
- Wan MW, Abel KM, Green J. The transmission of risk to children from mothers with schizophrenia: a developmental psychopathology model. *Clin Psychol Rev*. 2008;28(4):613–37.
- Ranning A, Munk Laursen T, Thorup A, Hjorthøj C, Nordentoft M. Children of Parents With Serious Mental Illness: With Whom Do They Grow Up? A Prospective, Population-Based Study. *J Am Acad Child Adolesc Psychiatry*. 2016;55(11):953–61.
- Brockington I, Chandra P, Dubowitz H, Jones D, Moussa S, Nakku J, et al. WPA guidance on the protection and promotion of mental health in children of persons with severe mental disorders. *World Psychiatry*. 2011; 10(2):93–102.
- Byrne M, Agerbo E, Eaton WW, Mortensen PB. Parental socio-economic status and risk of first admission with schizophrenia- a Danish national register based study. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(2):87–96.
- Asarnow JR. Children at risk for schizophrenia: converging lines of evidence. *Schizophr Bull*. 1988;14(4):613–31.
- Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disord*. 2006;8(2):103–16.
- Uher R, Cumby J, MacKenzie LE, Morash-Conway J, Glover JM, Aylott A, et al. A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. *BMC Psychiatry*. 2014;14(1):344.
- Ellersgaard D, Jessica Plessen K, Richardt Jepsen J, Soeborg Spang K, Hemager N, Klee Burton B, et al. Psychopathology in 7-year-old children with familial high risk of developing schizophrenia spectrum psychosis or bipolar disorder—The Danish High Risk and Resilience Study—VIA 7, a population-based cohort study. *World Psychiatry*. 2018;17(2):210–9.
- Hemager N, Plessen KJ, Thorup A, Christiani C, Ellersgaard D, Spang KS, et al. Assessment of Neurocognitive Functions in 7-Year-Old Children at Familial High Risk for Schizophrenia or Bipolar Disorder: The Danish High Risk and Resilience Study VIA 7. *JAMA Psychiatry*. 2018;75(8):844–52.
- Niemi LT, Suvisaari JM, Haukka JK, Lonnqvist JK. Childhood growth and future development of psychotic disorder among Helsinki high-risk children. *Schizophr Res*. 2005;76(1):105–12.
- Agnew-Blais J, Seidman LJ. Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: a quantitative and qualitative review. *Cogn Neuropsychiatry*. 2013;18(1–2):44–82.
- Burton BK, Hjorthøj C, Jepsen JR, Thorup A, Nordentoft M, Plessen KJ. Research Review: Do motor deficits during development represent an endophenotype for schizophrenia? A meta-analysis. *J Child Psychol Psychiatry*. 2016;57:446–56.
- Silk JS, Shaw DS, Skuban EM, Oland AA, Kovacs M. Emotion regulation strategies in offspring of childhood-onset depressed mothers. *J Child Psychol Psychiatry*. 2006;47(1):69–78.
- Frias A, Palma C, Farriols N, Salvador A. Characterizing offspring of bipolar parents: a review of the literature. *Actas Esp Psiquiatr*. 2015;43(6):221–34.

37. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. *Mol Psychiatry*. 2012;17(12):1228–38.
38. Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. *Br J Psychiatry*. 2014;204(2):122–8.
39. Blegen NE, Hummelvoll JK, Severinsson E. Mothers with mental health problems: a systematic review. *Nurs Health Sci*. 2010;12(4):519–28.
40. Connell AM, Goodman SH. The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychol Bull*. 2002;128(5):746–73.
41. Gearing RE, Alonzo D, Marinelli C. Maternal schizophrenia: psychosocial treatment for mothers and their children. *Clin Schizophr Relat Psychoses*. 2012;6(1):27–33.
42. Reupert AE, Maybery DJ, Kowalenko NM. Children whose parents have a mental illness: prevalence, need and treatment. *Med J Aust*. 2013;199(3 Suppl):S7–9.
43. Fraser C, James EL, Anderson K, Lloyd D, Judd F. Intervention Programs for Children of Parents with a Mental Illness: A Critical Review. Bendigo: Centre for Rural Mental Health, Bendigo Health Care Group; 2006.
44. Opler M, Sodhi D, Zaveri D, Madhusoodanan S. Primary psychiatric prevention in children and adolescents. *Ann Clin Psychiatry*. 2010;22(4):220–34.
45. Bayer J, Hiscock H, Scalzo K, Mathers M, McDonald M, Morris A, et al. Systematic review of preventive interventions for children's mental health: what would work in Australian contexts? *Aust N Z J Psychiatry*. 2009;43(8):695–710.
46. Veenstra-VanderWeele J, Warren Z. Intervention in the context of development: pathways toward new treatments. *Neuropsychopharmacology*. 2015;40(1):225–37.
47. Siegenthaler E, Munder T, Egger M. Effect of preventive interventions in mentally ill parents on the mental health of the offspring: systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2012;51(1):8–17.
48. Thanhauser M, Lemmer G, de Girolamo G, Christiansen H. Do preventive interventions for children of mentally ill parents work? Results of a systematic review and meta-analysis. *Curr Opin Psychiatry*. 2017;30(4):283–99.
49. Thorup AA, Jepsen JR, Ellersgaard DV, Burton BK, Christiani CJ, Hemager N, et al. The Danish High Risk and Resilience Study—VIA 7—a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. *BMC Psychiatry*. 2015;15(1):233.
50. Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry*. 1990;47(6):589–93.
51. Sanders MR. Triple P-Positive Parenting Program as a public health approach to strengthening parenting. *J Fam Psychol*. 2008;22(4):506–17.
52. Nowak C, Heinrichs N. A comprehensive meta-analysis of Triple P-Positive Parenting Program using hierarchical linear modeling: effectiveness and moderating variables. *Clin Child Fam Psychol Rev*. 2008;11(3):114–44.
53. Sanders MR, Kirby JN, Tellegen CL, Day JJ. The Triple P-Positive Parenting Program: a systematic review and meta-analysis of a multi-level system of parenting support. *Clin Psychol Rev*. 2014;34(4):337–57.
54. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377–81.
55. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry*. 1983;40(11):1228–31.
56. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–8.
57. Schorre BE, Vandvik IH. Global assessment of psychosocial functioning in child and adolescent psychiatry. A review of three unidimensional scales (CGAS, GAF, GAPD). *Eur Child Adolesc Psychiatry*. 2004;13(5):273–86.
58. Achenbach TM, Edelbrock C. CBCL, Manual for child behavior checklist and revised child behavior profile. Burlington: University of Vermont; 1983.
59. Henriksen J, Nielsen PF, Bilenberg N. New Danish standardization of the Child Behaviour Checklist. *Dan Med J*. 2012;59(7):A4462.
60. Bilenberg N. The Child Behavior Checklist (CBCL) and related material: standardization and validation in Danish population based and clinically based samples. *Acta Psychiatr Scand Suppl*. 1999;398:2–52.
61. Epstein N, Baldwin L, Bishop D. The McMaster family assessment device; 1983.
62. Caldwell BM, Bradley RH. Home Observation for Measurement of the Environment: Administration Manual. Tempe: Family & Human Dynamics Research Institute, Arizona State University; 2003.
63. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175–91.
64. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods*. 2009;41(4):1149–60.
65. Hanssen-Bauer K, Gowers S, Aalen OO, Bilenberg N, Brann P, Garralda E, et al. Cross-national reliability of clinician-rated outcome measures in child and adolescent mental health services. *Admin Pol Ment Health*. 2007;34(6):513–8.
66. Kabacoff RIMI, Bishop DS, Epstein NB, et al. A psychometric study of the McMaster Family Assessment Device in psychiatric, medical, and nonclinical samples. *J Fam Psycho*. 1990;3:431–9.
67. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci*. 2006;256(3):174–86.
68. Wahl P, Bruland D, Bauer U, Okan O, Lenz A. What are the family needs when a parent has mental health problems? Evidence from a systematic literature review. *J Child Adolesc Psychiatr Nurs*. 2017;30(1):54–66.
69. De Bellis MD, Zisk A. The biological effects of childhood trauma. *Child Adolesc Psychiatr Clin N Am*. 2014;23(2):185–222 vii.
70. Ruten BP, Hammels C, Geschwind N, Menne-Lothmann C, Pishva E, Schruers K, et al. Resilience in mental health: linking psychological and neurobiological perspectives. *Acta Psychiatr Scand*. 2013;128(1):3–20.
71. Ungar M. Practitioner Review: Diagnosing childhood resilience—a systemic approach to the diagnosis of adaptation in adverse social and physical ecologies. *J Child Psychol Psychiatry*. 2015;56(1):4–17.
72. Daley D, Sonuga-Barke EJ, Thompson M. Assessing expressed emotion in mothers of preschool AD/HD children: psychometric properties of a modified speech sample. *Br J Clin Psychol*. 2003;42(Pt 1):53–67.
73. Reynolds C, Kamphaus RW. RIAS: Reynolds Intellectual Assessment Scales; 2003.
74. Wechsler D. WISC-IV The Wechsler Intelligence Scale for Children. 4th ed. San Antonio: The psychological Corporation; 2003.
75. Meyers JE, Meyers KE. Rey Complex Figure Test and Recognition Trial: Professional Manual. Odessa: Psychological Assessment Resources; 1995.
76. Reynolds CR, Vores JK. Tomal 2 Test of Memory and Learning. 2nd ed; 2007.
77. Suonpaa E, Kresanov K, Ouvinen-Birgerstam P, Piha J. Self-concept of Finnish children on the second grade of normal elementary school. *Acta Paedopsychiatr*. 1989;52(3):157–64.
78. Ravens-Sieberer U, Gosch, A., Rajmil, L., Erhart, M., Bruil, J. KIDSCREEN-27 quality-of-life measure for children and adolescents, 2005. Report No.: 3.
79. Grabe HJ, Schulz A, Schmidt CO, Appel K, Driessen M, Wingenfeld K, et al. A brief instrument for the assessment of childhood abuse and neglect: the childhood trauma screener (CTS). *Psychiatr Prax*. 2012;39(3):109–15.
80. Liebenberg L, Ungar M, LeBlanc JC. The CYRM-12: a brief measure of resilience. *Can J Public Health*. 2013;104(2):e131–e5.
81. Joseph S, Becker S, Becker F, Regel S. Assessment of caring and its effects in young people: development of the Multidimensional Assessment of Caring Activities Checklist (MACA-YC18) and the Positive and Negative Outcomes of Caring Questionnaire (PANOC-YC20) for young carers. *Child Care Health Dev*. 2009;35(4):510–20.
82. Gerson AC, Gerring JP, Freund L, Joshi PT, Capozzoli J, Brady K, et al. The Children's Affective Liability Scale: a psychometric evaluation of reliability. *Psychiatry Res*. 1996;65(3):189–98.
83. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms and Profiles. Burlington: University of Vermont Research Center for Children, Youth, & Families; 2001.
84. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior rating inventory of executive function. *Child Neuropsychol*. 2000;6(3):235–8.
85. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-IV: Checklists, norms, and clinical interpretation. New York: Guilford Press; 1998.
86. Obel C, Dalsgaard S, Stax HP, Bilenberg N. Strengths and Difficulties Questionnaire (SDQ-Dan). A new instrument for psychopathologic screening of children aged 4–16 years. *Ugeskr Laeger*. 2003;165(5):462–5.
87. Constantino JN, Gruber CP. Social Responsiveness Scale-Second Edition (SRS-2). Los Angeles: Western Psychological Services; 2012.
88. Shields A, Cicchetti D. Emotion regulation among school-age children: the development and validation of a new criterion Q-sort scale. *Dev Psychol*. 1997;33(6):906–16.
89. Berry J, Jones WH. The Parental Stress Scale : initial psychometric evidence. *J Soc Pers Relat*. 1995;12(3):463–72.

90. Sanders MR, Morawska A, Haslam DM, Filus A, Fletcher R. Parenting and Family Adjustment Scales (PAFAS): validation of a brief parent-report measure for use in assessment of parenting skills and family relationships. *Child Psychiatry Hum Dev.* 2014;45(3):255–72.
91. Arnold DS, O'Leary SG, Wolff LS, Acker MM. The Parenting Scale: A measure of dysfunctional parenting in discipline situations. *Psychol Assess.* 1993;5:137–44.
92. Cutrona CE, Russell, D. SPS: Social Provisions-scale. 1987. Report No.: 1.
93. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med.* 1998;14(4):245–58.
94. Morosini P, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV social and occupational scales (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand.* 2000;101(4):323–9.
95. Attkisson C. The Client Satisfaction Questionnaire (CSQ) Scales; 1996.
96. McConaughy SHAT. Manual for the Test Observation Form (TOF) for Ages 2–18. Burlington: University of Vermont, Research Center for Children, Youth, & Families; 2004.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

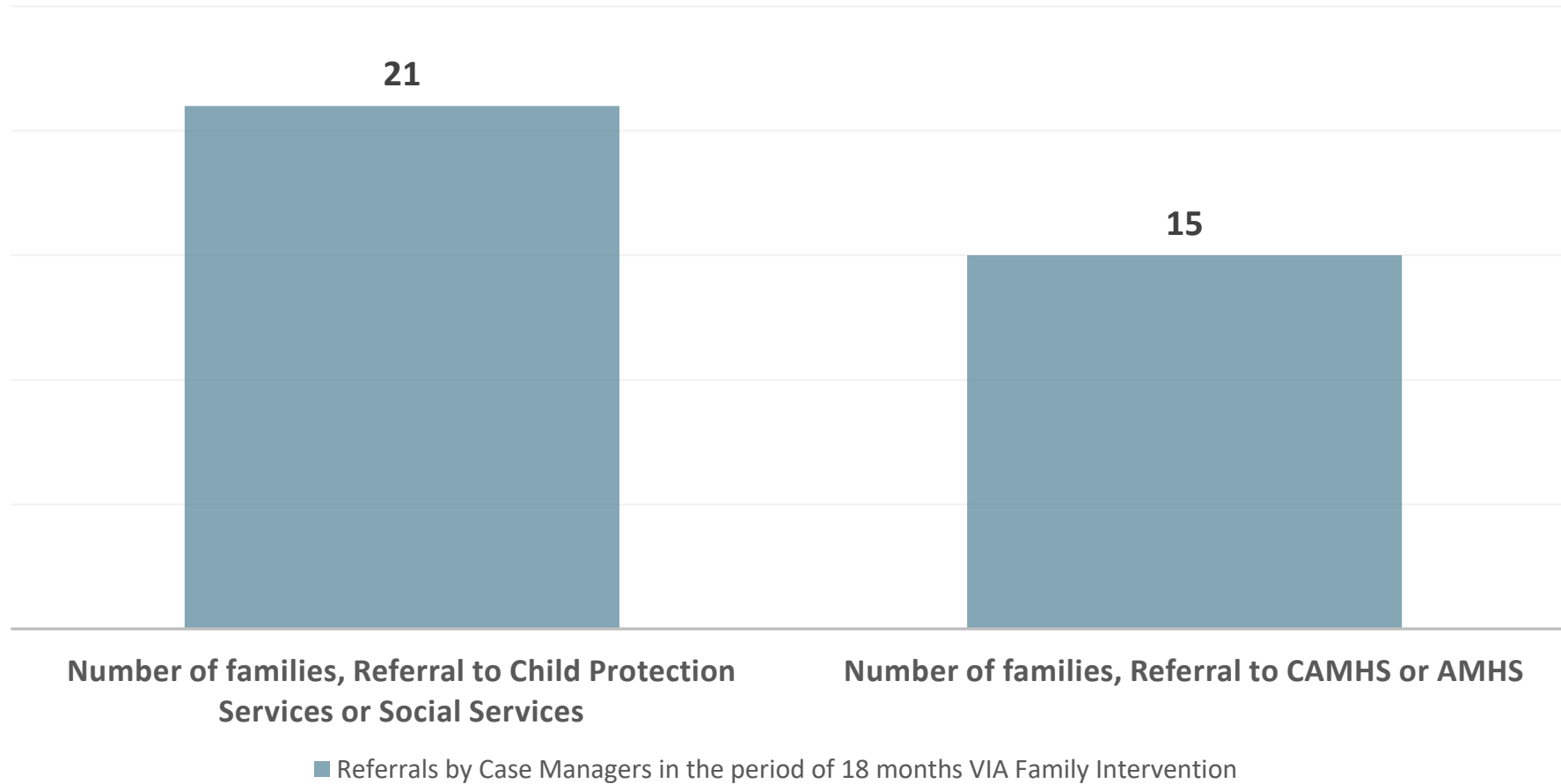
At BMC, research is always in progress.

Learn more biomedcentral.com/submissions



Supplementary 2

Number of Referrals by VIA Family Case Managers in the 18 months period of the intervention



Supplementary 3 Focus groups Guides

Guide Focus Group Discussion *Children*

(Translated from Danish)

Introduction: What are we doing today? (5 minutes)

Who am I?

Today, let us pretend we are detectives on a mission. I want to know what it was like for you as a kid in VIA Family, and since you have experienced it, I think of you as an experts. So, can you bring me onto your team and tell me more about what VIA Family is and how it has been for each of you? Are you up for it?

When we are on a mission, there are usually tasks to do. Today, we have three tasks to complete. Let me tell you the plan. I want to hear your own stories and experiences. All experiences are important, whether they are good or a bit tough. You only share what you want to. I am recording to remember all the good things you tell me.

Agenda

- Welcome and Introduction Round
- Task 1: Puzzle
- Task 2: Plus and Minus
- Break (10 minutes)
- Task 3: Rope Activity
- Thank you, and goodbye 😊

Check-in-exercise: picture cards (10 minutes)

Goal	Material	How-to
Creating a good and safe atmosphere among the children This helps children open up in front of their peers in the focus group discussion.	Picture Card	The pictures are laid out on a table. Each child chooses one card that depicts their experience in VF (likely referring to a specific context or place). The children share their stories (cards).

Task 1: Puzzle (20 minutes)

Introduction: When on a mission, people sometimes talk about certain pieces needing to be placed in a larger puzzle. The first task is about jointly putting together a puzzle. However, the pieces are blank, so we must draw something on them.

Question: *When I say VIA Family, what comes to your mind?*

Goal	Material	How-to
------	----------	--------

To gain an understanding of how the children perceive the VIA Family.	Puzzle pieces Markers Glue	The children each receive two puzzle pieces. They draw what they associate with VF (presumably a specific context or place). During the activity, the child shares their pieces, applies glue, and attaches them to a wall or board. The task is considered completed when the puzzle has assembled all its pieces.
---	----------------------------------	---

Assistant questions:

- When you were in VF, what did you do?
- If you had to explain VF to a friend, what would you say?
- Is it something you have participated in as a family or something you have attended individually?
- Who are the people involved in VF?
- How has it been that it has occurred here in the house?

Notes/observations:

Task 2: + and - (15 minutes)

Introduction: I would really like to understand what you think has been good and what has not been so good about being involved in VF. That is what the next task is about.

Goal	Material	How-to
To gain insight into the children's experience of being involved in VF.	Post-it Markers	The children receive three Post-its: "I think the best thing about VF has been that..." "I haven't liked that..." "When I had to go to VF, I've had a feeling of..." They write down everything they can think of, both positive and negative aspects of VF (5 minutes). Post-its are placed on the wall. Now, let's take a turn where I would like everyone to share what they have written down.

Assisting questions:

- Under 'The best...': Is it something you think you'll miss?
- Have you talked to your friends about what you've done in VF?
- Have you discussed at home what you've done in VF?

Notes/observations:

Task 3: The Rope (20 minutes)

Introduction: We are soon through with our mission, but there's one last task we need to complete. It can be challenging, so it is entirely okay if you need time to think. We need to go onto the floor.

You can stand where you feel it is right for you. It is completely okay to stand somewhere where no one else is standing.

Goal	Material	How-to
To gain an understanding of how the children have experienced VF affecting their family's everyday life. To show diversity. To demonstrate development.	A rope/cord. Papers with statements. Printed paper with "Fits me very well" and "Doesn't fit me at all."	The rope is laid out on the floor. The children line up and must position themselves on the rope according to how much they agree or disagree with the statements read aloud. After the children have placed themselves on the rope, this is followed by a dialogue about why they chose to stand where they did.

Statements:

- Sometimes, I think about what I have done or talked about in VF at home or school.
- I can feel a difference in how we are as a family after we have been in VF.
- I talk with my parents about different things than I did before we became part of VF.
- I talk with my friends about different things than I did before we became part of VF.
- I think something in my family has gotten worse by being a part of VF.

Assisting questions:

- Has VF changed anything in your and your family's everyday life (at home, at school)?
- Is there anything you and your family have discussed/done in VF that you have used at home or school?

Notes/observations:

Conclusion (11:20-11:30)

The mission was successful! Thank you for your help and all the knowledge you shared today. You have been so awesome, and I have learned a lot. Here is a brief summary of what we have discussed.

Before we conclude, I have one last activity. Here is a wish box. You will each receive a small piece of paper with the question, "Would you wish for VF to continue?" You can write 'yes' or 'no' on the paper, and if you'd like, you can also write why you answered yes or no. Afterwards, you place your wish in the wish box. Once you've done that, we are finished for today.

Thank you and Goodbye 🤝

Guide Focus Group Discussion *Parents*

(translated from Danish)

Agenda (30 min)

- Welcome: Information and Consent Forms
- Exercise 1: Introduction round with picture cards
- Exercise 2: My Journey through VIA Family
- Break
- Exercise 3: Draw-a-Question
- Thank you and Goodbye

Welcome: Information and Consent Forms (10:00-10:10)

Welcome, and thank you for joining us today. I am K, and along with S, I am involved with the VIA Family study as part of our anthropology thesis.

We have invited you here today because we want to hear about your experiences with being part of VIA Family. The information you share today will be used in the VIA Family Evaluation Study. To begin, I would like to pass around some consent forms. We hope you will sign them before we proceed. With these consent forms, you permit us to use the information you provided today in the evaluation. Any information you share will, of course, be anonymized.

➔ *Start the recorder and go through the agenda.*

Before we start, I want to emphasize that it's entirely up to you what and how much you want to share today. If there is something you do want to talk about, that is totally ok. I would also like to mention that the purpose of today's focus group is not necessarily to paint an overly positive picture of the VIA Family. We want to hear how you have experienced being a part of it, what has worked well, and what has not worked so well.

Exercise 1: Introduction round with picture cards (10 min)

As you can see, I have placed various picture cards on the table. What I would like to start with is for each of you to look at the different cards and choose one that best describes what VIA Family has been for you and your family. Then we will go around, and you can start by stating your name and explaining why you chose the card you did.

Exercise 2: My Journey through VIA Family (35 minutes)

With the next exercise, I want to gain insight into your journey through VIA Family. In this exercise, I will ask you to reflect on your entire experience with VIA Family, from the beginning when you were recruited for the project to now, where you (almost) completed your participation. I have created seven circles on the paper, and in each circle, you should note the answer to the corresponding question as indicated on the second piece of paper I have provided. This means that in circle number 1, you write the answer to question number 1. You will have 15 minutes for the exercise, after which we will discuss what you have noted.

➔ *The provided sheet*

Before: What were your initial thoughts when contacted by VIA Family?

Why did you choose to participate?

During: What has been helpful for you and your family?

What has not been helpful for you and your family?

What has been particularly challenging or difficult?

After: How do you feel about your participation in VIA Family coming to an end?

What is the most important thing you and your family will take away from this experience?

BREAK: 10:55-11:05

Exercise 3: Draw-a-Question (20 minutes)

I have now placed a bowl in the middle of the table containing slips of paper with questions. The idea is for each of you to take turns drawing a question. You will begin by answering the question you draw; others can contribute with their reflections.

The Questions:

- What has made the most impression on you during the process?
- What does it mean for you to have a contact person?
- If you were to tell a friend or colleague what VIA Family is, what would you say?
- How have you experienced your meetings with the researchers and the activities you have had to do when you have been at Frederiksberg Hospital?
- Has VIA Family been able to meet the needs that you and your family have had?
- Has it changed anything in your everyday life as a family to have been a part of VIA Family?

Thank you and Goodbye (5 minutes)

- Thank you for today.
- Gift cards.
- You are always welcome to contact us if you have any questions.

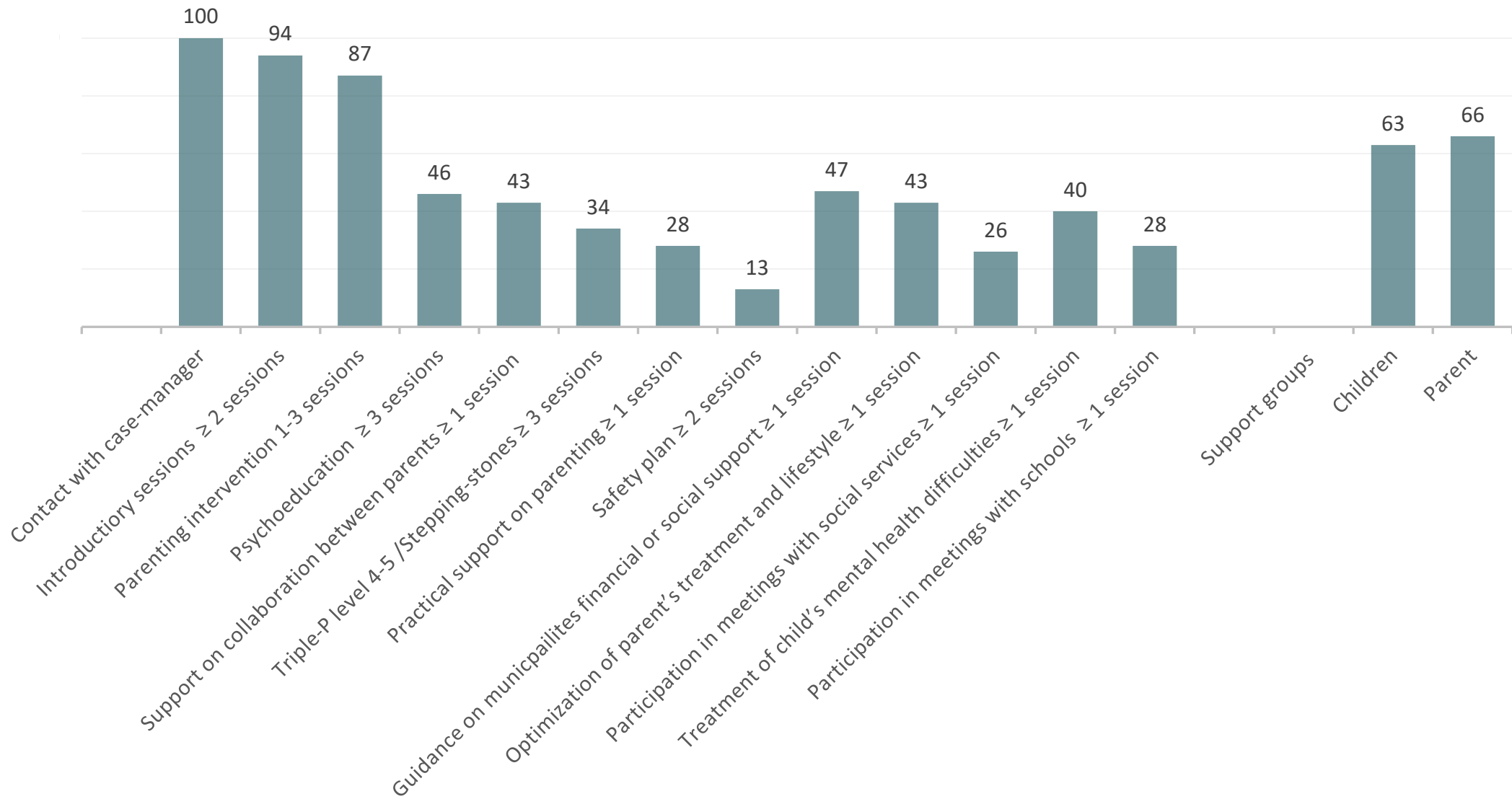
S4 Supplementary

Grouping of categories from baseline variable of main motivation for participation

Original variable from baseline sociodemographic interview	Dichotomization of the continuous variable	New variable for subgroup analysis
1) Help Science	—————→	Not motivated because of a need for support (A)
2) Get support for how we, as a family, are together	—————→	Motivated because of a need for support (B)
3) Get help with parenting/child rearing,	—————→	
4) Concerned about our child and want support or guidance for the child's well-being or mental health	—————→	
5) Get help on how to talk about mental illness in our family	—————→	
6) Other*		Not included*
7) Not Motivated		Not included
*If possible, category 6 was later categorized by the research team as either <i>not motivated because of a need for support (A)</i> or <i>motivated because of a need for support (B)</i> . If it was impossible to categorize, it was left as 'other' and not included.		

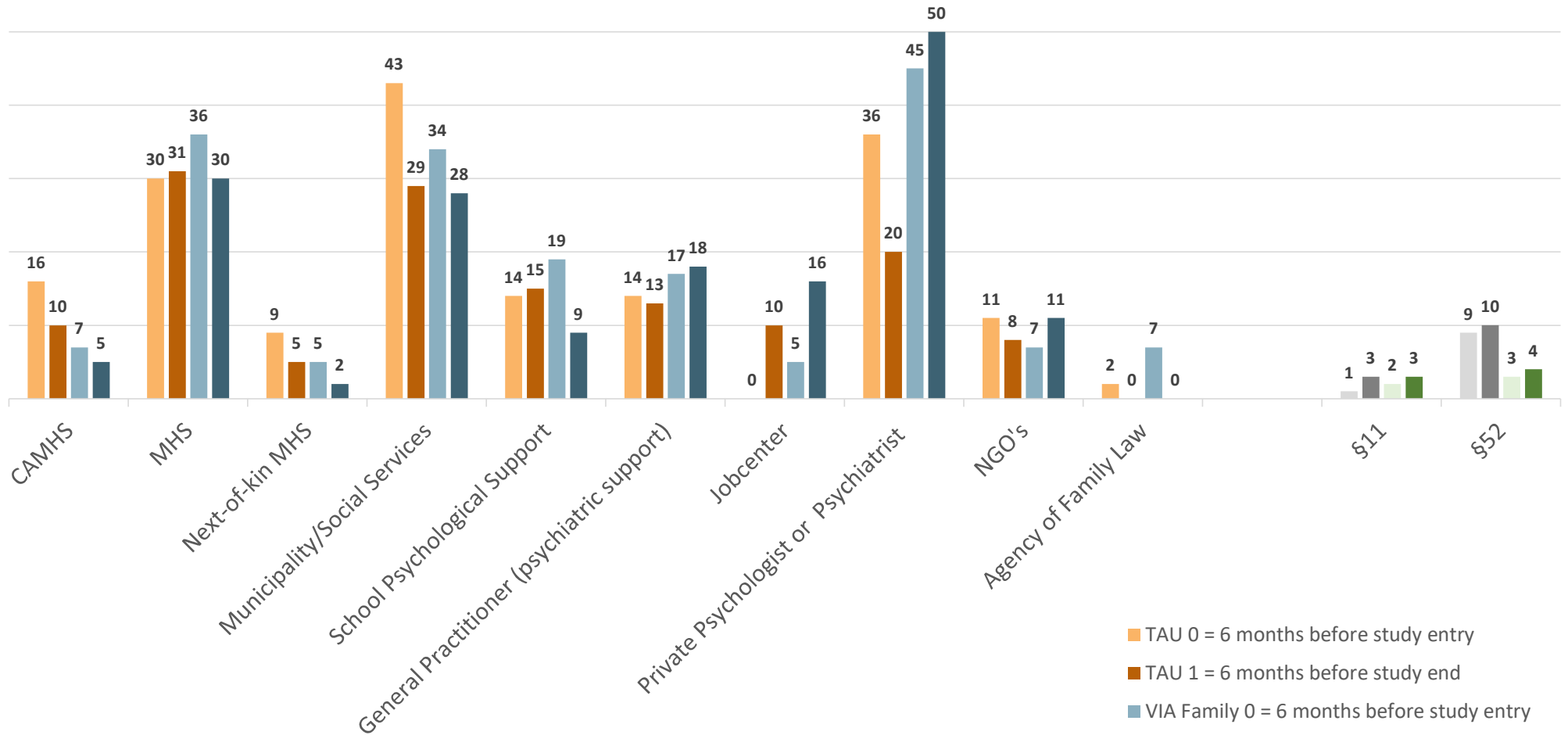
Supplementary 5

Families Use of VIA Family Intervention Elements in %



Families Use of Services (%)

6 months before study entry and 6 months before study end



CAMHS: Child and Adolescent Mental Health Services;
MHS : Mental Health Services