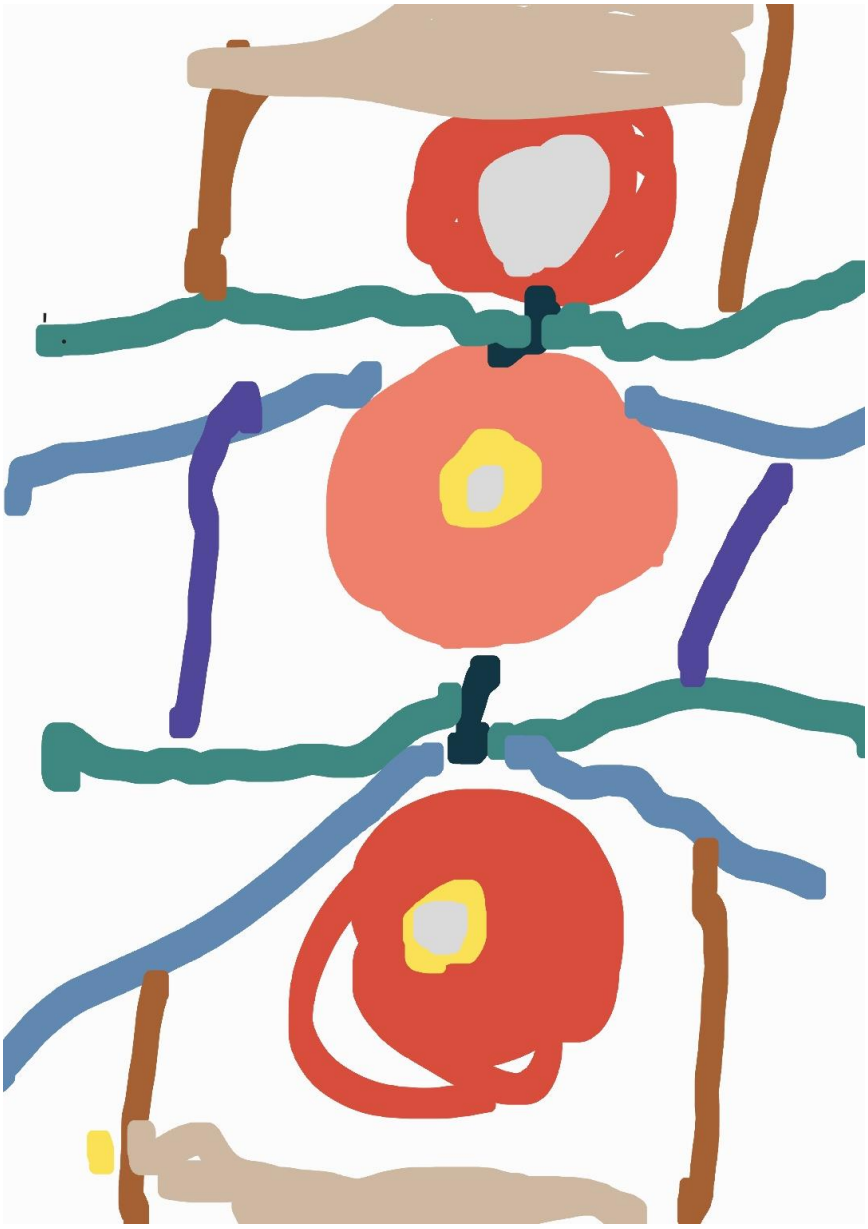
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES



FAMILIES AND CHILDREN IN THE CONTEXT OF PARENTAL SEVERE MENTAL ILLNESS

PREVENTIVE INTERVENTION AND ESTIMATES OF RISK

This thesis has been submitted to the Graduate School of Health and Medical Sciences
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Title: Families and children in the context of parental severe mental illness – preventive intervention and estimates of risk

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Contents

Summary

Children of parents with severe mental illness are at high risk of developing a mental illness throughout their lifespan. This thesis had two aims. First, to study the effectiveness of an 18-month preventive family-based intervention, VIA Family, offered to families with school-aged children in the context of parental severe mental illness. Second, to estimate the risk of mental disorders in children of parents with personality disorders.

Paper I

We analysed data from the randomised controlled VIA Family trial. We did not find differences between VIA Family and usual treatment on family functioning or levels of stimulation and support in the home environment. Parents with severe mental illness reported superior user satisfaction with VIA Family, and we cannot rule out clinically relevant effects on levels of stimulation and support in the home environment with VIA Family. We must consider the impact of the societal lockdown during COVID-19 and sample bias when interpreting our findings. Future studies could benefit from large enough sample sizes for subgroup analyses. Finally, future long-term follow-up can investigate preventive effects.

Paper II

We linked Danish nationwide registers to create a cohort of all children born from 1995 to 2016. We estimated incidence risk ratios and cumulative incidence up until age 18. We found that children of parents with personality disorders had a 2 to 2.5 times higher risk of mental disorders than the background population. The risk was associated with maternal and paternal personality disorders and increased across the full spectrum of mental disorders in the International

Classification of Diseases, 10th revision (ICD-10) for both daughters and sons (age 0-18). Finally, the risk was 3.5 times higher associated with having two parents with a personality disorder, and risk was increased across all parental personality subtypes in ICD-10 in the registers.

We found that the risk of mental disorders in children of parents with personality disorders was the same as found in other studies for children of parents with psychotic and affective disorders. Our findings can be interpreted considering complex gene-environment interactions, and early identification and preventive interventions are warranted and should involve mothers, fathers, daughters, and sons. The closing discussion in this thesis reflects a synthesis between theory, empirical research, and my clinical experiences interviewing families in the VIA Family trial, focusing on dimensional psychopathology, parenting, and stigma.

Summary in Danish

Børn af forældre med alvorlig psykisk sygdom er i øget risiko for selv at udvikle psykisk sygdom. Denne PhD afhandling havde to formål. Først, at undersøge effekten af en 18 måneders familiebaseret intervention, VIA Family, tilbudt familier med børn af forældre med alvorlig psykisk sygdom. Dernæst, at estimere risikoen for psykisk sygdom hos børn af forældre med en personlighedsforstyrrelse.

Artikel I

Vi analyserede data fra det randomiserede kontrollerede VIA Family studie, og fandt ikke forskel mellem VIA Family og standard behandling målt på familiefunktion og hjemmemiljø. Forældre med alvorlig psykisk sygdom rapporterede bedre tilfredshed med VIA Family end standard behandling, og vi kan ikke udelukke en klinisk relevant effekt af VIA Family målt på niveau af stimulation og støtte i hjemmemiljøet. Ved tolkning af vores resultater bør der tages højde for betydningen af nedlukningen af samfundet under COVID-19 pandemien samt potentielt sample bias. Fremtidige studier kan have gavn af tilstrækkelige antal deltagere og statistisk styrke til at foretage subgruppeanalyser. Endeligt skal bemærkes at fremtidig langtidstidsopfølgning af VIA Family vil kunne belyse eventuelle forebyggende effekter.

Artikel II

Ved at samkøre nationale danske registre skabte vi en kohorte af alle børn født fra 1995 til og med 2016. Vi estimerede incidens risiko ratios og kumulativ incidens til og med det 18. leveår og fandt, at børn af forældre med en personlighedsforstyrrelse havde en 2 til 2,5 højere risiko for at udvikle

psykisk sygdom sammenlignet med baggrundsbefolkningen. Risikoen var associeret med såvel mødre som fædre med personlighedsforstyrrelser og forøget på tværs af alle ICD-10 psykiatriske diagnoser hos såvel døtre som sønner (0-18 år). Risikoen var 3,5 gange højere hos børn, hvor begge forældre havde en personlighedsforstyrrelse, og endvidere var risikoen forøget uafhængig af hvilken type personlighedsforstyrrelse forældrene havde i registrene.

Vi fandt at risikoen for psykisk sygdom hos børn til forældre med en personlighedsforstyrrelse var den samme som tidligere studier har fundet hos børn til forældre med skizofreni, bipolar eller moderat til svær unipolar depression. Mulige forklaringer af vores fund indebærer komplekse gen-miljø interaktioner, og påkalder tidlig opsporing og forebyggende intervention målrettet mødre, fædre, døtre og sønner. Den afsluttende diskussion i denne afhandling reflekterer en syntese imellem teori, fund fra empiriske studier samt mine kliniske erfaringer i mødet med børnefamilier i VIA Family studiet – dette via et perspektiv på dimensionel psykopatologi, forældreskab og stigma.

List of publications

This thesis complies with the Graduate School of Medical Sciences, University of Copenhagen guidelines. Listed papers are referred to by their roman numerals throughout this thesis.

I. Ida C. T. Gjøde, Anne D. Müller, Carsten Hjorthøj, Sidsel Ingversen, Sofie H. Christensen, Lisbeth J. Mikkelsen, Signe S. Nielsen, Nicoline Hemager, Marianne Melau, Mala Moszkowicz, Julie Forman, Merete Nordentoft, Anne A. E. Thorup. *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.* [Under review]

II. Ida C. T. Gjøde, Thomas M. Laursen, Anne D. Müller, Anne Ranning, Mala Moszkowicz, Helene Speyer, Nicoline Hemager, Carsten Hjorthøj, Merete Nordentoft, Anne A. E. Thorup. *Association of Maternal and Paternal Personality Disorders With Risk of Mental Disorders in Children. A Nationwide, Register-Based Cohort Study of 1,406,965 Children* [Under review]

Supplementary paper:

III. Müller, A. D.[1], Gjøde, I. C. T.[1], 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

[1] shared first authorship

List of abbreviations

ADHD: Attention-Deficit/Hyperactivity Disorder
BP: Bipolar disorder
CI: Confidence interval
COPMI: Children of parents with a mental illness
CPR number: unique Identifier assigned to individuals at birth or immigration to Denmark
CSQ: Client Satisfaction Questionnaire
DSM: The Diagnostic and Statistical Manual of Mental Disorders
FAD: McMaster Family Assessment Device, 60-item version.
HOME-EA: Home Observation Measurement of the Environment Early-Adolescence
HOME-MC: Home Observation Measurement of the Environment Middle-Childhood
ICD: International Classification of Diseases
IRR: Incidence Risk Ratio
K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children
MDD: Major depressive disorder
NeQ: Negative Effects Questionnaire
OCD: Obsessive-Compulsive Disorder
PAFAS: Parenting and Family Adjustment Scales
PS: Parenting Scale
PSP: Personal and Social Performance Scale
PSS: Parenting Stress Scale
PTSD: Posttraumatic Stress Disorder
RCT: Randomised controlled trial
rMDD: recurrent major depressive disorder
SCAN: Schedules for Clinical Assessment in Neuropsychiatry
SD: Standard deviation
SPS: Social Provision Scale

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Preface

During my first years as a PhD student, I interviewed parents with severe mental illness, their children (ages 6-12), and co-parents in the VIA Family trial. At the same time, we began the nationwide register-based study on the risk of mental illness in children of parents with personality disorders. Engaging with essential research questions using high-quality data in both studies has been a privilege.

Family interventions represent a step forward in preventive interventions for familial-high-risk children and a step forward in family-focused care and recovery for individuals with severe mental illness. I hope this thesis will inspire attention to the needs of children and the potential of family involvement in mental health services.

Ethics

The VIA Family trial was approved by the Regional Committee on Health Research Ethics for the Capital Region of Denmark (H-17000450) and by the Danish Data Protection Agency. Deidentified data from Danish nationwide registers does not require approval by Committees on Health Research Ethics or similar in Denmark.

Terminology

In this thesis, *mental illness* refers to classified mental illness according to the Diagnostic Statistical Manual of Diseases or the International Classification of Diseases. *Mental disorder* is used synonymously with *mental illness. Severe mental illness* includes schizophrenia spectrum disorders, bipolar disorder, and major depressive disorder. In the literature, *serious* is used interchangeably with *severe*. *Severe/serious* annotates these mental illnesses' association with adverse life outcomes.

Children of parents with a mental illness (*COPMI*) refers to children of parents with both classified mental illness, substance use disorders, and unclassified ill mental health. In this thesis, *familial-high-risk children* is a narrower term that refers to children of parents with severe mental illness. The terms *familial-high-risk children* and *COPMI* are nested in a broader term: *young-next-of-kin,*[2] which includes children of parents with somatic illness, under palliative care, and children with ill or disabled siblings.

[2] e.g., in Martinsen EH, Weimand B, Norvoll R. Does coercion matter? Supporting young next-of-kin in mental health care. Nurs Ethics. 2020;27(5):1270-1281. doi:10.1177/09697330198716811.

Introduction

Parental psychopathology strongly predicts a substantial proportion of child mental disorders across countries (McLaughlin et al., 2012). Children of parents with a mental illness (COPMI) are from birth throughout their lifespan at higher risk of adverse outcomes, including mental illnesses (Brummelhuis et al., 2022; Leijdesdorff et al., 2017), injuries (Nevriana et al., 2020) and increased morbidity and mortality (Pierce et al., 2019; Ranning et al., 2019; Renneberg et al., 2023). Parental psychiatric disorders are further associated with offspring psychiatric work disability in adulthood (Halonen et al., 2019). Transgenerational concordance in mental illness symptomatology has been found, e.g., parental suicidal attempts increase the risk of suicidal attempts in children (Ranning, Madsen, et al., 2022; Ranning, Uddin, et al., 2022). In Denmark, 27% of children have a parent who has been hospitalised for their mental illness during the child's life, has attempted suicide, or has had a substance use disorder diagnosed. At age 26, these events are associated with an extra cost for society of 55.721 euros[3] per child (Rasmussen, R. & Kruse, M., 2022). Important research areas include preventive interventions supporting these families with potential benefits for individuals, families, and society.

This thesis had two aims. First, to investigate the effectiveness of an 18-month family-based preventive intervention for families with school-aged children in the context of parental schizophrenia spectrum disorder (SZ), bipolar affective disorder (BP), and recurrent major depressive disorder (rMDD). Second, to estimate the risk of mental disorders in children of parents with personality disorders.

[3] 415.000 Danish kroner, exchanged to euro according to the exchange-rate at the official website of the Danish National Bank on May 10, 2023 EUR 744.78 https://www.nationalbanken.dk/valutakurser

Severe mental illness

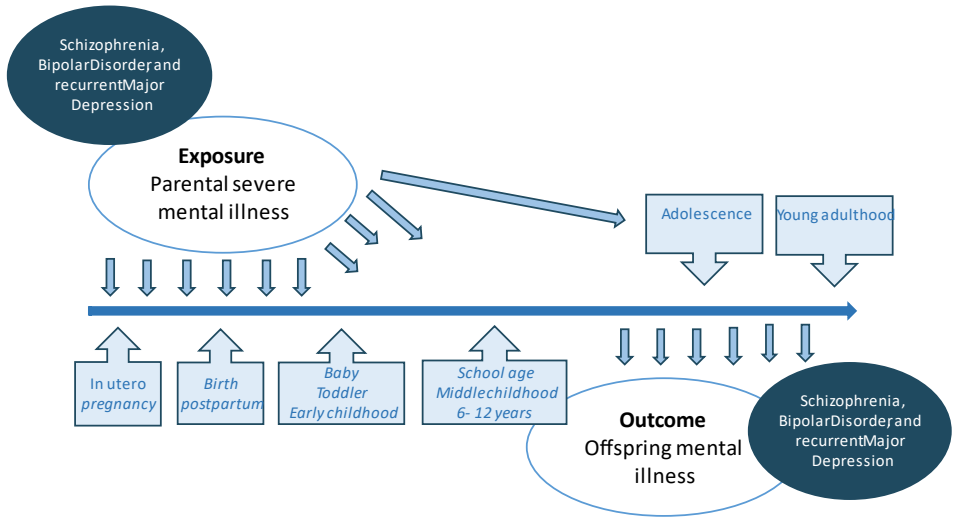
The three diagnostic groups, SZ, BP, and major depressive disorder (MDD), are referred to as severe mental illnesses due to their shared genetic liability and the high risk of adverse life outcomes associated with these illnesses (Duffy et al., 2023; “Global, Regional, and National Burden of 12 Mental Disorders in 204 Countries and Territories, 1990–2019”, 2022; Musliner et al., 2019; Rasic et al., 2014; Sandstrom et al., 2019; The Brainstorm Consortium et al., 2018).

Depression is a heterogeneous mental disorder in multiple aspects, including severity, duration, and recurrence (Sutherland et al., 2022). More severe depression reflects more substantial heritability due to additive and interacting effects from genetic and environmental factors (Kendler et al., 2020a, 2020b; Weissman, 2020). Bipolar disorder is characterised by fluctuations in mood and energy and is diagnosed based on episodes of depression in combination with at least one episode of mania or hypomania (Grande et al., 2016). Mania is a disabling state demanding care and is associated with a high risk of adverse events, and 75% of individuals with acute mania experience psychosis (ibid.). Depression and bipolar disorder are defined as affective or mood disorders and can be described along a continuum from uni-polar to bipolar type I and II. Depression is a leading cause of burden related to mental disorders worldwide, with the most significant impact on females (“Global, Regional, and National Burden of 12 Mental Disorders in 204 Countries and Territories, 1990–2019”, 2022). Schizophrenia impacts fewer individuals than depression; however, schizophrenia significantly impacts years lived with disability due to the weight of acute psychosis (ibid.).

Psychosis, consisting of hallucinations and delusions, is often a core feature of SZ (Owen et al., 2016). For most individuals with SZ, the psychosis is transient and can be treated pharmacologically and psychotherapeutically, and remission can be reached, partially or fully

(Hansen et al., 2023; Owen et al., 2016). However, a group of individuals with SZ experience persistent, disabling, and partially treatment-resistant psychotic symptoms and some have long-lasting negative symptoms defined by passivity, social withdrawal, and anhedonia.

Figure 1. Parental severe mental illness and child development



2

Children of parents with severe mental illness

Children of parents with severe mental illness are by early adulthood at a 2 to 4 times higher risk of developing a mental illness compared with nonexposed children (Rasic et al., 2014; Thorup et al., 2018), and one in three will develop severe mental illness by early adulthood (Rasic et al., 2014). Risk is increased in early childhood (Davidsen et al., 2022) and is increased across the full spectrum of child and adolescent mental disorders, including emotional, behavioural, and neurodevelopmental disorders (Ayano et al., 2019, 2021b, 2021a; Shayestehfar et al., 2023;

Thorup et al., 2018). **Figure 1** illustrates an epidemiological perspective of the risk of adverse outcomes for children of parents with severe mental illness.

Children of parents with severe mental illness are at increased risk of being placed in out-of-home care (Ranning et al., 2015, 2016) and missing early childhood universal preventive health care visits, including vaccinations (Davidsen et al., 2021). Results from a review of mixed studies (10 qualitative studies: n=361 COPMI; 21 quantitative studies; n=865.402 COPMI) found that growing up in the context of parental mental illness is challenging but not inevitably traumatic (Brummelhuis et al., 2022). However, school-aged children of parents with severe mental illness are at a higher risk of experiencing childhood trauma (Brandt et al., 2022), and at risk of increased levels of internalising and externalising psychopathology compared with nonexposed children (Ellersgaard et al., 2018; Gregersen et al., 2022). These children are at increased risk of developmental delays across developmental domains, including motor function (Burton et al., 2023), neurocognition (Hemager et al., 2018), and social cognition (Christiani et al., 2019). School-aged children of parents with SZ report significantly lower levels of quality of life when compared to matched controls, and their caregivers report a significantly increased risk of bullying victimisation at age seven and assessor-rated levels of stimulation and support in the home environment were found inadequate (Ellersgaard et al., 2018, 2019; Gantriis et al., 2019; Thorup et al., 2022).

Altogether, the risk posed to children of parents with severe mental illness calls for preventive interventions supporting families and children at risk, which is the aim of **paper I.** Before turning to children of parents with personality disorders, I will provide the methods, including PICO and search strings, underlying the later discussion of our findings in **paper I.**

Preventive interventions

Interventions supporting families affected by parental severe mental illness hold a twofold potential. First, according to meta-analyses, preventive interventions for children of parents with a mental illness can successfully reduce mental illness incidence in children by 47% (combined relative risk = 0.53, 95% CI = 0.34 to 0.84) (Lannes et al., 2021). Second, meta-analyses have found that family interventions can prevent relapse in schizophrenia with up to 80% reduction in odd ratios: family psychoeducation (OR, 0.18; 95% CI, 0.12-0.27) and community-based family interventions (OR, 0.63; 95% CI, 0.42-0.94) (Rodolico et al., 2022). Hence, family interventions can catalyse recovery and reduce relapse, benefiting patients, families, and society.

On April 11, 2023, I did a structured search in PubMed (Anon, 1966) aiming to do a pragmatic literature review of effects on family functioning and home environment of preventive interventions supporting children and families in the context of parental severe mental illness. I set criteria following PICO (Luijendijk, 2021) and selectively searched for meta-analyses and randomised controlled trials.

PICO criteria are listed in **Table 1**, and the search string is in **Table 2**. I excluded studies of children five years or younger. Due to too many articles (n=72,912), I pragmatically decided on a two-step procedure for selecting literature: first, selecting meta-analyses and reviews published within the past ten years (n=1,813) and second, choosing clinical trials (including all randomised trials) in the past five years (n=1,872).

Table 1. PICO: effectiveness on family functioning or the home environment of family-based preventive interventions for children of parents with severe mental illness

Population = children aged 4-18 of parents with schizophrenia spectrum disorder, bipolar affective disorder, or major depressive disorder
Intervention = family-based interventions
Control/**C**omparator intervention = usual treatment, waitlist control
Outcome = family functioning, home environment

Table 2. PubMed search string: effects on family functioning or the home environment of family-based preventive interventions for children of parents with severe mental illness

PubMed search string
("adolescent"[MeSH Terms] OR "child of impaired parents"[MeSH Terms] OR "child*"[Title/Abstract] OR "adolesce*"[Title/Abstract] OR "young adult"[Title/Abstract] OR "teenager*"[Title/Abstract] OR "offspring"[Title/Abstract] OR "young next-of-kin"[Title/Abstract]) AND ("parents/psychology"[MeSH Terms] OR "child of impaired parents"[MeSH Terms] OR "mothers/psychology"[MeSH Terms] OR "fathers/psychology"[MeSH Terms] OR "parent*"[Title/Abstract] OR "father*"[Title/Abstract] OR "mother*"[Title/Abstract] OR "caregiver*"[Title/Abstract] OR "famil*"[Title/Abstract] OR "home*"[Title/Abstract]) AND ("mental disorders"[MeSH Terms] OR "Bipolar and Related Disorders"[MeSH Terms] OR "Mood Disorders"[MeSH Terms] OR "Schizophrenia Spectrum and Other Psychotic Disorders"[MeSH Terms] OR "mental disorder*"[Title/Abstract] OR "mental illness*"[Title/Abstract] OR "Bipolar"[Title/Abstract] OR "mood disorder*"[Title/Abstract] OR "schizophr*"[Title/Abstract] OR "psychotic disorder*"[Title/Abstract] OR "depressi*"[Title/Abstract] OR "psycho*"[Title/Abstract]) AND ("interven*"[Title/Abstract] OR "treat*"[Title/Abstract] OR "therap*"[Title/Abstract] OR "program*"[Title/Abstract] OR “e-learning” [Title/Abstract])
Period: from 1946 up to April 11, 2023: Total 72,912

Since 2012, five meta-analyses have estimated the effect of preventive interventions for COPMI.

Three meta-analyses were published on preventive intervention for children of parents with any

mental illness (Lannes et al., 2021; Siegenthaler et al., 2012; Thanhäuser et al., 2017). Siegenthaler et al. (2012) found that interventions that targeted COPMI effectively prevented mental illness two years later. Thanhäuser et al. (2017) did an updated review in 2017 that confirmed the effectiveness of interventions for COPMI and found that interventions in which both children and parents participated produced the most significant effect sizes. Lannes et al. (2021) did an updated meta-analysis on interventions for children of parents with psychiatric disorders and found a significant reduction in offspring mental illness and a lasting diminution of internalising symptoms one year after the intervention.

Two meta-analyses were done on preventive interventions for children of parents with affective disorders (Havinga et al., 2021; Loechner et al., 2018). Interventions for children of parents with depression appeared effective in reducing depression symptoms and preventing the onset of depressive episodes at the end of intervention (Loechner et al., 2018). Havinga et al. (2021) studied the effect of preventive programs for children of parents with affective or anxiety disorders and concluded effectiveness but advised better descriptions of intervention programs (ibid.).

Interventions for parents with psychotic disorders are implemented in some countries. Still, they are not tested in controlled trials, as confirmed by a Cochrane review on interventions supporting parents with psychosis, which finds a single trial eligible for meta-analysis (Radley et al., 2020). A subsequent scoping review explored interventions relevant for parents with psychosis with parenting skills as the outcome (Radley, Sivarajah, et al., 2022).

I located no meta-analysis of effects on family functioning, the home environment or parenting, but one is currently underway by PhD student Matilde Vittrup at the University of Northern Denmark, Aalborg[4].

Children of parents with personality disorders

This study was initiated due to several cooccurring processes. First, personality disorders were frequent comorbidities in the VIA Family trial. Second, clinicians emphasised the need for family-based interventions for families and children in the context of parental personality disorders. Third, a narrative review pointed at children of parents with personality disorders beyond borderline personality as areas of future research (Leijdesdorff et al., 2017).

Personality disorders have been estimated to have a 6.1 % point prevalence globally (Tyrer et al., 2015), and emotionally unstable personality disorder is the fourth most frequent disorder, following schizophrenia, alcohol misuse, and adjustment disorders in Danish psychiatric hospital-based services (Munk-Jørgensen et al., 2010, s.). In DSM, personality disorders are categorised into three clusters. Cluster A is associated with psychotic disorders, including paranoid, schizoid, and schizotypal personality disorder[5]. Cluster B comprises antisocial, borderline, histrionic and narcissistic personality disorders[6]. Cluster C includes avoidant, dependent and obsessive-compulsive personality disorder. Personality disorders are common in combination with affective

[4] Registered protocol is available at prospero: crd.york.ac.uk/prospero/display_record.php?RecordID=390720

[5] Schizotypal personality disorder is not classified as a personality disorder in ICD-10, but as a psychosis spectrum disorder F21. Schizotypal disorder.

[6] Antisocial personality disorder equals ICD-10, F60.2. Dissocial personality disorder. Borderline personality disorder is classified under the category F60.3. Emotionally unstable personality disorder

disorders, with cluster B and C personality disorders most common in BP and cluster C most common in MDD (Friborg et al., 2014).

Difficulties with interpersonal functioning are a core feature of personality disorders, described by both clinical and longitudinal observational studies (Bohus et al., 2021; Tyrer et al., 2015; S. Wilson et al., 2017). Cluster B personality disorders are characterised by impulsivity and emotional dysregulation, especially in exposure to stressors. This symptomatology challenges parenting and family functioning (Adshead, 2015), and a Norwegian cohort study found that parental cluster B personality disorder symptoms predicted the incidence of anxiety and depressive disorders in school-aged offspring in the general population (Steinsbekk et al., 2019). Another cohort study found that parents' self-reported symptoms of borderline, antisocial, and narcissistic personality disorder were associated with offspring mental illness in preschool children (Berg-Nielsen & Wichström, 2012, s.) and predicted decreased social skills development at ages 8 and 10 (Wichstrøm et al., 2022). Parental personality disorders are associated with a higher risk of injuries in children throughout childhood and adolescence; however, not more than other types of parental mental disorders (Nevriana et al., 2020).

Altogether, research suggests that children of parents with personality disorders are at risk of mental illness. However, it is unclear whether the risk goes across different subtypes of personality disorders since most studies focus on parental cluster B personality disorder symptomatology. Estimating this risk, including across parental personality disorder subtypes, is the aim of the study in **paper II**.

Theoretical and conceptual framework

Developmental psychopathology

To understand mental illness, we must consider human development throughout the lifespan. Development begins as fetal programming in the intrauterine environment during pregnancy (Ahmadzadeh et al., 2021; Lautarescu et al., 2020). Psychopathology results from a series of complex processes throughout development involving biological, neurophysiological, psychological, social, and cultural factors interacting over time. Risk is probabilistic and not deterministic in the developmental psychopathology framework conceptualised as *equifinality* and *multifiniality* (Cicchetti, 2016; Cicchetti & Rogosch, 1996). *Multifiniality* means individuals with similar risk profiles can have different developments and outcomes later. Vice versa, *equifinality* refers to evidence that individuals with different risk profiles early on can later develop the same outcomes, e.g., a mental disorder.

Known environmental risk factors for developing mental disorders include early exposure to toxins or infections in the intrauterine environment, obstetric complications, e.g., a 5-min Apgar score <7 and early life stressors such as childhood physical or sexual abuse (Arango et al., 2021; McKay et al., 2021, 2022). Further, risk factors include parental criticism, overprotective parenting, childhood poverty, peer-relationships bullying, parental substance misuse, divorce, death, and hospitalisation (Agid et al., 1999; Barnes et al., 2021; Richards et al., 2019; Saarinen et al., 2023), and the risk increases with multiple adversities or traumatic experiences (the BELLA study group et al., 2008).

Having a biological parent with severe mental illness is one of the most substantial known risk factors for developing a mental disorder, which is due to shared genetics, shared environmental factors, parenting behaviours and family climate, and complex gene-environmental interactions (Duffy et al., 2023; Jami et al., 2020, 2021; Kendler et al., 2020b).

Intergenerational transmission of severe mental illness

> "Today, I treat the adult children of the patients I treated in the early years of my career [Psychiatric Hospital, Frederiksberg, Denmark]. (…) This is why I find your study is relevant and important" (Clinician, first phase of recruiting participants in 2017)

The heritability gap and gene-environment interactions

A child shares 50% of their genes with each parent. Research has established that traits such as mental health, educational attainment, cognitive functioning and other parent-offspring associations are partly explained by shared genes, hence reflecting genetic transmission (Jami et al., 2020, 2021), and are partly explained by environmental and complex gene-environment interactions, including epigenetic processes (Agid et al., 1999; Alameda et al., 2022; Bipolar Disorders Working Group of the Psychiatric Genomics Consortium et al., 2017; Kendler et al., 2020b, 2020a; Tan et al., 2023; Trerotola et al., 2015; Uher, 2014b, 2014a; van Os et al., 2010).

Results from studies of monozygotic twins suggest that rearing effects mediate genetic risk and liability to severe mental illness (Kendler et al., 2020a; Tienari et al., 1985). Children of mothers with schizophrenia were more sensitive to environmental stress and adversities than nonexposed children (Tienari et al., 1985). Results from an extended Swedish

national adoption study suggested that the transmission of BP across generations was primarily genetic, with rearing effects likely present, and that the cross-generational transmission from BP in parents to broad schizophrenia in offspring was entirely genetic. In contrast, the transmission between BP in parents and MDD in children was equally caused by genetic and rearing factors (Kendler et al., 2020a).

Figure 2. The heritability gap[7]

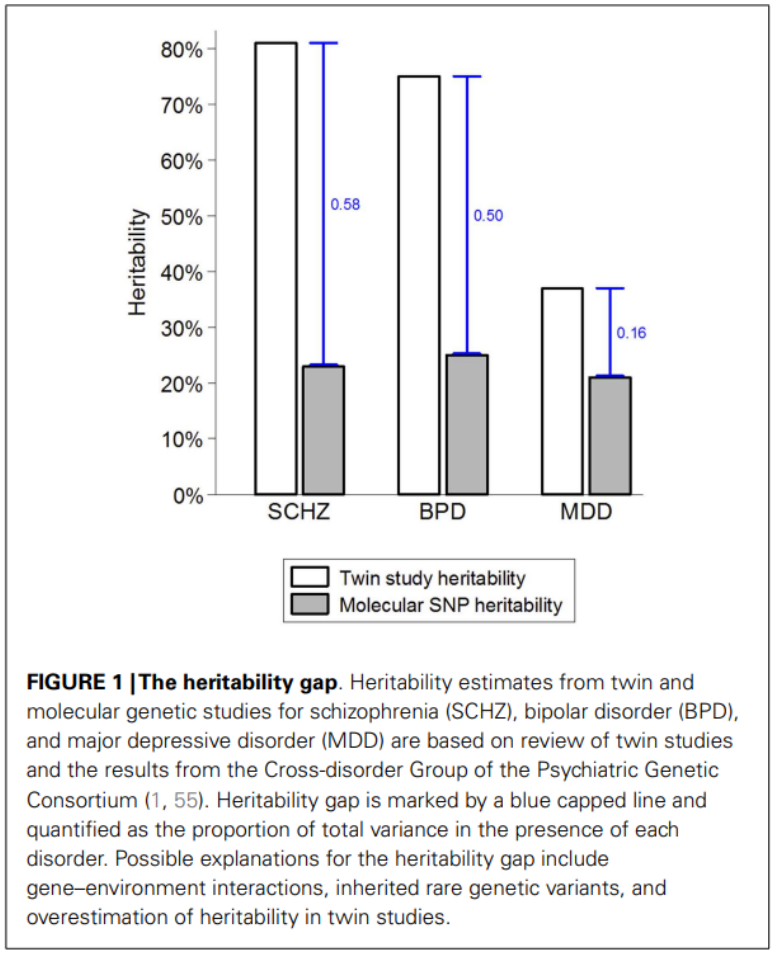


FIGURE 1 |The heritability gap. Heritability estimates from twin and molecular genetic studies for schizophrenia (SCHZ), bipolar disorder (BPD), and major depressive disorder (MDD) are based on review of twin studies and the results from the Cross-disorder Group of the Psychiatric Genetic Consortium (1, 55). Heritability gap is marked by a blue capped line and quantified as the proportion of total variance in the presence of each disorder. Possible explanations for the heritability gap include gene–environment interactions, inherited rare genetic variants, and overestimation of heritability in twin studies.

[7] Figure 1: The heritability gap (Uher, 2014a, p. 3) is used under CC BY 3.0

Figure 2. illustrates the *heritability gap*, which refers to evidence from molecular studies that does not explain why severe mental illness to such a large degree runs in families as found in twin studies (Uher, 2014a). Gene-environment interactions are central in explaining the heritability gap (ibid.). In the following, I will unfold the current knowledge considering environmental risk factors related to intergenerational transmission of severe mental illness.

Emotional family climate, family stability, and the home environment

Considering environmental factors, a German survey study of 2,863 families reported frequencies and impact of risk and protective factors on children's mental health; they found that emotional family climate stood as the main factor that could negatively impact children's mental health (the BELLA study group et al., 2008). Supporting this finding, a prospective population-based study of 3502 children in the general population in Finland has shown that family environments characterised by frequent events of early life stress predicted non-affective psychotic disorders in children with Odds Ratio (OR) 2.04, *P*=.001 (Saarinen et al., 2023). Further, impaired emotional family functioning (impairment in parenting practices, life satisfaction, parental mental disorders combined with alcohol intoxications) predicted affective disorders with OR=1.58, *P*=.013 in the same population (ibid.).

A meta-synthesis of qualitative research has shown that dysfunctional home environments are related to children developing interpersonal and relational difficulties that can continue into adulthood (Källquist & Salzmann-Erikson, 2019). This finding is aligned with evidence of expressed emotions and emotion regulation in the parent-child relationship being a central mechanism in the intergenerational transmission of mental illness (Fahrer et al., 2022; Loechner et al., 2020).

Further, studies have found positive associations between good family functioning and lower levels of child psychopathology in the context of parental mental illness (Sell et al., 2021; Wiegand-Grefe et al., 2019). Stimulating and nurturing rearing environments have shown protective effects by preventing depression in children at familial high risk of MDD (Kendler et al., 2020b). The preventive effects of such high-quality rearing environments disappeared in cases of family disruption due to parental death or divorce during childhood or adolescence (ibid.).

FHR-SZ offspring are at high risk of growing up in families with inadequate levels of stimulation and support (Gantriis et al., 2019) and experiencing early life trauma (Brandt et al., 2022). Family environments in families of parents with BP are heterogeneous, with a large proportion functioning similarly to the general population (Gantriis et al., 2019; Stapp et al., 2020). FHR-BP offspring are at higher risk of experiencing traumatic events in childhood (Brandt et al., 2022; Moulin et al., 2022), and findings from prospective longitudinal cohort studies suggest that childhood traumatic events mediate the transmission of early-onset MDD in FHR-BP offspring (Moulin et al., 2022).

Altogether, children at familial risk of severe mental illness are at increased of having a genetic predisposition via shared genes with the parent with severe mental illness. Further, the child is at higher risk of early life stress and trauma than the background population. However, many children of parents with severe mental illness fare well, and there is a consensus in the field that more research is needed to understand and predict, either by stratification or individual

prediction, who is at risk to better target preventive efforts. At the same time, as such research is undertaken, there is an urgent need to address families' current needs for support.

Additive and cumulative effects from stress are mechanisms in the aetiology of neuropsychiatric disorders such as SZ (Debbané & Fonseca Pedrero, 2023; O'Hare et al., 2023; Veenstra-VanderWeele & Warren, 2015). There is a need for interventions to decrease stress levels in early childhood development to prevent the risk of adverse cascading effects across development. As elaborated above, family functioning and the home environment partly mediate familial risk to severe mental illness; hence, they were conceptualised as the primary context of risk versus protective factors addressed by VIA Family to lower stress as a selective targeted preventive intervention.

Aims and objectives

In **paper I** we aimed to test the superiority of VIA Family compared with usual treatment on family functioning and levels of support and stimulation in the home environments. Further, we aimed to test user satisfaction and analyse exploratory outcome data. In **paper II** we aimed to investigate the association between any diagnosis of parental personality disorder and risk of mental illness in offspring. We hypothesised that a higher risk of mental disorders would be found in children of parents with personality disorders compared with nonexposed children. We also hypothesised that emotionally unstable personality disorder and dissocial personality disorder would be associated with higher incidence risk ratios than other parental personality disorder subtypes.

Methods

The first section in methods covers Danish nationwide registers used in both papers. The following sections provide methods for each paper separately.

Danish nationwide registers

Danish nationwide health registers provide a valuable source for epidemiological research, including multigenerational health research (Erlangsen & Fedyszyn, 2015; Hamm et al., 2021). Danish nationwide registers cover data on the complete Danish population with no loss to follow-up, and the estimated accuracy of linkage in registers between children and their legal parents is 100 percent (Erlangsen & Fedyszyn, 2015) with the limitation that individuals at immigration to Denmark are not linked to their legal parents. Research on deidentified data from Danish nationwide registers does not require informed consent.

The Danish Civil Registration System

Since 1968, all individuals in Denmark have been assigned a unique identification number (CPR number) at birth or immigration to Denmark. The CPR number is registered in the Danish Civil Registration System (Pedersen, 2011), which holds information on each individual's name, gender, date and place of birth, citizenship, legal parents' CPR numbers and is routinely updated concerning vital status, emigration, immigration, and place of residence. The CPR number enables the linkage of deidentified data from multiple registers on an individual level. The Danish Civil Registration System allows the establishment of family structures, e.g. parent-child relationships

can be linked via legal parents' CPR numbers or with the Danish Adoption Registry (Petersen & Sørensen, 2011). Siblings can be linked through parent's CPR numbers.

The Danish Psychiatric Research Register

From 1970 to 1995, information on patients treated in the secondary sector, i.e. hospital-based mental health services in Denmark, including start and end of treatment, types of referrals and admission, diagnostic codes, and municipality residence, were routinely registered by the Danish Psychiatric Central Register (Mors et al., 2011). This register is considered close to complete in covering severe mental illness. In contrast, the Danish Psychiatric Register did not register information from the primary sector covering mild to moderate mental illness (ibid.).

Up until 1995, the Danish Psychiatric Research Register was independent, but since 1995, The Danish National Patient Register has registered information previously registered in the Danish Psychiatric Research Register. The current thesis uses data from before 1995, whereby both registers were used when establishing the cohort of participants.

The Danish National Patient Register

Since 1977, the Danish National Patient Register has registered information on inpatient and somatic hospitalisations. Since 1995, simultaneously with the move from ICD-8 to ICD-10, the Danish National Patient Register has additionally captured information on outpatient contacts, emergency rooms, and psychiatric wards (Lynge et al., 2011). This means that data concerning inpatient admissions from 1970 to 1994 can be extracted from the Danish National Patient Register, whereas outpatient contacts can be extracted from 1994 onwards.

Statistics Denmark

Statistics Denmark routinely updates and maintains data in public registers to inform research, public administration, and education in Denmark. Since 2022, Statistics Denmark has been administered by the Danish Ministry of Digital Government and Gender Equality[8]. Data from Statistics Denmark were used to enable analyses adjusting for mothers' and fathers' highest levels of education in **paper II**. The variable on the highest level of education is derived from two register sources: The Student Register and The Qualification Register[9].

[8] https://english.digmin.dk/digital-government

[9] Statistics Denmark - https://www.dst.dk/en/Statistik/dokumentation/documentationofstatistics/highest-education-attained The variable of highest level of education was previously found in the Integrated Database for Labour Market Research (Danmarks statistik, 1991), but is today found directly at Statistic Denmark's website.

Methods paper I

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

Study design and participants

We did a parallel, assessor-blind, randomised controlled superiority trial to test the effectiveness of an 18-month, multidisciplinary, multicomponent, tailored, and family-based intervention, VIA Family, compared with usual treatment. Nationwide registers were used to perform a cohort of eligible families of parents with schizophrenia spectrum disorder (SZ), bipolar disorder (BP), or recurrent major depressive disorder[10] (rMDD) with school-aged children (6-12 years old). The trial took place at a single mental health centre in Copenhagen, Denmark. Families were randomly assigned to either VIA Family or usual treatment using an algorithm with varying block sizes, stratified by parental diagnostic group. Trial assessors were masked to group allocation. Outcomes were assessed at 0 and 18 months.

Eligibility criteria are listed in **Table 3**. Trained clinical psychologists conducted diagnostic interviews with parents and children after completing training in the schedules for clinical assessment in neuropsychiatry (SCAN) (Wing, 1990) and the Schedule for affective disorders and schizophrenia for school-aged children (K-SADS) (Kaufman et al., 1997).

[10] synonymous with recurrent moderate to severe depression

Table 3. VIA Family eligibility criteria

Inclusion criteria	The official address of the participating child had to be in the municipality of Frederiksberg or Copenhagen, the Capital Region of Denmark.
	At least one child was 6–12 years old at inclusion.
	At least one parent met criteria for: 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 recurrent major depression (recurrent moderate to severe depression) • ICD-10 codes F33.1, F33.2, or F 33.3, or • ICD-8 codes: 296.0, 298.0 or 300.4 AND The diagnosis was confirmed at an expert clinical conference based on ratings with the clinical diagnostic SCAN interview (Wing, 1990). AND The parent had at least one inpatient or outpatient contact with mental health services in the child's lifetime.
Exclusion criteria	Caregivers did not speak and understand Danish to be able to give informed consent for their own participation and the child's participation. However, due to funding, this criterion was changed to: Caregivers must speak Danish sufficiently to participate in VIA Family without translators.
	All family members were currently engaged in family intervention.

Parents with severe mental illness gave oral consent before contact was attempted with other parents/caregivers. In some cases, this was a crucial step before contacting the parent with child custody was possible. All parents gave written informed consent for their participation. Legal caregivers gave written consent before the inclusion of children in the trial. After baseline assessments, all families were offered oral feedback based on the evaluation of children's daily functioning and mental health, together with a formalised orientation of services available in the usual treatment they could contact, listed in **Table 4**.

Table 4. Manualised information about services in usual treatment[11]

Before randomisation, all families received a brief telephone call, which included general information about the available support services for families and children in the context of parental mental illness, focusing on geographical areas in Frederiksberg and Copenhagen. Information was standardised: 1: Telephone advice/support services. Hotlines focusing on children and parents are offered by "Børns Vilkår" and "Psykiatrifonden". Other hotlines are offered by "Depressionslinjen" and "Livslinjen". 2: Support groups for children born to parents with mental illness. Currently "Psykiatrifonden" and "Psych-Info" offer those services. 3. General services within the municipalities: How to reach support for psychiatric and psychological problems for parents and children, including that the families' general practitioners were to be contacted for further referrals to specialists. Further information considering how to access a school psychologist (PPR) or social worker at the school.

Baseline assessments

At baseline, information was obtained via interviews, patient self-report questionnaires, semi-structured interviews, and home visits, including observational measures. All diagnoses were concluded at expert clinical conferences with a child and adolescent psychiatrist present (AT, MM). Data was kept in the Research Electronic Data Capture (Harris et al., 2009). A thorough anamnestic interview was conducted to obtain child development and parents' socio-economic information. Information on sexual orientation, self-defined gender or ethnicity was not obtained. A full assessment battery and further details on data collection can be found in **paper III**.

[11] Re-use of supplementary in paper III

> "The families report a need for proximity and predictability in their situation, so that the know what will happen in case of worsening of the illness and [a need for] a person they can contact. They wish to have a 'family contact' that follows them over time, comes to their homes, gets to know/understand them and their situation, takes the initiative and co-ordinate help/support, and can be contacted by both parents and children when needed" (Ruud et. al, 2015, p. 10)[12]

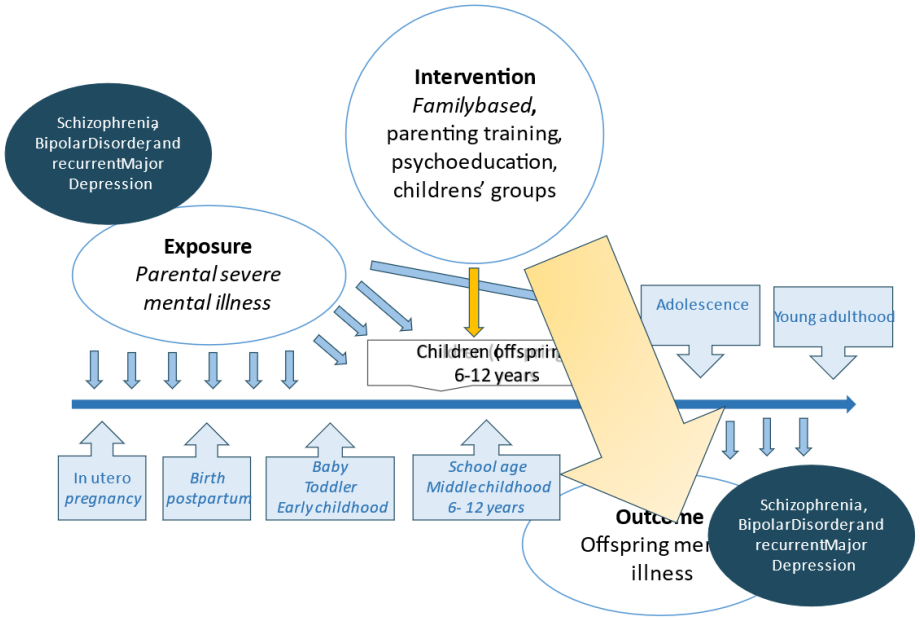
VIA Family

VIA Family was a flexible and tailored intervention tailored to the needs and wishes of the individual family. The core component was a case manager, similar to the 'family contact' described in the quotation above (Ruud, T., 2015). The case manager worked in a multidisciplinary team, followed the family for 18 months, and monitored and tailored the intervention according to the family's wishes. The multidisciplinary team consisted of an experienced child and adolescent psychologist, an experienced specialised psychiatric nurse, a family therapeutic trained social worker and a child pedagogue.

VIA Family took place in a community setting, deliberately not at the hospital, to create a child-friendly and non-stigmatizing setting (Müller et al., 2019). The case managers aimed to build a trusting relationship and support parents, co-parents, and children at the 'VIA Family community clinic' or in families' homes. Children participated if parents and children accepted.

[12] Translated to English by Ida Gjøde from Norwegian: "Familiene etterspør nærhet og forutsigbarhet i situasjonen, slik at de vet hva som skal skje ved en forverring av sykdommen og har en person de kan kontakte. De ønsker en familiekontakt, som følger dem over tid, kommer hjem til dem, blir kjent med dem og deres situasjon, tar initiativ til og koordinerer hjelp, og som kan kontaktes av både voksne og barn ved behov" (Ruud, T., 2015, p. 10)

Figure 3. VIA Family preventive intervention in child development



The Positive Parenting Program – Triple P

All multidisciplinary team members were accredited in the Triple P – Positive Parenting Program (Triple P) before the onset of the trial. Triple P is a flexible intervention program involving universal preventive, selective, and at-risk targeted intervention modules. As such, Triple P works to promote healthy child development and can be applied both in the general population as well for selective at-risk groups, such as the Triple P Stepping Stones that are designed for families with children with special needs and/or disabilities (Sanders, 1999, 2012; Sanders et al., 2004, 2014) Triple P draws theoretically on the 1960-70s social learning theory together with later developments in cognitive behavioural theory (Sanders, 2012). Social learning theory developed by Albert Bandura and others theoretically conceptualised self-efficacy (Bandura, Albert; Walters, Richard H., 1963), which in Triple P is a central component in parental self-care. Triple P was a core element of VIA Family (Müller et al., 2019).

A multicomponent intervention

Various components listed in **Table 5** were offered to families based on their needs and motivation, always aiming to increase levels of protective factors and decrease risk factors. Domains of the environment which VIA Family seeks to address include parenting skills and affective responsiveness in the family (via parents mentalisation), structure of everyday life, and openness about talking about parental mental illness (psychoeducation and peer support groups for parents and children), which contributes to anti-stigma and increased mental-health literacy known to be factors of resilience (Abel et al., 2019; Beardslee et al., 2003; Focht-Birkerts & Beardslee, 2000).

Additionally, case managers worked actively to initiate, monitor, and support the maintenance of families' use of services in usual treatment, such as participating in meetings at job centres or social services, network meetings at children's schools, or writing referrals to Child Protection Services and fast-track referrals to child and adolescent mental health services.

Further, case managers focused on children's relationships with peers and teachers at school/day-care, children's engagement with leisure activities and extended family. The aim was not selectively to target parenting skills but to actively consider children's environments at school and with peers. Also, it sought to elevate parents' sense of self-efficacy to improve collaboration with schools and help child and adolescent offspring build healthy relationships with peers. Moreover, to inform and support the parents in encouraging the child's activities out of home, such as sports, other leisure activities, social gatherings, and friendships with peers.

Table 5. VIA Family treatment components

Positive Parenting Program - Triple P and Steppingstones
Psychoeducation – on symptoms, diagnosis, or emotions in general "Talking about mental illness."
Support on handling conflicts over time children spend with each parent, divorced families
Practical support on parenting and structure of daily activities in homes
Safety plans
Counselling and guidance regarding financial, social, or practical support
Optimisation of the ill parent's treatment and lifestyle
Specialised treatment of the child's (transient or subthreshold) mental health difficulties
Children's peer-groups
Parent's peer-groups

VIA Family is foremost characterised as a long-term tailored support for the whole family. VIA Family incorporates talking about parental mental illness as central to the psychoeducational elements. Additionally, parenting advice, the use of Triple P together with practical parenting training of skills and planning of structures of daily lives in homes. Finally, VIA Family offered peer support groups for children, teenagers, and parents.

Usual treatment

Usual treatment was defined as free-of-charge services such as mental health services, psychiatrists, or general practitioners (incl. prescription on psychotropics) and social services. Further, use of services in the private sector and services offered by not-for-profit organisations or private funds such as *Psykiatrifonden* that offer peer groups for children and adolescents[13].

[13] https://psykiatrifonden.dk/hjaelp-raadgivning/raadgivning/boernegrupper (25.05.2023)

The level of support received by families was hypothesised to vary. Therefore, we did semi-structured interviews with all participating families, asking which services they had used, how often and for how long. These semi-structured interviews were done at 0 (baseline) and 18 months (end of intervention).

Outcomes

Figure 5 illustrates the grouping of outcomes presented in the protocol **paper III** (Müller et al., 2019). The study in **paper I** reported on key secondary outcomes conceptualising the family as a whole and unit of analysis.

Figure 4. Grouping of outcomes in the VIA Family trial

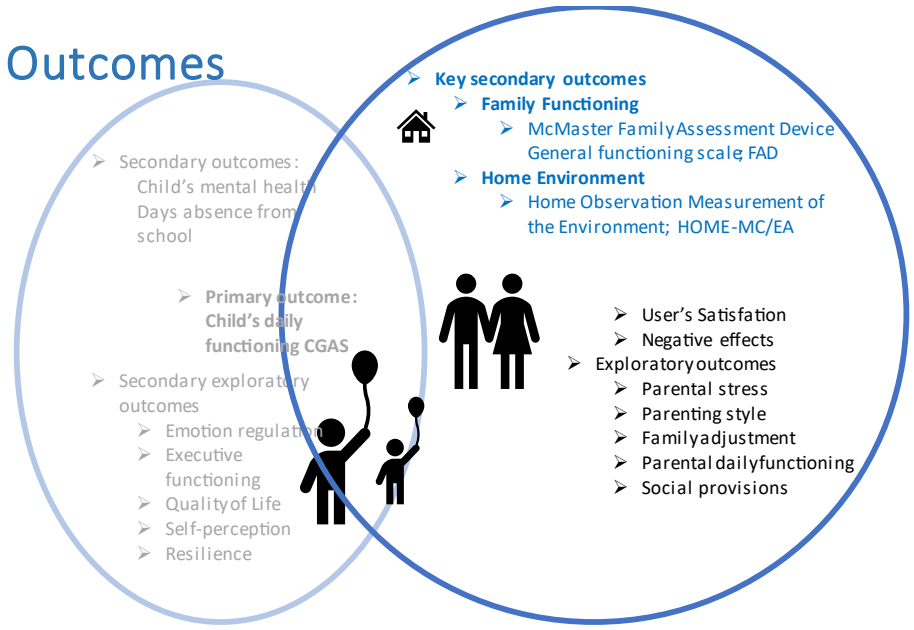


Figure 4. illustrates that **paper I** in this thesis focuses on the family and the home environment as the unit of analysis. Child global functioning, psychopathology, and resilience outcomes are reported in an independent study (in preparation).

The McMaster Family Adjustment Device

The McMaster Family Adjustment Device (FAD) was constructed based on inductive interviews with families (Epstein et al., 1983; Friedmann et al., 1997; Kabacoff et al., 1990) and theoretically conceptualised in a family systemic framework. A family is conceptualised as more than the sum of individual family members, and that illness or other disturbance for one family member creates a disturbance for the whole family (Friedmann et al., 1997; Staccini et al., 2015). A qualitative review of the clinimetric properties of FAD covered 148 studies. It concluded that FAD adequately estimates family functioning in clinical and research settings and efficiently differentiates between control and clinical populations. Further, FAD is found to have good test-retest reliability (Staccini et al., 2015) but modest sensitivity to measuring the change from treatments (ibid.).

The Home Observation Measurement of the Environment

We visited all families at their homes to observe and interview the child and the caregiver to assess levels of support and stimulation in the home environments with the Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence (HOME-MC/EA). This tool has shown sensitivity to discriminating between the home environment of 7-year-old FHR children and the home environment in control families in a Danish setting (Gantriis et al., 2019). Assessors were accredited by conducting at least five HOME interviews accompanied by an accredited HOME interviewer and final approval by the study program leader (AT) based on video-recorded interviews.

Statistical analyses

The trial was registered at ClinicalTrials.gov (NCT03497663), and the statistical analysis plan published in Trials: “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"(Müller et al., 2019). In PhD courses, I learned to add further quality to our data modelling:

1. *Adjust for the stratum variable(s).* Therefore, I planned to adjust analyses for the stratum variable of the parental diagnostic group: SZ, BP, and rMDD.
2. *Children* are dependent units of analysis as they share genes and environment. Hence, we add a random effect to our data analysis involving siblings (Gjøde & I., 2023a). Strictly speaking, this makes our model a linear mixed model, not a traditional ANCOVA.
3. *Adjust for parents' gender* (legal gender derived from parents' CPR numbers) since gender is a culturally important identity marker, especially regarding how motherhood and fatherhood are perceived.

Power calculation[14]

Danish norms are unavailable, but a Canadian psychiatric population had a FAD general functioning score normally distributed SD = 0.51 (scale: 1–4, mean: 2.27) (Friedmann et al., 1997). A clinically relevant difference between VIA Family and usual treatment on FAD would be 0.4 (80 % of SD) (Müller et al., 2019). We needed to study 35 families in each group to reject the null hypothesis with a probability (power) of 0.90 and a probability of a type I error at 0.056.

[14] A sample size of 37 families in each treatment group was defined by power calculations for the primary outcome child global functioning (Müller et al., 2019).

Methods paper II

Association of Maternal and Paternal Personality Disorders With Risk of Mental Disorders in Children. A Nationwide, Register-Based Cohort Study of 1,406,965 Children

Study design and participants

We did a nationwide register-based cohort study using Danish nationwide health registers to investigate the association between parental personality disorders and the risk of mental disorders in children during childhood and adolescence. We created a cohort of children born from January 1, 1995, until December 31, 2016, by linking the Danish Psychiatric Central Register (Mors et al., 2011), the Danish National Patient Registry (Lynge et al., 2011), and Statistics Denmark (Statistics Denmark, u.å.). Our cohort contained information on the child's legal gender, child age, child mental disorder diagnosis, and legal parents of children, together with the information on parents' mental disorders and the highest level of education as a proxy for socioeconomic status.

Exposure

In the primary analysis, the exposure was any parental personality disorder before the child's birth. ICD-8 and ICD-10 diagnostic codes are listed in **Table 6**. In the secondary analysis of the risk of mental illness in the children associated with the parental personality disorder subtype, exposure was defined as the diagnostic code selectively in the ICD-10. We refrained from using ICD-8 diagnoses in the secondary analysis across parental personality disorder subtypes since ICD-8 and ICD-10 personality disorder subtypes are incompatible. Hence, the secondary analysis included parents with personality disorder diagnostic codes in ICD-8 in the control group.

Additionally, substance use disorder diagnoses were used in exploratory analysis to investigate interactions with parental personality disorders and the association with children's risk of mental disorders during childhood and adolescence. Substance use disorders diagnostic codes: ICD8 = '303', '304', '291', '5711', '57109'; ICD10 = F1. Any parental psychiatric disorder: ICD8 = 290-315; ICD10 = F. In the exploratory analysis, our model was adjusted for sex, age, calendar time and father unknown.

Table 6. Exposure: Parental personality disorders[15]

ICD-10	ICD-8
F60 + F61 (excl. F62-69).	301.x9 (not 301.19), 301.80, 301.81, 301.82, 301.84
F60.0 Paranoid personality disorder F60.1 Schizoid personality disorder F60.2 Dissocial personality disorder F60.3 Emotionally unstable personality disorder F60.4 Histrionic personality disorder F60.5 Obsessive personality disorder F60.6 Anxious-avoidant personality disorder F60.7 Dependent personality disorder F60.8 Other specific disorder of personality structure Incl. Narcissistic and passive-aggressive personality disorder F60.9 Disorder of personality structure, unspecified F61.0 Disorder of personality structure, combined and other type	301.09, 301.29, 301.39, 301.49, 301.59, 301.69, 301.79, 301.89, 301.99, 301.80, 301.81, 301.82, 301.84.

The background population

The comparison group were children born to parents who did not have a personality disorder diagnosed before the child's birth but included children of parents with any other mental disorders

[15] Re-use of supplementary material in paper II. eTable 1. Exposure: Parental personality disorders, ICD-10 diagnosis (and corresponding ICD-8 diagnoses)

(ICD-8 and ICD-10). Thus, we did not create an ultra-healthy comparison group. In the secondary analysis, parents with ICD-8 personality disorders were included in the comparison group since personality disorder subtypes are incompatible between ICD-8 and ICD-10.

Table 7. Outcomes: Diagnostic codes[16]

Child and adolescent mental disorders	ICD-10
Any child or adolescent mental disorder	F00–99
Organic mental disorders	F00-09
Mental and behavioral disorders due to substance use	F10-19
Schizophrenia spectrum disorders and acute psychoses	F20-29
Affective disorders	F3, F92.0
Anxiety disorders and OCD	F40-F42 F44-F49, F93, F94.0
PTSD and adjustment disorders	F43
Eating disorders	F50, F98.2
Sleep disorders	F51
Personality disorders	F60, F61 (excl. F62-69)
Intellectual disability	F70-79
Developmental disorders	F80, F81, F82, F83
Autism spectrum disorders	F84.0, F84.1, F84.5-84.9
Attention-deficit/hyperactivity disorder	F90 + 98.8
Oppositional defiant disorders and conduct disorders	F91
Other mixed disorders of conduct and emotions	F92.8, F92.9
Attachment disorders	F94.1, F94.2, F94.8, F94.9
Tic and Tourette's disorders	F95
Other developmental disorders include enuresis, encopresis	F98.0, F98.1, F98.3-F98.7, F98.9

[16] Re-use of supplementary material in paper II. eTable 2. Diagnostic codes for all outcomes: ICD-10 diagnoses in offspring throughout childhood and adolescence.

Outcomes and statistical analyses

The primary aim of this study was to estimate risk across ICD-10 mental disorders (listed in **Table 7**) in children of parents with any personality disorder (listed in **Table 6**). The second aim was to study one outcome: any mental disorder in offspring across different parental personality disorder subtypes. We calculated incidence risk ratios (IRRs) based on Poisson regression analyses with the logarithm of person-years as offset. All analyses were adjusted for child age, legal gender, and calendar period.

> "For each outcome follow-up of a child ended when a diagnosis was registered. If child x was registered with ADHD at age 7, then child x was excluded at age 7 in the analysis with ADHD as outcome. Child x remained in analyses of other outcomes. In the analysis with "any mental disorder" as outcome, child x was excluded at first registered diagnosis" (Gjøde et. al., 2023)

Sensitivity analyses were performed adjusting for parents' highest level of education as a proxy for socioeconomic status. We did not adjust the multiplicity of analysis. A complete statistical analysis plan can be found in **paper II**.

Results

Results paper I

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

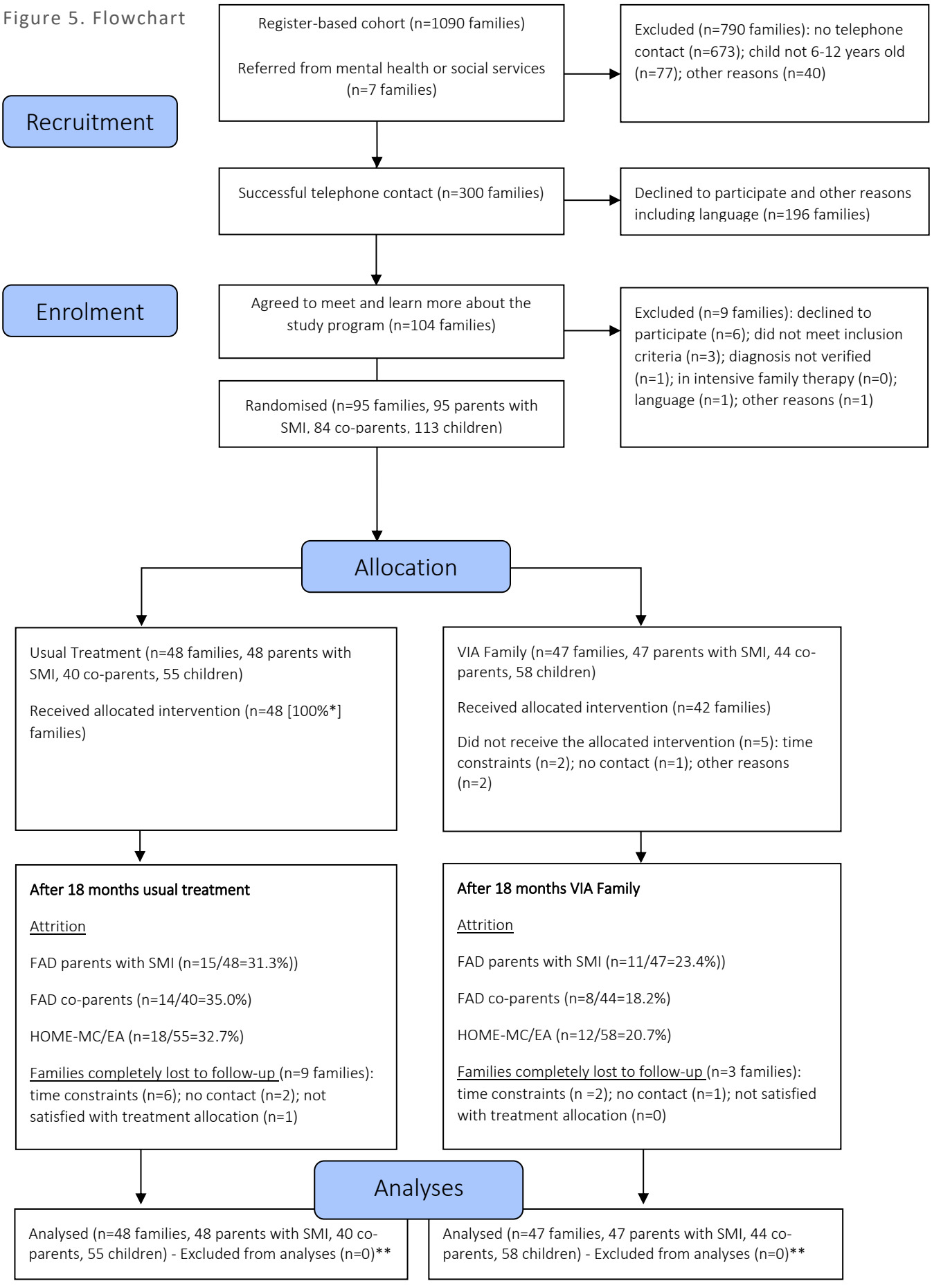
The flow of participants

By linking Danish nationwide health registers, we produced a cohort of 1090 families to whom we sent physical and electronic invitation letters with information about the research program. We reached 300 (27.5%) families by telephone, from which 111 (10.2%) agreed to meet to learn more about the implications of attending the research program. 104 (9.5%) parents with severe mental illness completed SCAN interviews of 95 (8.7%) parents with severe mental illness, and thus, 95 families with at least one child aged 6-12 years were included in this study. Forty-seven families (47 parents with severe mental illness, 44 co-parents, 58 children) were allocated to VIA Family and 48 families (48 parents with severe mental illness, 40 co-parents, 55 children) to usual treatment. See **Figure 5.**

Baseline characteristics of parents

Table 8 shows the baseline characteristics of participating families. Most parents with severe mental illness were female (24 [75%]). The average age of parents was approximately 42 years. The most frequent diagnosis for parents with severe mental illness was recurrent moderate to severe depression (58 [61%]), followed by bipolar affective disorder (25 [26%]), and schizophrenia spectrum disorder (12 [13%]).

Figure 5. Flowchart



Re-use of figure in **paper I**. Data are observed n (%). *Note:* FAD=McMaster Family Assessment Device. HOME-MC/EA=Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence. SMI=severe mental illness.

*Since no fidelity criteria were applied to usual treatment, it could not be characterised as discontinued. **Analyses were performed in the intention-to-treat population with missing data handled by multiple imputations, see *Methods* for further information.

Based on self-report, we found that approx. 6% of parents with severe mental illness had a comorbid substance use disorder (predominantly alcohol), and 37% had comorbidities, including eating disorders, ADHD, PTSD, substance use disorders and personality disorders. Daily functioning at baseline for parents with severe mental illness was characterised by high heterogeneity (PSP mean 60.9, SD 16.3) and a span from a minimum of 20 (hospitalisation) to a maximum of 90 (full recovery). Co-parents were predominantly male (60 [71%]). A total of 6 (7%) co-parents met the criteria for a lifetime severe mental illness, daily functioning PSP-scores were 77.53 (SD, 10.90), and close to 5% met the criteria for a substance use disorder, predominantly alcohol.

Table 8. VIA Family sample characteristics at baseline[17]

Parents with severe mental illness		Usual treatment (n=48)	VIA Family (n=47)	All parents with severe mental illness (n=95)
Age	Years	42.05 (6.55)	42.56 (5.63)	42.30 (6.08)
Gender	Female	35 (72.9%)	36 (76.6%)	71 (74.7%)
	Male	13 (27.1%)	11 (23.4%)	24 (25.3%)
Diagnostic group[1]	SZ	6 (12.5%)	6 (12.8%)	12 (12.6%)
	BP	12 (25.0%)	13 (27.7%)	25 (26.3%)
	rMDD	30 (62.5%)	28 (59.6%)	58 (61.1%)
Comorbidities[2]		18 (37.5%)	17 (36.2%)	35 (36.8%)
Substance misuse[1]	Alcohol	3 (6.3%)	3 (6.4%)	6 (6.3%)
	Cannabis, cocaine	..	..	≤ 2
Daily functioning	PSP	60.94 (16.28)	59.60 (14.79)	60.27 (15.48)
Participated as primary caregivers[3]		33 (68.8%)	32 (68.1%)	65 (68.4%)
Co-parents		(n=40)	(n=44)	All co-parents (n=84)
Age	Years	42.31 (5.84)	42.56 (5.18)	42.44 (5.47)
Gender	Female	13 (32.5%)	11 (25.0%)	24 (28.6%)
	Male	27 (67.5%)	33 (75.0%)	60 (71.4%)
Severe mental illness[1]	SZ/BP/rMDD	> 3	< 3	6 (7.1%)

[17] Re-use of table in paper I

Substance misuse[1]	Alcohol misuse	2 (5.0%)	2 (4.5%)	4 (4.8%)
	Cannabis, cocaine	..	..	≤ 2
Daily functioning	PSP	77.56 (10.81)	77.50 (11.11)	77.53 (10.90)
Participated as primary caregivers[3]		15 (37.5%)	15 (34.1%)	30 (35.7%)
Children		Usual treatment (n=55)	VIA Family (n=58)	All children (n=113)
Age	Years	9.70 (2.02)	9.78 (1.92)	9.74 (1.96)
Gender	Girls	28 (50.9%)	25 (43.1%)	53 (46.9%)
	Boys	27 (49.1%)	33 (56.9%)	60 (53.1%)
Mental disorders	DSM-IV or DSM-5[4]	21 (38.2%)	15 (25.9%)	36 (31.9%)
Families		(n=48)	(n=47)	All families (n=95)
Parents living together		18 (37.5%)	25 (53.2%)	43 (45.3%)
Education[5]	Primary or lower secondary	4 (8.3%)	9 (19.1%)	13 (13.7%)
	Upper secondary, vocational, or short-cycle tertiary	13 (27.1%)	12 (25.5%)	25 (26.3%)
	Bachelor's degree or higher	31 (64.6%)	26 (55.3%)	57 (60.0%)
Employment[5,6]		35 (72.9%)	34 (72.3%)	69 (72.6%)

Unless otherwise specified, data are mean (SD) or n (%). *Note*: BP=bipolar disorder. DSM= Diagnostic and Statistical Manual of Mental Disorders. PSP=Personal and Social Performance Scale. rMDD=recurrent major depressive disorder. SZ=schizophrenia spectrum disorder.

[1] Diagnoses were concluded at expert clinical conferences based on interviews with the Schedules for Clinical Assessment in Neuropsychiatry and classified according to the International Classification of Diseases' tenth revision.

[2] Self-reported diagnosis verified by hospital journals: substance misuse, eating disorder, ADHD, PTSD, or personality disorders.

[3.] The primary caregiver was the parent who gave information about the child with the criteria of knowing the child well and living with the child a minimum of 50% of the time.

[4] Criteria were met within the past eight weeks. Diagnoses were concluded at expert clinical conferences based on interviews with the Kiddie Schedule for Affective Disorders and Schizophrenia for school-aged children. Excl. Elimination disorder, simple phobia, and tics/Tourette's syndrome.

[5] Self-reported by the primary caregivers (n=95).

[6.] Any form of employment with no minimum working hours. Studying and absence from work (e.g., sick leave, maternity/paternity leave) were defined as employment.

Baseline characteristics of children

Children were equally distributed according to gender (53 [47%] girls, 60 [53%] boys) and age (mean, 9.74; SD, 1.96). 36 (32%) of participating children met the criteria for a present (symptoms

present within the previous eight weeks) mental disorder according to the DSM-IV or DSM-5 when interviewed and assessed with the K-SADS. Assessors sent referrals to child and adolescent mental health services at baseline in a total of 8 (8.4%) families and 18 (12.1%) families at 18-month follow-up assessments (referrals by case managers in VIA Family are listed in **Supplementary**).

Baseline characteristics of families and home environments

Out of 95 families, 43 (45%) families consisted of parents living together. Families were characterised by primary caregivers (n=95) having educational attainment equal to upper secondary, vocational, or short-cycle tertiary (25 [26%]) or bachelor's degree or higher (57 [60%]). Hence, only a few (13 [14%]) of primary caregivers had an educational attainment equal to primary or lower secondary education. 69 (73%) of family primary caregivers were employed or studying (no minimum working hours, including sick and maternity/paternity leave).

Levels of stimulation and support in the families' home environment were measured with HOME-MC/EA. The lowest levels were found in the homes of children of parents with a schizophrenia spectrum disorder (n=14; mean, 43.93; SD, 8.16). The standard deviation of 8.16 reflects a small sample size and high heterogeneity in measured levels of support and stimulation in the home environments in families in the context of schizophrenia spectrum disorder. Levels of support and stimulation in the home environment in families of parents with bipolar disorder was mean (SD): 48.70 (4.35), and in families of parents with recurrent major depressive disorder, it was 46.27 (5.76).

Lockdown during the COVID-19 pandemic

Table 9 shows how the societal lockdown during the COVID-19 pandemic impacted the VIA Family trial.

Table 9. VIA Family during the COVID-19 lockdown

Families active in VIA Family during the COVID-19 lock-down in Denmark 12.03.2020 – 09.05.2020	20 (42.55 %)
Families participating virtually in VIA Family during the COVID-19 lock-down (cut off one telephone or video call)	18 (18/20 = 90.0 %)

Treatment effects

Table 10 shows our main findings. Compared with usual treatment, VIA Family did not lead to significant improvement in family functioning for parents with severe mental illness (mean difference, 0.11; 95% CI, -0.10 to 0.31; *P*=.296), nor for co-parents (mean difference, -0.07; 95% CI, -027 to 0.13; *P*=.482). Levels of support and stimulation in the home environment improved, however, not significantly more for families allocated to VIA Family than usual treatment (mean difference, 1.79; 95% CI, -0.37 to 3.95; *P*=.104).

Table 11 shows user satisfaction results from the questionnaire Client Satisfaction Scale (Attkisson, 1996). User satisfaction was significantly better for parents with severe mental illness (mean difference, 3.58; 95% CI, 0.79 to 6.37; *P*=.013). Also higher, however not significantly, for co-parents (mean difference, 2.48; 95% CI, -1.20 to 6.16; *P*=.179). Exploratory outcome data can be found in the supplement.

Table 10. Estimated treatment effects on family functioning and levels of stimulation and support in the home environment[18]

FAD general family functioning[1]				
Parents with severe mental illness (n=95)	Usual treatment (n=48)	VIA Family (n=47)	Adjusted mean difference[2] (95% CI)	*P*-value
0 months	2.08 (0.50); n=44 (91.7%)	1.91 (0.51); n=42 (89.4%)	-	
18 months	1.77 (0.46); n=33 (68.8%)	1.82 (0.53); n=36 (76.6%)	0.11 (-0.10 to 0.31)	.296
Co-parents (n=84)	(n=40)	(n=44)		
0 months	1.91 (0.38); n=37 (92.5%)	1.89 (0.48); n=38 (86.4%)	-	
18 months	1.67 (0.36); n=26 (65.0%)	1.62 (0.47); n=36 (81.8%)	-0.07 (-0.27 to 0.13)	.482
HOME-MC/EA Levels of stimulation of support in the home environment[3]				
Children (n=113)	Usual treatment (n=55)	VIA Family (n=58)	Adjusted mean difference[4] (95% CI)	*P*-value
0 months	46.74 (5.85); n=53 (96.4%)	46.42 (6.07); n=55 (94.8%)	-	
18 months	45.86 (5.31); n=37 (67.3%)	47.17 (5.58); n=46 (79.3%)	1.79 (-0.37 to 3.95)	.104

Unless otherwise specified, data are observed unadjusted mean (SD) or n (%). *Note:* FAD=McMaster Family Assessment Device. HOME-MC/EA=Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence.
[1] FAD: lower scores, better family functioning.
[2] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, with missing data handled by multiple imputations.
[3] HOME-MC/EA: higher scores, higher levels of stimulation of support in the home environment.
[4] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and child's gender, including a random effect of family. Multiple imputations handle missing data.

[18] Re-use of table in paper I

Table 11. VIA Family user satisfaction and negative effects[19]

CSQ User satisfaction[1]			Adjusted mean difference[2] (95% CI)	*P*-value
Parents with severe mental illness (n=95)	(n=48)	(n=47)		
18 months	23.55 (6.11); n=31 (64.5%)	27.19 (4.14); n=37 (78.7%)	3.58 (0.79 to 6.37)	**.013**
Co-parents (n=84)	(n=40)	(n=44)		
18 months	24.07 (5.27); n=14 (35.0%)	26.55 (3.59); n=33 (75.0%)	2.48 (-1.20 to 6.16)	.179
NeQ Negative effects				
Parents with severe mental illness (n=95)	(n=48)	(n=47)		
Negative effects due to allocated treatment	1.80 (2.71); n=35 (72.9%)	1.78 (2.75); n=37 (78.7%)	-0.03 (-1.28 to 1.22)	.960
Impact of negative effects due to allocated treatment	2.10 (0.64); n=18 (37.5%)	1.77 (0.98); n=20 (42.6%)	-0.12 (-0.96 to 0.73)	.777
Negative effects due to other causes	2.77 (2.94); n=35 (72.9%)	1.46 (1.98); n=37 (78.7%)	-1.33 (-2.44 to -0.22)	**.019**
Impact of negative effects due to other causes	2.25 (0.91); n=23 (47.9%)	2.12 (0.79); n=21 (44.7%)	-0.12 (-0.80 to 0.55)	.710
Co-parents (n=84)	(n=40)	(n=44)		
Negative effects due to allocated treatment	0.22 (0.64); n=27 (67.5%)	0.23 (0.60); n=35 (79.5%)	-0.02 (-0.32 to 0.29)	.901
Impact of negative effects due to allocated treatment	0.75 (0.96); n=4 (10.0%)	0.60 (0.55); n=5 (11.4%)	0.87 (-0.91 to 2.65)	.329
Negative effects due to other causes	0.11 (0.32); n=27 (67.5%)	0.89 (1.95); n=35 (79.5%)	0.86 (0.20 to 1.53)	**.012**
Impact of negative effects due to other causes	0.33 (0.58); n=3 (7.5%)	1.18 (0.80); n=11 (25.0%)	0.87 (-0.91 to 2.65)	.329

Unless otherwise specified, data are observed unadjusted mean (SD) or n (%). *Note:* CSQ=Client Satisfaction Questionnaire. NeQ=Negative Effects Questionnaire.

[1] CSQ: higher scores, better user satisfaction

[2] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.

[3] NeQ: higher scores, more negative effects

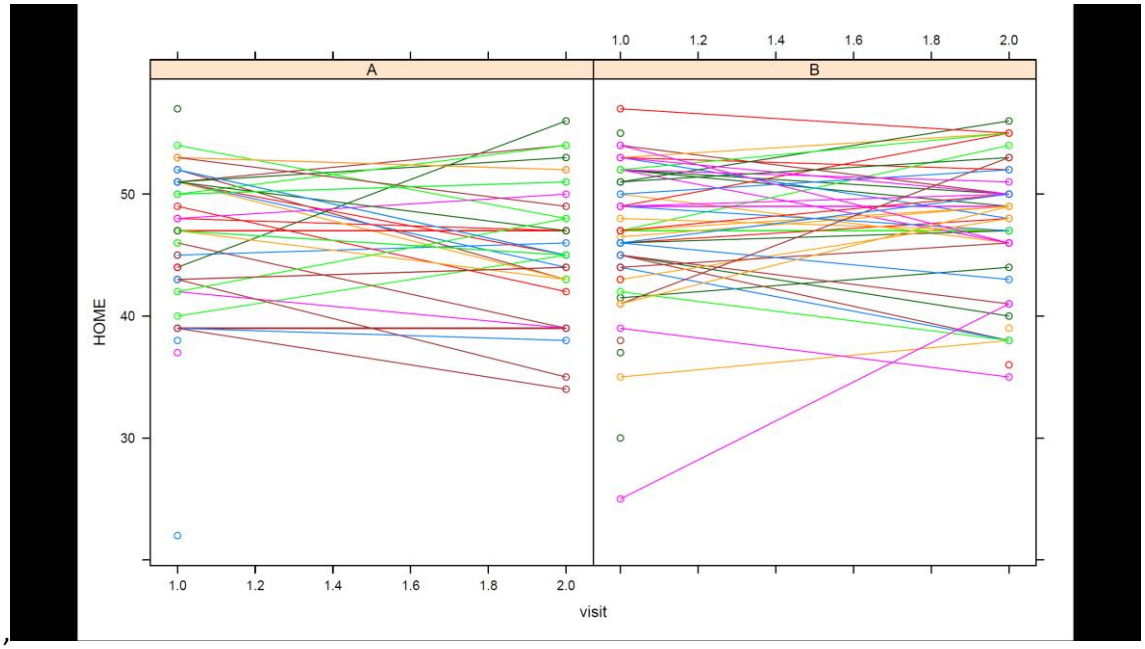
[19] Re-use of table in paper I

Sensitivity analyses

Sensitivity analyses of effects on family functioning reported by parents with severe mental illness and co-parents confirmed the main findings. Complete case analyses approximated a significant mean difference (2.12 [95% CI -0.06 to 4.29], *P*=.056), indicating that our multiple imputations handling missing data considered outliers at baseline with low HOME scores that were lost-to-follow-up assessments. Removing outliers impacted the estimate of treatment effects, drawing the result towards the null hypothesis (1.45 [-0.64 to 3.54], *P*=.173). The per-protocol analysis confirmed the main findings (1.92 [95% CI -0.29 to 4.13]; *P*=.089) and further moved the estimates in favour of VIA Family. See **paper I** for the full description of sensitivity analyses.

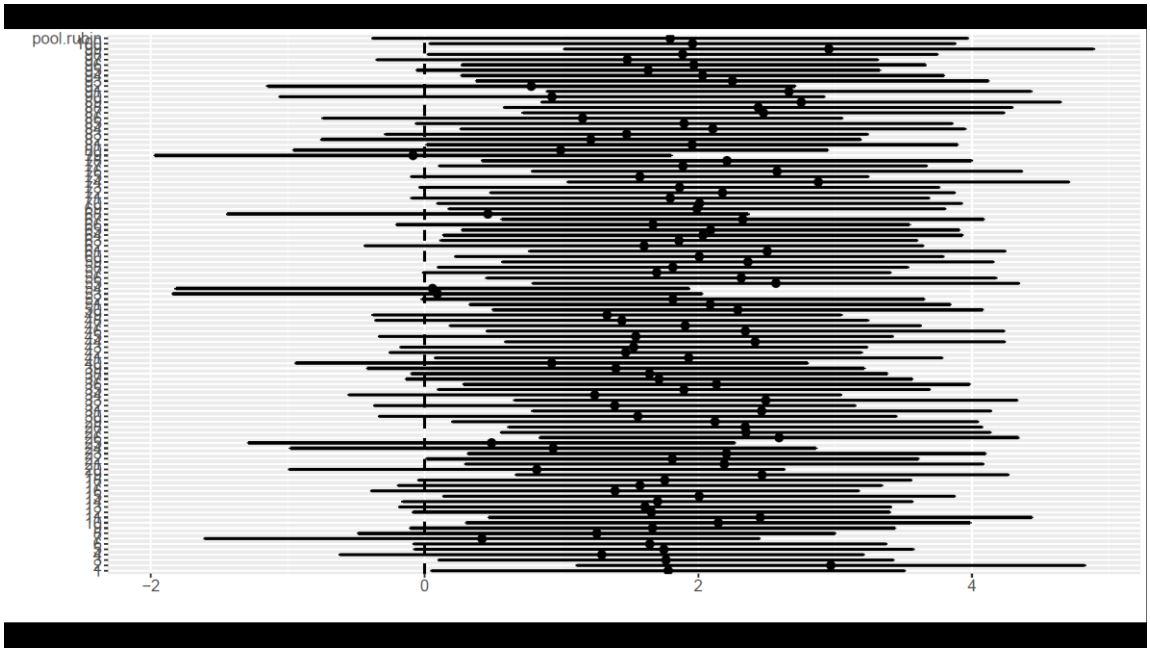
Outliers can be seen in **Figure 6,** which visualises data with group A=usual treatment and B=VIA Family. Spaghetti plots are ideal for visualising dependent data across two time points, such as children's home environments. **Figure 7 i**llustrates our primary analysis of treatment effects on HOME-EA handled with multiple imputations. Both figures illustrate the variance impacted by outliers and the loss to follow-up of those with low HOME scores at baseline.

Figure 6. Spaghetti plots visualising HOME-MC/EA



Scores at 0 months (baseline) and after 18 months of intervention (follow-up). A=Usual treatment, B=VIA Family. An individual colour represents each child.

Figure 7. Forest plot multiple imputations in the analysis of HOME-MC/EA



The forest plot illustrates 100 imputed datasets of estimated treatment effects on levels of support and stimulation in the home environment measured with the HOME Inventory (HOME-MC/EA) at the end of 18-month VIA Family Intervention compared with usual treatment.

Results paper II

Association of Maternal and Paternal Personality Disorders With Risk of Mental Disorders in Children. A Nationwide, Register-Based Cohort Study of 1,406,965 Children

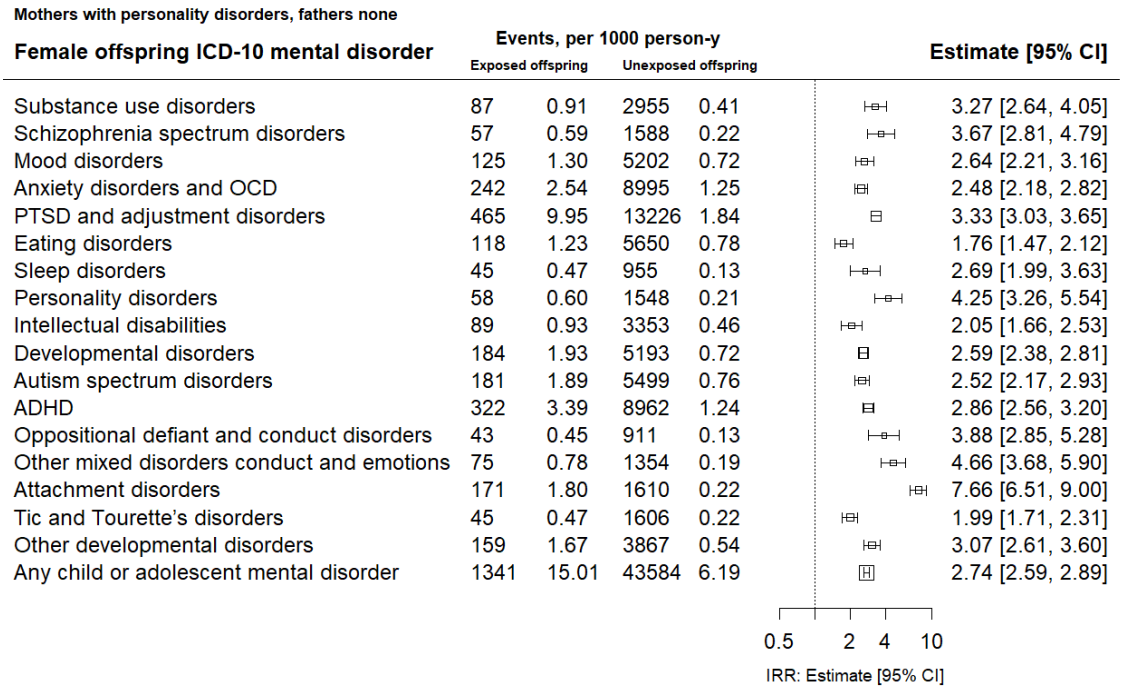
Cohort characteristics

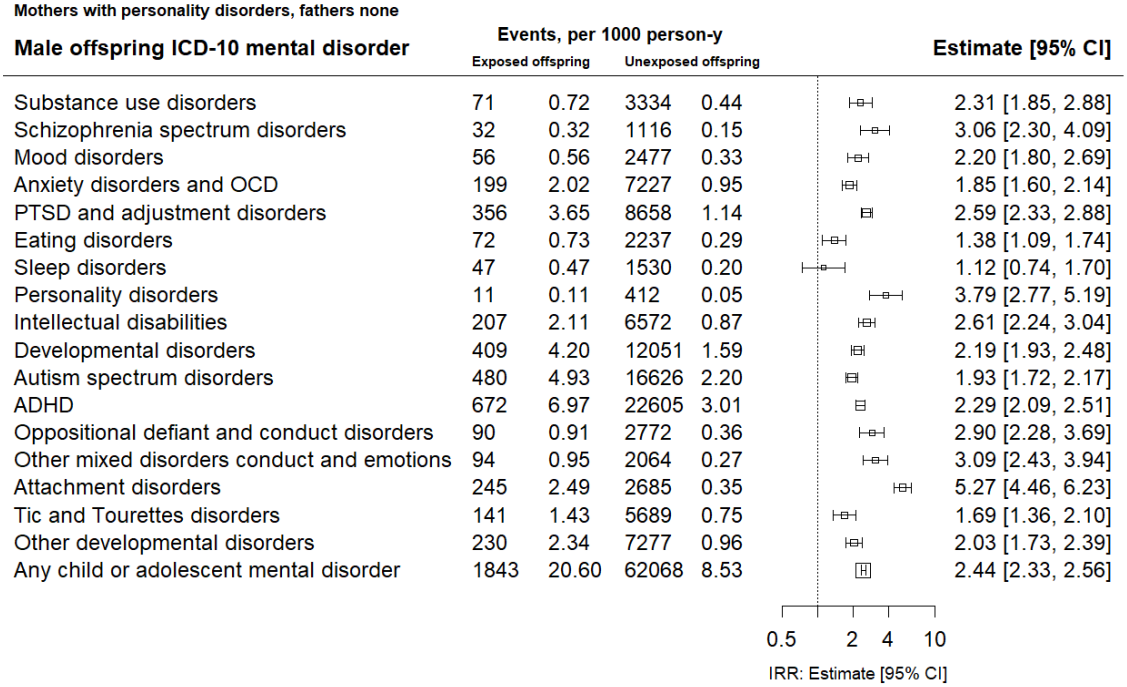
In our cohort of 1,406,965 children, 35,484 (2.5%) children were born to one or two parents diagnosed with a personality disorder. A total of 108,853 (7.7%) children (44,933 [6.6%] girls and 63,920 [8.9%] boys) developed a mental disorder during follow-up. The maximum number of follow-up years was 15,057,110, which produced 10.7 years at risk.

Relative risk

For girls and boys combined, exposure to two parents, mothers only, or fathers only with a personality disorder was associated with up to 4-times higher risk of mental disorder (IRR, 3.69 [95% CI, 3.15-4.33]; IRR, 2.61, [95% CI, 2.52-2.71]; IRR, 2.17 [95% CI, 2.06-2.28]). **Figure 8** and **Figure 9** illustrate IRRs for female and male offspring in the context of both maternal and paternal personality disorders. Both female and male offspring had significantly increased risks of mental disorders across the full spectrum of ICD-10 mental disorders. Substance misuse markedly moderated the risk of mental disorders in children but did not explain the association (**Table 13**), and sensitivity analyses adjusted confirmed our main findings.

Figure 8. Maternal personality disorder and risk of mental disorders in female and male offspring[20]

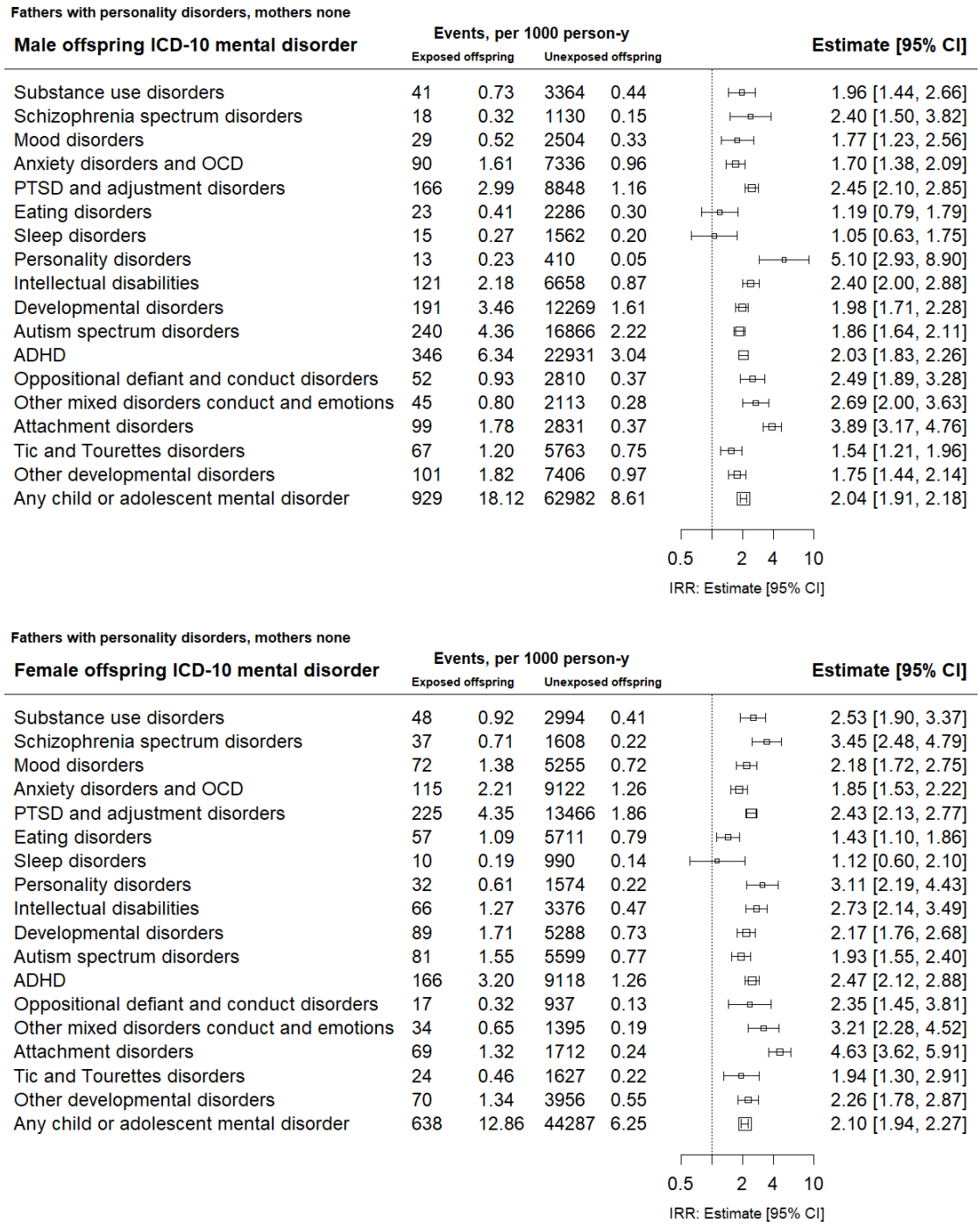




Incidence rate ratios (IRR) are analysed by Poisson regression. Analyses were adjusted for offspring age, sex, and calendar period. Estimates are visualised on a log scale. Square markers represent IRR, and horizontal lines represent 95 % confidence intervals. The size of square markers indicates the size of combined events.

[20] Re-use of figure in paper II

Figure 9. Paternal personality disorder and risk of mental disorders in female and male offspring[21]



Incidence rate ratios (IRR) are analysed by Poisson regression. Analyses were adjusted for offspring age, sex, and calendar period. Estimates are visualised on a log scale. Square markers represent IRR, and horizontal lines represent 95 % confidence intervals. The size of square markers indicates the size of combined events.

[21] Re-use of figure in paper II

Table 13. Substance use disorders[22]

	Offspring any mental disorder before age 18. IRR (95% CI)
Paternal personality disorder (PPD) and substance use disorder	
PPD and substance use disorder	2.23 (2.07 - 2.40)
PPD, no substance use disorder	1.91 (1.79 - 2.04)
No PPD, substance use disorder	1.60 (1.55 - 1.65)
No PPD, no substance use disorder	1
Maternal personality disorder (MPD)	
MPD and substance use disorder	2.97 (2.76 - 3.19)
MPD, no substance use disorder	2.42 (2.33 - 2.52)
No MPD, substance use disorder	1.84 (1.77 - 1.91)
No MPD, no substance use disorder	1
Incidence Risk Ratios (IRR) for any psychiatric disorder in offspring with a parent with substance misuse and a diagnosed personality disorder diagnosed before the child's birth. Parents were diagnosed before the birth of the child. Children were followed from age 0-18 in 1995 to ultimo 2016. Substance use disorders diagnostic codes: ICD10 = F1; ICD8 = '303', '304', '291', '5711', '57109'. Any parental psychiatric disorder: ICD8 = 290-315; ICD10 = F. Our model was adjusted for sex, age, calendar time and father unknown.	

Table 14. Parental personality disorder subtypes and risk of mental disorders in offspring[23]

n, IRR 95% CI	Mother	Father
Reference group No personality disorder	106,205 1	107,770 1
F60.0 Paranoid personality disorder	27 2.78 (1.90-4.05)	26 1.50 (1.02-2.20)
F60.1 Schizoid personality disorder	25 2.00 (1.35-2.97)	31 1.61 (1.13-2.29)
F60.2 Dissocial personality disorder	44 3.39 (2.52-4.56)	173 2.31 (1.99-2.69)
F60.3 Emotionally unstable personality disorder	1291 2.89 (2.73-3.05)	284 2.42 (2.16-2.72)
F60.4 Histrionic personality disorder	29	22

[22] Re-use of supplementary table in paper II

[23] Re-use of supplementary table in paper II

	1.95 (1.36-2.81)	2.02 (1.33-3.07)
F60.5 Obsessive personality disorder	37 2.55 (1.85-3.52)	
F60.6 Anxious-avoidant personality disorder	224 2.00 (1.75-2.28)	59 1.59 (1.23-2.05)
F60.7 Dependent personality disorder	137 2.29 (1.94-2.71)	30 1.62 (1.13-2.32)
F60.8 Other specific disorder of personality structure*	106 2.42 (2.00-2.93)	96 1.99 (1.63-2.43)
F60.9 Disorder of personality structure, unspecified	589 2.33 (2.15-2.53)	284 1.96 (1.74-2.20)
F61.0 Disorder of personality structure, combined and other type	125 2.41 (2.02-2.87)	64 2.22 (1.73-2.83)

Incidence rate ratios (IRR) of psychiatric disorders in offspring born to parents diagnosed personality disorder subtypes. Parental subtypes of personality disorders according to the International Classifications of Diseases 10th edition. All children were born between January 1st, 1995- December 31st, 2016. Estimates of IRR and 95 % CIs were obtained with Poisson regression models adjusted for the child's age, sex and calendar time. Since our cohort comprises less than five fathers diagnosed with F60.4 and F60.5, they are combined in this table. ADHD, Attention-deficit/hyperactivity-disorders; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder. * Incl. Narcissistic and passive-aggressive personality disorder

Table 14 shows that parental emotionally unstable personality disorder in mothers (IRR, 2.89 [95% CI, 2.73-3.05]) and fathers (IRR, 2.42 [95% CI, 2.16-2.72]) together with dissocial personality disorder in mothers (IRR, 3.39 [95% CI, 2.52-4.56]) were associated with a higher risk of mental disorder in children than nonexposed children. Considering our second hypothesis of finding a higher risk associated with dissocial and emotionally unstable personality disorder, our findings are highlighted in **Table 14** with the green colouring of relevant table cells. In alignment with our secondary hypothesis, maternal anxious-avoidant personality disorder (IRR, 2.00 [95% CI, 1.75-2.28]) had a lower IRR than maternal, both dissocial and emotionally unstable personality disorder. Maternal dependent personality disorder (2.29 [1.94-2.71]) was associated with a lower IRR than maternal emotionally unstable personality disorder but not maternal dissocial personality disorder. Paternal anxious-avoidant personality disorder (1.59 ([1.23-2.05]) was associated with a lower risk than paternal emotionally unstable personality disorder but not lower than paternal

dissocial personality disorder. All in all, risk is associated with all parental personality disorders with IRRs from 1.5 to 3.4, and our estimates indicate that personality disorders characterised by impulsivity and emotion dysregulation might be associated with the highest risk.

Absolute risk

At age 18, the absolute risk was 34.1% (95% CI, 33.0-35.1), more than twice the risk in nonexposed children: 15.2% (95% CI, 15.1 to 15.3). **Figure 10** illustrates cumulative incidence in girls and boys with one or two parents with a personality disorder compared with nonexposed children. At age 18, girls with one or two parents with a personality disorder had an absolute risk of 33.0% (95% CI, 31.5 to 34.6), whereas nonexposed girls had an absolute risk of 14.7% (95% CI, 14.5 to 14.8). The absolute risk in boys with one or two parents with a personality disorder was 35.1% (95% CI, 33.7 to 36.5) compared with nonexposed boys at a 15.7% (95% CI, 15.5 to 15.8) absolute risk.

Attachment disorders

At age 18, having one or two parents with a personality disorder was associated with an absolute risk of attachment disorder of 3.8% (95% CI, 3.43-4.16) in exposed offspring compared with 0.6% (95% CI, 0.54-0.57) in the background population. Maternal personality disorder was associated with an increased risk of attachment disorders in girls: IRR, 7.66 (95% CI, 6.51-9.00). Likewise, the risk of attachment disorders was increased for sons of mothers with a personality disorder: IRR, 5.27 (4.46-6.23). Also, paternal personality disorder was associated with an increased risk of attachment disorders in girls: IRR, 4.63 (3.62-5.91) and in boys: IRR, 3.89 (3.17-4.76).

Figure 10. Cumulative incidence of mental disorders in offspring[24]

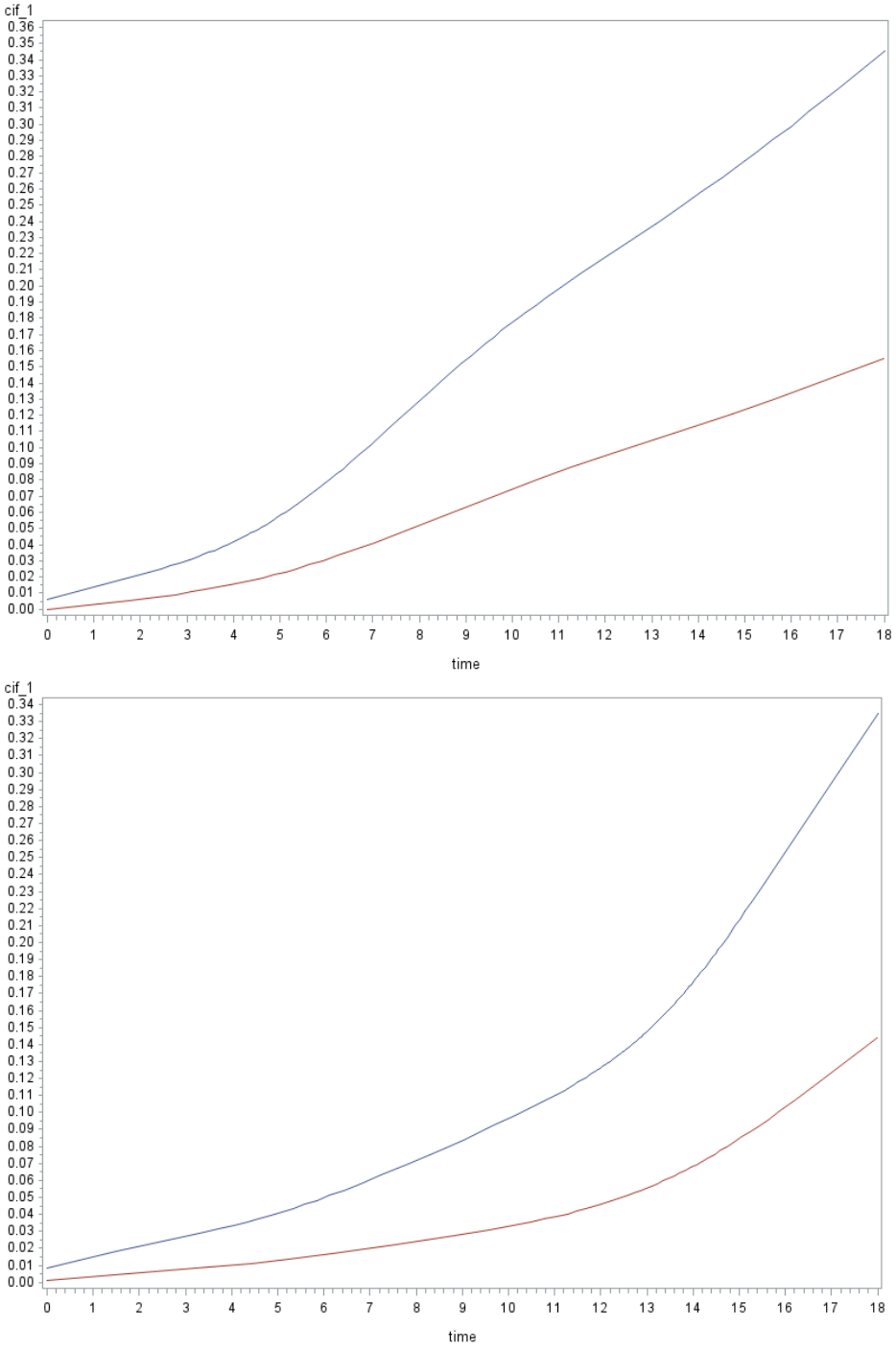


Figure 9 illustrates the cumulative incidence of any mental disorder. The x-axis represents the child's age from 0 to 18th birthday. The y-axis illustrates absolute risk as cumulative incidence over time. **The top graph (female offspring) and the bottom graph (male offspring) demonstrate the** incidence of mental disorders in offspring. Personality disorders blue line, and unexposed children red line. All children were followed from birth until either their 18th birthday, diagnosis of any mental disorder was registered, or until death, immigration, disappearance or until December 31st, 2016.

[24] Re-use of supplementary figure in paper II.

Discussion

Due to the differences in population and study design, I will first discuss the findings of each paper sequentially. Then, I will discuss the results of the two papers combined, considering dimensional psychopathology and parenting.

Paper I

Compared with usual treatment, we did not find superior effects of VIA Family on family functioning or levels of support and stimulation in the home environment. However, we cannot rule out a type II error and a clinically relevant effect on levels of support and stimulation in the home environment. User satisfaction (effectiveness and acceptability) reported by parents with severe mental illness allocated to VIA Family were better than those with severe mental illness assigned to usual treatment. Sensitivity analyses confirmed our main findings.

Recruiting families was challenging, which aligns with previous studies recruiting for preventive interventions (Havinga et al., 2021) and is possibly related to stigma, shame and parental overburden (ibid.). We primarily recruited families from a register-based cohort, and our procedure might have led to sample bias, e.g., by excluding those unable to speak Danish and those with secret addresses or telephone numbers (discussed in detail in **paper I**). Researchers and team members in the VIA Family were positively surprised by the level of recovery many parents showed. Daily functioning for parents with severe mental illness was characterised by significant variance and spanned from hospitalisation to full clinical recovery. In our study sample, 7% of co-parents met the lifetime severe mental illness criteria reflecting non-random mating, also

found in a nationwide Danish clinical cohort study (Greve et al., 2021). Additionally, in our study, 32% of children met the DSM-IV or DSM-5 mental disorder diagnosis criteria, and one in ten families had referrals sent to child protection or social services. I hypothesise that families with multiple family members with a mental disorder and referrals sent to child protection and social services are *"families with complex needs".* Further, I hypothesise that these families need long-term tailored support.

In the following, I will contextualise our findings concerning comparable studies. First, in the context of case-manager-based preventive interventions for COPMI, and second, in the context of family-based preventive interventions for children of parents with severe mental illness.

Case-manager-based preventive interventions for COPMI

Based on my systematic and pragmatic literature review, I found one intervention providing case management: the *preventive essential care management* program was offered to families of parents with depression and other axis one psychopathology and was studied in an RCT in the Netherlands. Similar to our findings, *preventive essential care management* did not find effects on levels of stimulation and support in the home environment measured with HOME (Wansink et al., 2015, 2016). There are central differences in treatment components, eligibility criteria and sample characteristics when comparing *preventive essential care management* with VIA Family. First, *preventive essential care management* does not provide treatment elements but coordinates families' use of already established and available services. Second, inclusion criteria for the *preventive essential care management* involve all diagnostic groups of parents currently in treatment in mental health services, that (both) parents agree to engage in the intervention, and

that the family meets a set of cut-offs of indication for treatment defined as a minimum of 3 out of 16 risk markers (e.g., sole caregiver or the child having mental health problems). Third, HOME scores were high and indicated ceiling effects in the Dutch study (ibid.), which indicate differences in sample characteristics and challenge the comparison with our findings.

Preventive interventions for children of parents with affective disorders

A vast body of research has studied preventive interventions for COPMI, including children of parents with affective disorders, and meta-analyses have established effectiveness in reducing child psychopathology (Havinga et al., 2021; Lannes et al., 2021). To interpret our findings, I will consider RCTs that measure the effects on family functioning and the home environment of family-based interventions directed at children of parents with severe mental illness.

Family Talk is a manualised intervention developed for parents with depression (Beardslee et al., 2003; Gladstone et al., 2015), is implemented in Sweden (Strand & Meyersson, 2020), Finland (Solantaus & Toikka, 2006), has been studied in England (Beardslee et al., 2003; Focht-Birkerts & Beardslee, 2000), Greece (Giannakopoulos et al., 2021), and is currently tested in RCTs in Ireland and Denmark (Furlong et al., 2021; Nielsen et al., 2023). Family Talk and a briefer version, *Let's Talk Children*, was found to be effective for parents with affective disorders in improving family functioning measured with FAD (Giannakopoulos et al., 2021); however, with the limitation that no control group was involved (ibid.).

A Chinese RCT study of a *multiple family therapy* intervention for parents with depression did not find an improvement in family functioning measured with FAD (Ma et al., 2023). However, they

did find an effect for the subgroup of parents not treated with anti-depressant medicines, which authors interpret to suggest that *multiple family therapy* was effective in improving family functioning in families of parents with milder depression and better functioning at baseline (ibid.). To interpret their findings, I hypothesise that families of parents with more severe depression have complex needs that demand long-term, tailored, and multicomponent intervention.

Preventive interventions for children of parents with psychotic disorders

No evidence is established considering interventions for children of parents with psychotic disorders (Lannes et al., 2021) nor interventions supporting parents with psychosis (Radley et al., 2020). Parents with psychosis have reported a need for support in talking with their children about their mental illness beyond the 6-7 sessions of the manualised Family Talk (Strand & Meyersson, 2020), which I hypothesise suggests a need for interventions with a longer duration, which might reflect that families in the context of parental psychotic disorders are often *families with complex needs.*

Since no trials have studied preventive intervention for children of parents with psychotic disorders, it would be beneficial to investigate whether children of parents with psychosis benefit from manualised parenting programs such as Triple P and whether Triple P works sufficiently for *families with complex needs* regardless of parental diagnosis., a case-series study of the intervention The Triple P Self-Help Workbook for ten parents with psychosis found a “clinically significant change (>25% improvement) in mental health, parenting and child behaviour measures post-intervention for the 50% who completed all ten sessions and improvements were maintained at 3 and 6 months follow up” (Wolfenden et al., 2022). Findings further suggested that Triple P

could help decrease psychotic symptoms by improving family functioning and that Triple P was perceived as acceptable and helpful to parents with psychosis (ibid.). Replicating such findings, if feasible in randomised designs, could help provide valuable knowledge regarding children of parents with psychotic disorders.

Strengths and limitations

The main strengths of our study in **paper I** were the thorough assessor-masked assessments, the low attrition rate, and the confirmation of parental diagnoses at expert clinical conferences before inclusion into the study. The main limitation of this study is that it was underpowered regarding subgroup analysis and estimation of effects on levels of support and stimulation in the home environment. Further, the lockdown during the COVID-19 pandemic affected our study program and the interventions and significantly impacted families' lives in Denmark, which challenges the ecological validity of our findings.

Paper II

Main findings

We found that maternal and paternal personality disorders were associated with a 2 to 3.5 times higher risk of mental disorders in children compared with nonexposed children. The risk was increased across the full spectrum of ICD-10 mental disorders, and both boys and girls were at increased risk. The risk was highest when both parents had a personality disorder. Different parental ICD-10 personality disorder subtypes were similarly associated with the risk of mental disorders in offspring.

The risk of mental disorders in children was 2 to 2.5 enfolded in association with mothers and fathers with personality disorders, which is similar to the estimated risk of mental disorders in children of parents with severe mental illness in register-based and clinical cohort studies (Ayano et al., 2019, 2021b, 2021a; Rasic et al., 2014; Shayestehfar et al., 2023; Thorup et al., 2018). These findings could reflect shared genetic liability between these disorders. E.g., a Swedish register-based study indicated notable heritability in personality disorders such as borderline personality disorder (Fatimah et al., 2019), and findings from a large-scale genome-wide association study found shared genetics overlap of borderline personality disorder with SZ, BP and MDD (Bipolar Disorders Working Group of the Psychiatric Genomics Consortium et al., 2017). We found that risk was increased across the full spectrum of ICD-10 disorders, including emotional, behavioural, affective, psychotic, and neuropsychiatric disorders, which might also reflect pleiotropy and shared genetic liability within mental disorders (Derks et al., 2022; Paananen et al., 2021; Rasic et al., 2014; The Brainstorm Consortium et al., 2018).

We found an absolute risk at age 18 of being diagnosed with a mental disorder in Danish children at 15%, similar to previous estimates of the Danish population (Dalsgaard et al., 2019). Children of parents with a personality disorder were at a twofold risk (34%). The highest risk (3.5 times higher) was associated with having two parents with a diagnosed personality disorder, confirming previous register-based and clinical studies also found the highest risk associated with two parents with a mental illness compared with having one affected parent (Gottesman et al., 2010; Paananen et al., 2021; Suess et al., 2022; Thorup et al., 2018). We found that the risk of a mental disorder was increased in both female and male offspring and associated with maternal and paternal personality disorders, similar to risk findings in children of parents with a history of inpatient psychiatric treatment (Paananen et al., 2021).

The risk was increased across parental personality disorder subtypes with no clear pattern of any personality disorder subtype causing a higher risk than the other. We did find a higher risk associated with parental emotionally unstable personality disorder compared with anxious avoidant personality disorder, suggesting that the group of children of parents with emotionally unstable and impulsive symptoms may be at high risk in alignment with literature findings evidence that impairment in parenting in the domains of emotion regulation, mentalisation, which are essential for healthy child development (Adshead, 2015). Further, impulsivity traits might be associated with comorbid conditions such as ADHD and could explain the higher risk in offspring due to shared genetic variants (Pingault et al., 2023). Aligned with this hypothesis, a meta-analysis found an increased risk of ADHD in children of parents with antisocial personality disorder (Robinson et al., 2022).

When interpreting our findings, we must consider potential detection bias and potential confounders such as early life stress, birth complications, exposure to toxins, substances, etc., that we did not adjust for in this study. Detection bias means that parents who have contact with mental health and social services have a higher chance of professionals writing referrals to child and adolescent mental health services and social services that can evaluate the child's needs. E.g., we found that the risk of attachment disorders in children of parents with personality disorders was remarkably high, especially for daughters of mothers with personality disorders, which can be both interpreted in light of impairment in the parent-child relationship due to emotional dysregulation and impulsivity affecting the offspring (Adshead, 2015), and also in light of shared genetics between parent and offspring. Besides gene-environment interaction, we must consider the impact of stigma around personality disorders concerning parenting (R. Wilson et al., 2018). Since we did not have variables considering parenting, family emotional climate, early life stress or trauma, it is difficult to detangle or conclude the underlying mechanisms at play. However, we can highlight the urgent need for preventive and early intervention measures.

Strengths and limitations

The main strength of this study was the large sample size with no loss to follow-up and the nearly complete and accurate linkage of children with their legal parents. A further strength of our study is that it poses no selection or sample bias and that we allowed for comorbidities in parents. Concerning limitations, first, we did not preregister the statistical analysis plan for this study, which could have improved the quality of the reporting of our findings. Second, we did not access the adoption register to establish a linkage between biological parents and their children. Future studies could benefit from undertaking analysis of biological relationships, preferably including

genetic information to enable adjusting for the shared genetics variants between parent and offspring to correctly interpret associations between parental characteristics such as mental illness and child outcomes (Jami et al., 2021; Pingault et al., 2018, 2023). We could not adjust for potential mediators of risk, including birth complications, gestation age and low birth weight, since we did not have access to such variables, and it was not in consideration in the design phase of the study.

Danish nationwide registers – strengths and limitations

A strength of this thesis is the use of Danish nationwide health registers, which have good quality with no loss to follow-up (Erlangsen & Fedyszyn, 2015). Another strength of this thesis is the inclusion of fathers, an often overlooked and understudied area within research on COPMI (Leijdesdorff et al., 2017; Scarlett et al., 2023). A limitation of the combined findings in this thesis is generalising results to countries not comparable to the Danish welfare state free-of-charge health, educational and social services. This thesis has studied children of parents who have had contact with secondary sector mental health services in Denmark. This thesis has not addressed parental mental illness treated in the primary sector, such as private psychologists, private psychiatrists, or psychopharmacological treatment issued by general practitioners and those who never seek help. Hence, there is a limitation to the generalisability of our findings to such contexts as the primary sector.

Dimensional psychopathology

Psychiatric disorders are not based on complete theories of aetiology, comorbidity within mental disorders is prevalent, and individuals are often diagnosed with different mental disorders over time (Plana-Ripoll et al., 2019). The categorical approach to understanding and treating mental illness is insufficient, and transdiagnostic frameworks have been proposed (van Os et al., 2019). Further, there is a call for genome-wide analyses and research into epigenetics to understand gene-environment interactions in the aetiology of mental disorders to improve the classification and treatment of mental disorders (Alameda et al., 2022; Maj, 2020; Uher, 2014b; van Os et al., 2019). These perspectives are reflected in current developments in the ICD and DSM classifications of mental disorders: in the DSM-5 represented by the alternative model (Bohus et al., 2021) and in the ICD-11 by a shift from a categorical to a dimensional classification of psychotic, autistic, and personality disorders. Further, these perspectives align with the developmental psychopathological framework introduced at the beginning of this thesis, and together, these perspectives imply that development must always be considered when conceptualising mental disorders. The timing of early life stress and the timing of preventive efforts are essential. The complexity demands various research disciplines since no single theory or study can account for everything.

Parenting

There is a remarkable heterogeneity in prognosis, recovery processes and life for people who experience severe mental illness, including personality disorders. This is important when considering parenting, family life, and the home environment. We need a coherent and adequate conceptualisation of parenting to understand the mechanisms at play in how family functioning

and the environment mediate the risk in offspring. The following perspectives draw on my clinical experiences working with families in the context of parental severe mental illness.

Being a parent is demanding and stressful for most parents (Pontoppidan et al., 2018). Suppose a parent is struggling with severe mental illness, either episodically or chronically, perhaps with associated cognitive deficits. In that case, there is a high chance that parenting is too demanding and causes stress, which can be reflected in experiences of caregiver helplessness among parents with severe mental illness and their co-parents (Rohd et al., 2023), which is likely related to parental over-burden, shame and stigma about parenting and severe mental illness (Harries, Smith, Gregg, & Wittkowski, 2023; Havinga et al., 2021; R. Wilson et al., 2018).

Family functioning and parenting skills are negatively affected by parental psychopathology, much dependent on symptom severity and parental psychosocial functioning (L. E. Campbell et al., 2018; Shalev et al., 2019). Besides symptoms and potential side-effects from medication, cognitive impairment such as difficulties with executive functioning (e.g., planning and performing daily activities) and lack of social network and comorbidities, including anxiety, personality disorders, and substance use disorders, are likely to challenge parenting.

Parenting and affective disorders

The association between maternal depression and child functioning depends on depression chronicity (long duration and frequent episodic recurrence) and severity (Brennan et al., 2000; Sutherland et al., 2022) and is modified by maternal sensitive parenting and sociodemographic risk factors that are interrelated with depressive symptom severity (S. B. Campbell et al., 2007). Lack of

sleep and disturbance of diurnal rhythms are related to the onset of affective illness episodes (Li et al., 2016). In contrast, parenthood, associated with sleep disruptions, especially in the perinatal period (Fu et al., 2023), involves the risk of catalysing or worsening affective disorders. Hence, the parent's access to social support and resources, such as grandparents and other secondary caregivers, is essential.

Parenting and psychotic disorders

More than one in three people with psychosis have children (Radley, Barlow, et al., 2022a), and qualitative research finds parents with psychosis express parenthood as a valued aspect of identity (Harries, Smith, Gregg, Allott, et al., 2023; Radley, Barlow, et al., 2022b). However, parenting is demanding and, at times, stressful for most caregivers (Pontoppidan et al., 2018), and a cyclic relationship between parental stress and positive psychotic symptoms is theorised (Radley, Barlow, et al., 2022b). Mothers with schizophrenia are more often single caregivers than mothers in the background population (Ranning et al., 2016), which adds to the demands of a parent and increases the risk of stress and parental overburden.

There is a remarkable heterogeneity in the prognostic course in psychotic disorders. A meta-analysis found a clinical recovery rate of approximately 21% among individuals with first-episode schizophrenia (Hansen et al., 2023). Research indicates that people with psychotic disorders who have become parents on a group level are better functioning and have better socio-economic status than those with a psychotic disorder that have not become parents (Radley, Barlow, et al., 2022a).

Active psychotic symptoms can take up parents' attention, and parents with psychotic disorders have reported withdrawing from their family and children, aiming to spare their children from experiencing parental distress or unusual behaviour (Radley, 2022; Radley, Barlow, et al., 2022b). Further, symptoms of anhedonia, fatigue and depression are likely to decrease affective responsiveness and limit the parent's social life, affecting the whole family's social life, especially the children. Similarly, in episodes of MDD, the parent's symptomatology is also associated with withdrawal and decreased affective responsiveness. Further, social withdrawal in the broader social context may imply that children do not see their parents in social interaction with adult peers. They might see their parent actively avoiding social gatherings such as school meetings, school concerts, etc. and will not learn how to participate in these events through role-modelling. Hence, children might lack a role model for making and keeping friendships with peers and might not have sufficient help taking the initiative and facilitating play dates. School-aged children (6-12 years) need their parents' support, guidance, and role modelling in forming their own lives socially across contexts. This further adds to the importance of other parental figures and secondary caregivers providing protective factors as alternative role models.

Parenting, emotion regulation and attachment

Emotional expression in the family, emotion regulation in parents, and children's adverse life events are partial mediators in the association between parental severe mental illness and children's risk of mental disorders (Fahrer et al., 2022; Loechner et al., 2020). Severe symptoms can reduce the caregiver's ability to mentalise their child's state of mind and can limit parents' ability to help their child regulate emotions. The child is thereby not helped, mirrored by its own emotions, which negatively affects the child's emotional development. If an insecure attachment

develops, this attachment pattern between the child and the primary caregiver will likely be a decisive factor in how the child forms relationships with other adults and peers. Supporting this notion, a Norwegian population-based study found that parental cluster B personality disorder symptoms during early childhood predicted decreased social skills in school-aged children (Wichstrøm et al., 2022). If not supported and helped in developing attachment and friendships with peers, this will, over time, be a vulnerability, which elevates the risk of cumulative stress for personality traits to be exaggerated and a potential risk of developing mental illnesses.

Secure attachment is the fundamental core of the individual for building resilience, meaning the ability to cope with adversities and negative life experiences (Adshead, 2015). Secure attachment enables healthy psychological functioning, including the ability to mentalise one's own emotions and thoughts about others and to empathise and mentalise the experiences, thoughts, and emotions of others. Results from a self-report online study of 32,827 (age 18-85 years) participants found adaptive coping, rumination, and self-blame are critical psychological processes that mediate to which extend a family history of mental illness, social deprivation, and traumatic life experiences predict anxiety and depression in adulthood (Kinderman et al., 2013).

Reflective functioning, emotion regulation, and mentalisation are related to these psychological processes, essential to handling parental stress and providing adequate affective responsiveness to young children (Adshead, 2015). Ongoing parenting interventions target mentalisation and psychological reflectivity for parents with personality disorders, e.g., the Light House parenting programme (Byrne et al., 2019). Based on my engagement with research and my clinical experience, I suggest such parenting programs are likely appropriate and beneficial for parents with severe mental illness.

Stigma and family involvement

Stigma and fear of having children placed out of the home are central to parenting and severe mental illness (Harries, Smith, Gregg, & Wittkowski, 2023) and central to parenting and the experience of parenting intervention in the context of personality disorders (Tyrer et al., 2015; R. Wilson et al., 2018). To secure ecological validity in future studies, it is imperative to understand the barriers and facilitators of recruiting and including *families with complex needs* in clinical trials (to secure ecological validity). Related to this, there is a need to better conceptualise stigma, shame and parental overburden when conducting clinical trials to support parents with severe mental illness and their children. Moreover, we must better understand the barriers and facilitators for recruiting families for research and preventive interventions. Inspiration for such future work is the work on the implementation of family involvement in persons with psychotic disorders in Norway, which includes findings on the importance of educating mental health professionals about the concept of confidentiality to facilitate family involvement (Hansson, Romøren, Pedersen, et al., 2022; Hansson, Romøren, Weimand, et al., 2022). Family involvement is recommended by international and national guidelines (Baandrup et al., 2016) but is rarely effectively implemented. To involve children as young-next-of kin, and especially to reach *families with complex needs* who might be vulnerable to the experience of stigma, parental overburden and possibly fear of having children placed in out-of-home care, we must generate knowledge of facilitators and barriers.

To sum up the findings of this thesis, considering the theoretical and conceptual framework provided in the introduction and the further perspective on dimensional psychopathology and parenting in this discussion, I will on one hand argue that there is a need for a focus on

psychological functioning conceptualised around reflective functioning, attachment styles and mentalisation capacity in parents. Furthermore, on the other hand, there is a need to conceptualise the role of stigma, including stigma among mental health professionals, self-stigma, and the stigma children of parents with mental illness encounter in their everyday lives. Further, we need better observational and standardised tools to evaluate the parent-child relationship in school-age children, including emotion regulation, attachment and reflective functioning, and future studies on the effects of preventive interventions and studies on intergenerational risk of mental illness could benefit from better conceptualisation and measurement of these central psychological processes that play an essential role in the mechanisms underlying intergenerational transmission of severe mental illness.

Clinical implications

Children of parents with severe mental illness, including children of parents with personality disorders, are a high-risk population in need of preventive programs. Further, much can be gained from family-focused practice in mental health services, including prevention of mental illness in children, protection of the child, and improving chances of successful recovery for the parent with severe mental illness, as well as offering much-needed support to other caregivers including partners and extended family.

Today and tomorrow, clinicians face multiple and sometimes conflicting demands in mental health services that are often under-financed, increasing the risk of burnout in mental health personnel. Proper financing is urgently needed, especially considering individuals and families affected by the high complexity of psychopathology and social marginalisation. Having two parents with ill mental health is associated with a further increase in children's risk of mental illness. Hence, there is a need to consider the needs of families where both parents have a mental. Single caregivers with severe mental illness are vulnerable, and interventions ought to consider how to address the specific needs of these families.

Future research

Detangling mechanisms and understanding the heritability gap

This thesis confirms findings from previous studies that children of parents with a mental illness are at high risk of mental disorders. There is a need to understand better the mechanisms underlying intergenerational transmission of mental illness from parent to child. A move towards a dimensional and transdiagnostic approach to psychopathological classifications might enable studies in the genetic architecture of endophenotypes using machine learning techniques. This might help us better predict which children are at risk and who is not. Precision medicine in psychiatry holds promises to inform preventive interventions. However, such promises have long perspectives, and in the here and now, pragmatic preventive interventions are warranted together with studies designed to explore mechanisms and change in children and families.

Preventive family-based interventions

Our findings suggest that VIA Family is perceived as effective and acceptable by parents with severe mental illness. However, to fully understand the potential of family-based preventions, we need large sample sizes, replication of studies and long-term follow-ups using mediation- and moderator analyses. Future studies could benefit from pre-planned analysis on different groups of families, such as children with low daily functioning, severe parental psychopathology, impairment in family functioning or the home environment.

Mechanisms of change

We need to conceptualise better how these preventive interventions' mechanism of change is expected to work. We recommend a stepped-care approach for future studies, which aligns with the heterogeneity of families. We need to understand better which treatment components in preventive interventions are effective and which families profit from which interventions. Analyses of long-term effects and cost-effectiveness are warranted, and future studies could benefit from integrating variables on the severity of symptoms and power studies appropriately to enable subgroup analyses.

Service user involvement

We involved service users during the design and piloting phase of the VIA Family trial. However, we did not involve service users throughout data analysis and reporting of data from the study, which is recommended (Skivington et al., 2021) and could have been valuable in translating our findings. Future studies are encouraged to involve service users by communicating findings from similar studies whenever feasible.

The needs of co-parents and partners

The needs of co-parents and other vital caregivers seem understudied and overlooked, considering parental severe mental illness. A study found that using QoL screening helped identify the partners and co-parents struggling the most, which can help reach families with high stress levels (Birkeland et al., 2017). More research in this field is warranted.

Preventive intervention beyond the family

Preventive interventions can target domains other than family, home environments and parenting. To point to examples of preventive interventions beyond the family also crucial for future research, the following types of preventive interventions can be highlighted:

Preventive interventions could consider research on the markers of vulnerabilities in familial-high-risk children's cognitive, motor, language, and emotional development, as an example by use of physiotherapy and physical exercise stimulating motor development. Also, nutritional interventions for children of parents with bipolar type I disorder are developed and studied in RCTs. McNamara et. al. (2020) found that fish oil monotherapy was not superior to placebo for reducing depressive symptoms in adolescents at high risk for bipolar disorder type I disorder (McNamara et al., 2020). However, the same research group found that nutritional fish oil supplements successfully altered emotion-generated corticolimbic functional connectivity in depressed adolescent children of parents with bipolar I disorder (McNamara et al., 2022), suggesting the potential of such nutritional interventions for familial-high-risk children.

Another approach is E-learning interventions. In Japan, e-learning interventions have been developed to educate mental health nurses and school teachers on detecting and supporting COPMI (Kageyama et al., 2022, 2023; Kageyama & Yokoyama, 2018). Kageyama et al. (2023) found promising evidence of the effectiveness of an e-learning program for training teachers in elementary schools on how to notice and help meet the needs of COPMI in Japan.

Third and finally, a different approach to preventive intervention beyond the family is a community-based approach along the concept of “It takes a village to raise a child” drawing systemic approaches emphasising the importance of the broader social and cultural resources that families are nested in (Reupert et al., 2022), such as the project entitled “The Village” in Tyrol, Austria (Christiansen et al., 2019), which through co-participation, implementation, and evaluation sought to support COPMI directly.

Future research could profit from combining the different modalities of intervention and, if possible, investigate which modalities of interventions and which treatment components are effective for which families at which time. Moreover, further to study if some intervention modalities are better suited to build trust with the most vulnerable families and children with sensitivity to child age and development, a social network around the families, and episodes of parental severe mental illness, fluctuations and severity in symptoms and its impact on family functioning, the home environment, and parenting abilities.

Conclusions

This thesis had two aims. The first was to study the effectiveness of an 18-month family-based preventive intervention, VIA Family, on family functioning and levels of support and stimulation in the home environment. The second aim was to estimate the risk of mental illness in children of parents with personality disorders based on nationwide register data.

First, compared with usual treatment, we did not find superior effects of VIA Family on family functioning and levels of support and stimulation in the home environment. Parents with severe mental illness reported better user satisfaction, effectiveness, and acceptability with VIA Family, and we cannot rule out a clinically relevant effect of VIA Family. The impact of the societal lockdown during the COVID-19 pandemic, sample bias, and the lack of power to conduct subgroup analyses are essential when interpreting our findings.

Second, we found that as in children of parents with severe mental illness, children of parents with personality disorders also have a 2.5 to 3 times higher risk of developing a mental disorder than nonexposed children, which is most likely understood considering shared genetic variants between parent and child, environmental exposures, and gene-environment interactions.

In this thesis, I have proposed that future preventive interventions could benefit from detangling the complex mechanisms underlying intergenerational transmission of severe mental illness. Also, preventive interventions depend on a coherent conceptualisation of parenting and parental emotion regulation skills and the availability of other parental figures and caregivers. Importantly, we need a better conceptualisation of stigma, shame, and parental overburden to understand and overcome the barriers to engaging the most vulnerable families and children. Further, intervention

modalities beyond the family, such as nutritional supplements, physiotherapy, e-learning, and community interventions, could be integrated into future multicomponent interventions.

The lesson learnt in this thesis is that we need more studies of complex interventions offered to the heterogeneous population of families and children in the context of parental severe mental illness, including personality disorders. Finally, and to repeat the main argument of this thesis, based on my research in the field and my clinical experience, I believe that *families with complex needs* rely on sensitive recruitment and long-term interventions. To the best of my knowledge, I would recommend interventions sensitive to stigma – and flexibly tailored to the needs and wishes of the unique family and its members.

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Appendices

Supplementary VIA Family exploratory outcomes

VIA Family exploratory outcomes[25]

Parents with severe mental illness (n=95)	Usual treatment (n=48)	VIA Family (n=47)	Adjusted mean difference[1] (95% CI)	*P*-value
PSS Parental Stress Score[2]				
0 months	40.27 (10.36); n=44 (91.7%)	39.19 (9.40); n=43 (91.5%)	-	
18 months	38.0 (9.38); n=35 (72.9%)	37.92 (9.88); n=36 (76.6%)	0.20 (-4.02 to 4.41)	.925
PSP Daily Functioning Score[3]				
0 months	60.94 (16.28); n=47 (97.9%)	59.60 (14.79); n=47 (100%)	-	
18 months	65.17 (15.99); n=36 (75.0%)	64.44 (16.67); n=39 (83.0%)	-0.56 (-6.23 to 5.13)	.847
SPS Social Provisions Score[4]				
0 months	81.25 (10.53); n=40 (83.3%)	78.46 (9.99); n=41 (87.2%)	-	
18 months	83.29 (10.36); n=34 (70.8%)	80.71 (11.68); n=35 (74.5%)	-1.54 (-6.89 to 3.81)	.565
Parents with severe mental illness reporting on n=113 children	(n=55)	(n=58)	Adjusted mean difference[5] (95% CI)	
PS Parenting Score[6]				
0 months	3.25 (0.61); n=44 (80.0%)	2.93 (0.56); n=51 (87.9%)	-	
18 months [no imputations][5b]	3.08 (0.67); n=33 (60.0%)	2.79 (0.60); n=37 (63.8%)	0.05 (-0.15 to 0.25)	.631
18 months [with imputations]			0.00 (-0.33 to 0.33)	.991
PAFAS Parenting Score[7a]				
0 months	15.06 (3.91); n=48 (87.3%)	14.25 (4.54); n=52 (89.7%)	-	
18 months	14.08 (4.78); n=37 (67.3%)	13.63 (4.51); n=41 (70.7%)	-0.40 (-2.81 to 2.01)	.746

[25] Table taken from Paper I.

PAFAS Family Adjustment Score[7b]				
0 months	10.14 (4.68); n=49 (89.1%)	9.23 (4.79); n=52 (89.7%)	-	
18 months	9.67 (4.44); n=36 (65.5%)	8.00 (4.32); n=43 (74.1%)	-0.67 (-2.72 to 1.38)	.523
Co-parents (n=84)	Usual treatment (n=40)	VIA Family (n=44)	Adjusted mean difference[1] (95% CI)	*P*-value
PSS Parental Stress Score[2]				
0 months	36.47 (8.95); n=38 (95.0%)	36.03 (8.53); n=38 (86.4%)	-	
18 months	34.07 (8.19); n=27 (67.5%)	32.24 (7.33); n=34 (77.3%)	-1.71 (-5.66 to 2.25)	.390
PSP Daily Functioning Score[3]				
0 months	77.56 (10.81); n=39 (97.5%)	77.50 (11.11); n=42 (95.5%)	-	
18 months	79.55 (10.54); n=29 (72.5%)	82.08 (7.91); n=38 (86.4%)	1.67 (-2.67 to 6.01)	.442
SPS Social Provisions Score[4]				
0 months	87.81 (5.81); n=37 (92.5%)	86.42 (9.74); n=36 (81.8%)	-	
18 months	87.37 (8.19); n=27 (67.5%)	88.73 (7.60); n=33 (75.0%)	1.76 (-2.67; 6.20)	.427
Co-parents reporting on n=102 children	(n=47)	(n=55)	Adjusted mean difference (95% CI)[5]	
PS Parenting Score[6]	(n=47)	(n=55)		
0 months	2.97 (0.49); n=41 (87.2%)	2.97 (0.57); n=49 (89.1%)	-	
18 months [no imputations][5b]	2.89 (0.56); n=30 (63.8%)	2.67 (0.54); n=36 (65.5%)	-0.16 (-0.40 to 0.08)	.196
18 months [with imputations]			-0.07 (-0.41 to 0.27)	.679
PAFAS Parenting Score[7]				
0 months	14.90 (4.67); n=42 (89.4%)	14.20 (4.71); n=44 (80.0%)	-	
18 months	14.41 (3.76); n=32 (68.1%)	12.45 (3.84); n=40 (72.7%)	-0.24 (-2.35 to 1.87)	.824
PAFAS Family Adjustment Score[8]				
0 months	6.51 (3.40); n=43 (91.5%)	6.84 (3.98); n=49 (89.1%)	-	
18 months	6.81 (3.28); n=31 (66.0%)	4.62 (3.30); n=42 (76.4%)	-2.46 (-4.04 to -0.87)	**.002**

Unless otherwise specified, data are observed unadjusted mean (SD) or n (%). *Note:* PSS=Parental Stress Scale. PSP: Personal and Social Performance Scale. SPS: Social Provisions Scale. PS=Parenting scale. PAFAS=Parenting and Family Adjustment Scales.
[1] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.
[2] PSS: higher scores, higher levels of stress
[3] PSP: higher scores, better daily functioning
[4] SPS: higher scores, higher levels of social functioning
[5] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and child's gender, including a random effect of family, and with missing data handled by multiple imputations.
[5b. In] cases with more than 40% missing data, analysis with and without multiple imputations is performed to evaluate the influence of imputations.
[6] PS: Higher scores indicate more problematic parenting behaviours.
[7a] PAFAS Parenting Score: Higher scores indicate more impairment in parenting practices and the quality of parent–child relationships.
[7b] PAFAS Family Adjustment Score: Higher scores indicate more impairment in parental emotional adjustment and partner and family support in parenting.

Supplementary VIA Family referrals to mental health, child protection, or social services

Referrals by case managers Families, n = 47	Referrals by the VIA Family Case Managers during the 18-month intervention period
Number of families referred to Child Protection Services or Social Services	10 (21.28 %)
Number of families referred to CAMHS or AMHS[26]	7 (14.89 %)

Referrals by trial assessors	0 Months (October 2017 to April 2019); n=95 Families, n=113 Children	18 Months (April 2019 to January 2021); n=83 Families, n=95 Children
Referral to Child Protection Services	8 Families, 8/95 (8.4%) 8 Children, 8/113 (7.1%)	10 Families, 10/83 (12.1%) 11 Children, 11/95 (11.6%)
Referral to CAMHS	3 Families, 3/95 (3.2%) 3 Children, 3/113 (2.7%)	6 Families, 6/83 (7.2%) 7 Children, 7/95 (7.4%)

[26] Can be either parent or any child in family

Supplementary VIA Family unadjusted analyses

Treatment Effects on Levels of support and stimulation in the home environment and Family Functioning - Adjusted and Unadjusted Analysis

HOME-MC/EA Levels of support and stimulation in the home environment[27]						
Children (n=113)	Treatment as Usual (n=55)	VIA Family (n=58)	Adjusted mean difference[28] (95% CI)	*P*-value	Unadjusted mean difference (95% CI)	*P*-value
0 months	46.74 (5.85); n=53 (96.4%)	46.42 (6.07); n=55 (94.8%)	-			
18 months	45.86 (5.31); n=37 (67.3%)	47.17 (5.58); n=46 (79.3%)	1.79 (-0.37 to 3.95)	.104	1.59 (-0.51 to 3.69)	.136
FAD General Family Functioning Score[29]						
Parents with Severe Mental Illness (n=95)	(n=48)	(n=47)	Adjusted mean difference (95% CI) [30]	*P*-value	Unadjusted mean difference (95% CI)	*P*-value
0 months	2.08 (0.50); n=44 (91.7%)	1.91 (0.51); n=42 (89.4%)	-			
18 months	1.77 (0.46); n=33 (68.8%)	1.82 (0.53); n=36 (76.6%)	0.11 (-0.10 to 0.31)	.296	0.11 (-0.10 to 0.31)	.281
Co-parents (n=84)	(n=40)	(n=44)				
0 months	1.91 (0.38); n=37 (92.5%)	1.89 (0.48); n=38 (86.4%)	-			
18 months	1.67 (0.36); n=26 (65.0%)	1.62 (0.47); n=36 (81.8%)	-0.07 (-0.27 to 0.13)	.482	-0.07 (-0.27 to 1.12)	.457

Unless otherwise specified, data are observed unadjusted mean (SD) or n (%).
Note: FAD=McMaster Family Assessment Device. HOME-MC/EA= Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence.

[27] HOME-MC/EA: higher scores, higher quality of home environment

[28] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and child's gender, including a random effect of family, and with missing data handled by multiple imputations.

[29] FAD: lower scores, better family functioning

[30] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.

Exploratory Outcomes Reported by Parents with Severe Mental Illness - Adjusted and Unadjusted Analysis

Parents with severe mental illness (n=95)	Treatment as Usual (n=48)	VIA Family (n=47)	Adjusted mean difference (95% CI)[31]	*P*-value	Unadjusted mean difference (95% CI)	*P*-value
PSS Parental Stress Score[32]						
0 months	40.27 (10.36); n=44 (91.7%)	39.19 (9.40); n=43 (91.5%)	-		-	
18 months	38.0 (9.38); n=35 (72.9%)	37.92 (9.88); n=36 (76.6%)	0.20 (-4.02 to 4.41)	.925	0.33 (-3.89 to 4.55)	.877
PSP Daily Functioning Score[33]						
0 months	60.94 (16.28); n=47 (97.9%)	59.60 (14.79); n=47 (100%)	-		-	
18 months	65.17 (15.99); n=36 (75.0%)	64.44 (16.67); n=39 (83.0%)	-0.56 (-6.23 to 5.13)	.847	-0.34 (-6.01 to 5.33)	.905
SPS Social Provisions Score[34]						
0 months	81.25 (10.53); n=40 (83.3%)	78.46 (9.99); n=41 (87.2%)	-		-	
18 months	83.29 (10.36); n=34 (70.8%)	80.71 (11.68); n=35 (74.5%)	-1.54 (-6.89 to 3.81)	.565	-1.58 (-6.91 to 3.74)	.554
Children (n=113) reported by parents with severe mental illness	(n=55)	(n=58)	Adjusted mean difference (95% CI)[35]		Unadjusted mean difference (95% CI)	*P*-value
PS Parenting Score	(n=55)	(n=58)				
0 months	3.25 (0.61); n=44 (80.0%)	2.93 (0.56); n=51 (87.9%)	-		-	
18 months	3.08 (0.67); n=33 (60.0%)	2.79 (0.60); n=37 (63.8%)	0.00 (-0.33 to 0.33)	.991	-0.03 (-0.35 to 0.30)	.873
PAFAS Parenting Score						

[31] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.

[32] PSS: higher scores, higher levels of stress

[33] PSP higher scores, better daily functioning

[34] SPS: higher scores, higher levels of social provisions/social functioning

[35] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and child's gender, including a random effect of family, and with missing data handled by multiple imputations.

0 months	15.06 (3.91); n=48 (87.3%)	14.25 (4.54); n=52 (89.7%)	-		-	
18 months	14.08 (4.78); n=37 (67.3%)	13.63 (4.51); n=41 (70.7%)	-0.40 (-2.81 to 2.01)	.746	-0.53 (-2.85 to 1.79)	.649
PAFAS Family Adjustment Score						
0 months	10.14 (4.68); n=49 (89.1%)	9.23 (4.79); n=52 (89.7%)	-		-	
18 months	9.67 (4.44); n=36 (65.5%)	8.00 (4.32); n=43 (74.1%)	-0.67 (-2.72 to 1.38)	.523	-0.78 (-2.75 to 1.19)	.431
Unless otherwise specified, data are observed unadjusted mean (SD) or n (%). *Note:* PAFAS=Parenting and Family Adjustment Scale. PS=Parenting Scale. PSP=Personal and Social Performance Scale. PSS=Parental Stress Scale. SPS=Social Provisions Scale.						

Exploratory Outcomes Reported by Co-Parents - Adjusted and Unadjusted Analysis

Co-Parents (n=84)	Treatment as Usual (n=40)	VIA Family (n=44)	Adjusted mean difference[36] (95% CI)	*P*-value	Unadjusted mean difference (95% CI)	*P*-value
PSS Parental Stress Score						
0 months	36.47 (8.95); n=38 (95.0%)	36.03 (8.53); n=38 (86.4%)	-			
18 months	34.07 (8.19); n=27 (67.5%)	32.24 (7.33); n=34 (77.3%)	-1.71 (-5.66 to 2.25)	.390	-1.61 (-5.49 to 2.28)	.410
PSP Daily Functioning Score						
0 months	77.56 (10.81); n=39 (97.5%)	77.50 (11.11); n=42 (95.5%)	-			
18 months	79.55 (10.54); n=29 (72.5%)	82.08 (7.91); n=38 (86.4%)	1.67 (-2.67 to 6.01)	.442	1.96 (-2.30 to 6.22)	.360
SPS Social Provisions Score						
0 months	87.81 (5.81); n=37 (92.5%)	86.42 (9.74); n=36 (81.8%)	-			
18 months	87.37 (8.19); n=27 (67.5%)	88.73 (7.60); n=33 (75.0%)	1.76 (-2.67; 6.20)	.427	1.86 (-2.43 to 6.16)	.387

[36] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.

Children (n=113) reported by parents with SMI	(n=55)	(n=58)	Adjusted mean difference (95% CI)[37]		Unadjusted mean difference (95% CI)	*P*-value
PS Parenting Score	(n=47)	(n=55)				
0 months	2.97 (0.49); n=41 (87.2%)	2.97 (0.57); n=49 (89.1%)	-			
18 months	2.89 (0.56); n=30 (63.8%)	2.67 (0.54); n=36 (65.5%)	-0.07 (-0.41 to 0.27)	.679	-0.06 (-0.41 to 0.29)	.721
PAFAS Parenting Score						
0 months	14.90 (4.67); n=42 (89.4%)	14.20 (4.71); n=44 (80.0%)	-			
18 months	14.41 (3.76); n=32 (68.1%)	12.45 (3.84); n=40 (72.7%)	-0.24 (-2.35 to 1.87)	.824	-0.15 (-2.30 to 2.01)	.891
PAFAS Family Adjustment Score						
0 months	6.51 (3.40); n=43 (91.5%)	6.84 (3.98); n=49 (89.1%)	-			
18 months	6.81 (3.28); n=31 (66.0%)	4.62 (3.30); n=42 (76.4%)	-2.46 (-4.04 to -0.87)	**.002**	-2.30 (-3.94 to -0.66)	**.007**

Unless otherwise specified, data are observed unadjusted mean (SD) or n (%).
Note: PAFAS=Parenting and Family Adjustment Scale. PS=Parenting Scale. PSP=Personal and Social Performance Scale. PSS=Parental Stress Scale. SMI=Severe Mental Illness. SPS=Social Provisions Scale.

[37] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and child's gender, including a random effect of family, and with missing data handled by multiple imputations.

User Satisfaction and Negative Effects reported by Parents with Severe Mental Illness - Adjusted and Unadjusted Analysis

Parents with severe mental illness (n=95)	Treatment as Usual (n=48)	VIA Family (n=47)	Adjusted mean difference[38] (95% CI)	*P*-value	Unadjusted mean difference (95% CI)	*P*-value
CSQ User Satisfaction[39]	23.55 (6.11); n=31(64.5%)	27.19 (4.14); n=37 (78.7%)	3.58 (0.79 to 6.37)	**.013**	3.57 (0.81 to 6.33)	**.012**
NeQ Negative Effects[40]						
Negative effects, sum (SD). 0 to 20 effects	4.57 (4.21); n=35 (72.9%)	3.24 (3.57); n=37 (78.7%)	-0.99 (-3.04 to 1.07)	.341	-0.99 (-3.10 to 1.11)	.348
Negative impact, mean SD Scale range: 0 to 4	2.11 (0.80); n=28 (58.3%)	1.83 (0.89); n=29 (61.7%)	-0.32 (-0.85 to 0.22)	.236	-0.34 (-0.89 to 0.21)	.226
[without imputations]			-0.27 (-0.70 to 0.17)	.223	-0.28 (-0.73 to 0.17)	.217
Negative Effects Due to Allocated Treatment						
Negative effects due to treatment	1.80 (2.71); n=35 (72.9%)	1.78 (2.75); n=37 (78.7%)	-0.03 (-1.28 to 1.22)	.960	-0.02 (-1.27 to 1.22)	.971
Negative impact due to treatment received	2.10 (0.64); n=18 (37.5%)	1.77 (0.98); n=20 (42.6%)	-0.12 (-0.96 to 0.73)	.777	-0.14 (-0.99 to 0.71)	.737
[without imputations]			-0.23 (-1.94 to 1.48)	.731	-0.15 (-1.34 to 1.04)	.775
Negative Effects Due to Other Causes						
Negative effects due to other causes	2.77 (2.94); n=35 (72.9%)	1.46 (1.98); n=37 (78.7%)	-1.33 (-2.44 to -0.22)	**.019**	-1.32 (-2.45 to -0.19)	**.023**
Negative impact due to other causes	2.25 (0.91); n=23 (47.9%)	2.12 (0.79); n=21 (44.7%)	-0.12 (-0.80 to 0.55)	.710	-0.14 (-0.82 to 0.54)	.676
[without imputations]			0.83 (-0.36 to 2.02)	.148	0.85 (-0.24 to 1.94)	.116

[38] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.
[39] CSQ: higher scores, better user's satisfaction
[40] NeQ: higher scores, more negative effects

User Satisfaction and Negative Effects reported by Co-Parents - Adjusted and Unadjusted Analysis

Co-Parents (n=95)	Treatment as Usual (n=40)	VIA Family (n=44)	Adjusted mean difference[41] (95% CI)	*P*-value	Unadjusted mean difference (95% CI)	*P*-value
CSQ User Satisfaction	24.07 (5.27); n=14 (35.0%)	26.55 (3.59); n=33 (75.0%)	2.48 (-1.20 to 6.16)	.179	2.53 (-1.18 to 6.23)	.174
NeQ Negative Effects[42]						
Negative effects, sum (SD). 0 to 20 effects	0.33 (0.73); n=27 (67.5%)	1.11 (2.04); n=35 (79.5%)	1.06 (0.21 to 1.91)	**.015**	0.98 (0.13 to 1.83)	**.025**
Negative impact, mean SD Scale range: 0 to 4	0.58 (0.80); n=6 (17.6%)	1.05 (0.75); n=14 (31.8%)	3.38 (1.16 to 5.59)	**.003**	3.27 (1.06 to 5.48)	**.004**
[without imputations]			0.43 (-0.34 to 1.19)	.251	0.47 (-0.32 to 1.25)	.228
Negative Effects Due to Allocated Treatment						
Negative effects due to treatment	0.22 (0.64); n=27 (67.5%)	0.23 (0.60); n=35 (79.5%)	-0.02 (-0.32 to 0.29)	.901	0.00 (-0.30 to 0.30)	.991
Negative impact due to treatment received	0.75 (0.96); n=4 (10.0%)	0.60 (0.55); n=5 (11.4%)	-29.42 (-2133.89 to 2075.05)	.976	-36.96 (-1989.34 to 1915.42)	.968
[without imputations]			-0.23 (-1.94 to 1.48)	.731	-0.15 (-1.34 to 1.04)	.775
Negative Effects Due to Other Causes						
Negative effects due to other causes	0.11 (0.32); n=27 (67.5%)	0.89 (1.95); n=35 (79.5%)	0.86 (0.20 to 1.53)	**.012**	0.78 (0.11 to 1.44)	**.023**
Negative impact due to other causes	0.33 (0.58); n=3 (7.5%)	1.18 (0.80); n=11 (25.0%)	0.87 (-0.91 to 2.65)	.329	0.22 (-2.20 to 2.63)	.856
[without imputations]			0.83 (-0.36 to 2.02)	.148	0.85 (-0.24 to 1.94)	.116

[41] Estimated treatment difference from analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.

[42] NeQ: higher scores, more negative effects

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Papers


PAPER I

Psychological Medicine

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

--Manuscript Draft--

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Title: 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

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Results Effects on family functioning did not differ between the two groups. Neither reported by parents with severe mental illness (0.11; 95% CI = -0.10 to 0.31), *P* = .296, nor by co-parents (-0.07; 95% CI = -0.27 to 0.13), *P* = .482. Assessor-rated levels of stimulation and support in the home environment improved in VIA Family, however, not significantly compared with usual treatment (mean difference: 1.79; 95% CI = -0.37 to 3.95, *P* = .104). Sensitivity analyses confirmed our main findings.

Conclusions Effects on family functioning and the home environment did not differ between VIA Family and usual treatment. We cannot rule out a clinically relevant effect of VIA Family on levels of stimulation and support in the home environment. Long-term follow-up is needed to investigate potential preventive effects.

Keywords: intergenerational, psychosis, bipolar, depression, parent, offspring

Introduction

Preventive interventions for familial-high-risk children targeting environmental risk factors are warranted (Duffy et al., 2023; Fusar-Poli et al., 2021; Raballo et al., 2021; Seidman & Nordentoft, 2015). Preventive interventions have shown a reduction in psychopathology in children of parents with depression and other mental illnesses (Havinga et al., 2021; Lannes et al., 2021; Loechner et al., 2018; Siegenthaler et al., 2012; Thanhäuser et al., 2017). However, there is a lack of evidence regarding interventions in the context of parental psychotic disorders (Lannes et al., 2021; Radley et al., 2020).

Based on shared genetic liability, severe mental illness (SMI) refers to schizophrenia, bipolar disorder, and major depressive disorder (Rasic et al., 2014; Sandstrom et al., 2019). Children of parents with SMI are at risk of one in three developing SMI by their late twenties caused by complex genetic, environmental and gene-environment mechanisms (Rasic et al., 2014). Families of parents with SMI are at higher risk of reporting impaired family functioning (Friedmann et al., 1997; Staccini et al., 2015; Wiegand-Grefe et al., 2019) and insufficient levels of stimulation and support in the home environments (Gantriis et al., 2019; Uddin et al., 2021). Previous research has indicated that family and home environment mediate the transmission of mental illness from parent to child (Agid et al., 1999; Moulin et al., 2022; Paananen et al., 2021; Saarinen et al., 2023; van Os et al., 2010), hence identified as targets for preventive interventions.

In the VIA Family trial we set out to develop a multidisciplinary, multicomponent, tailored, family-based preventive intervention, VIA Family (Müller et al., 2019). Family functioning and levels of stimulation and support in the home environment represent the main context of protective versus risk factors for school-aged children (6-12 years) in the conceptual framework of VIA Family. Based on the diathesis-stress model (Walker & Diforio, 1997), VIA Family was designed to provide an effective reduction of stressors for the whole family. This was done by making the intervention flexible and tailored to the individual family and by

offering support to the whole family: parents with SMI, co-parents, and all children/adolescents living in the family.

The VIA Family trial was powered to detect effectiveness on family functioning (this study) and children's daily functioning (in preparation) (Müller et al., 2019). This study is nested in the VIA Family trial and reports on key secondary outcomes conceptualising the family as the unit of analysis. We hypothesised that VIA Family would significantly improve family functioning and levels of stimulation and support in the home environment compared with usual treatment (i.e., standard mental health and social services, services in the private sector and at not-for-profit organisations). We also aimed to test user satisfaction, negative effects, and a series of exploratory outcomes: parental stress, parents' daily functioning, social provision, parenting, and family adjustment.

Methods

Study design

We did a pragmatic randomised controlled superiority trial with assessor-masked assessment in two parallel groups, VIA Family and usual treatment, in a single centre in Copenhagen, Denmark. Families were recruited from a cohort constructed by linking Danish health registers using the unique personal identification numbers in the Danish Civil Registration System (Pedersen, 2011). Families in this cohort were contacted by physical and electronic mail followed by telephone contact if telephone numbers were publicly available. Families were also recruited directly from mental health and social services. Written informed consent was first obtained from parents with SMI including consent for contacting co-parents. All parents signed written consent regarding their own participation in the study, and all legal parents signed written consent before the inclusion of children in the trial.

Assessments were carried out at 0 months, and 18 months (post-intervention) with parents with SMI, co-parents, and children aged 6-12 years. Ethics approval was obtained from the Regional Committee on Health Research Ethics for the Capital Region of Denmark (H-17000450). Data approval was obtained from the Danish Data Protection Agency. The trial was registered prospectively at ClinicalTrials.gov registration: NCT03497663 and a protocol was published at the beginning of the trial (Müller et al., 2019). Findings are reported in alignment with Consolidated Standards of Reporting Trials (Boutron et al., 2017; Moher et al., 2010).

Participants

Families were eligible if one or more children were 6-12 years at baseline and if one or both parents had been in contact with inpatient or outpatient mental health services within the child's lifetime (pregnancy included) and diagnosed with a schizophrenia spectrum disorder, bipolar affective disorder, or recurrent major depressive disorder according to the International Classification of Diseases (ICD) eight or tenth revision (diagnostic codes listed in **Supplementary**). Families were eligible if children had their official address in the municipalities of Frederiksberg or Copenhagen, the Capital Region of Denmark (parents could live in other municipalities if not living with the child). We excluded families in intensive family therapy and those not able to speak Danish (since funding did not cover translator salaries for 18 months). Parental or child psychiatric or somatic comorbidity were not exclusion criteria. Gender of participants was defined as the legal gender in the Danish Civil Registry (Pedersen, 2011). Information on nationality, race or ethnicity was not obtained.

Before inclusion parental diagnoses were verified at expert clinical conferences based on assessor-rated interviews with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing, 1990). Before

randomisation, we evaluated child psychopathology with the diagnostic interview Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997). All families were offered feedback on child mental health status and given information on how to access mental health and social services in a standardised manner (Müller et al., 2019). By indication and in collaboration with parents, assessors sent referrals to child and adolescent mental health services and/or child protection services.

Randomisation and masking

Families were assigned to either VIA Family or usual treatment based on a concealed block-size algorithm stratified by the parental diagnostic group and set up in the Research Electronic Data Capture (Harris et al., 2009). The team leader in VIA Family informed families about their allocation. To secure the masking of assessors, VIA Family took place geographically separated from the research clinic. If an assessor was unmasked to randomisation status of a family, a masked assessor finalised the remaining assessments. Researchers were masked to group allocation throughout data processing and interpretation of findings. Sensitivity analyses were performed unmasked by the first author (IG).

VIA Family

As a collaborative care model, all families were assigned to a case manager working in a multidisciplinary team consisting of a clinical psychologist specialising in child and adolescent psychiatry, a mental health nurse, a social worker, and a pedagogue. All case managers had multiple years of experience in mental health or social services and were supervised in the context of systemic family therapy A consultant child and adolescent psychiatrist (AT) regularly supervised the team.

During the 18-month intervention, parents were first invited to two to six introductory sessions involving building a working alliance and co-construction of parents' life narratives. After the introduction period (approx. two months) families received approx. 16 months' tailored VIA Family according to needs and choice of treatment elements. Families were recommended to begin with psychoeducation (six to eight sessions), and three to ten sessions Positive Parenting Program (Triple P) Level 2-5 (Sanders, 1999). Stepping Stones was offered to families where a child had a disability and/or a mental disorder (Sanders et al., 2004). Additional treatment components included support groups for children and parents separately (8 sessions), and cognitive behavioural therapy for children who showed signs of mental health difficulties, together with guidance regarding financial, social, or practical support from the municipality. Two pilot families gave feedback to case managers on their experience with VIA Family before the trial began.

The frequency and number of sessions with VIA Family varied between families. Fidelity was defined as the family having a minimum of 15 sessions with VIA Family.

Usual Treatment

Usual treatment was pragmatically defined as combined services in the free-of-charge mental health and social services in Denmark including services at licenced psychiatrists and general practitioners (incl. prescription on psychotropics), and services at not-for-profit organizations or in the private sector, such as psychotherapy, private psychologists etc.

We applied no fidelity criteria to usual treatment. We asked parents to report use of services during the at baseline and 18-month assessments**.**

Outcomes

McMaster Family Assessment Device (FAD): Self-report questionnaire (60 items, score: 1 to 4, scale range: 1 to 4). The general family functioning score covers communication, affective responsiveness, etc. (Epstein et al., 1983; Friedmann et al., 1997). Higher scores indicate more impairment in family functioning, and scores above two indicate unhealthy family functioning found associated with increased risk of relapse and drop-out (Staccini et al., 2015). No Danish norms are available. ***Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence*** (HOME-MC/HOME-EA): A semi-structured interview at families' homes with child and a caregiver present. Assessor-rated scores (MC: 59 items, score: 0 or 1, scale range: 0 to 59. EA: 60 items, score: 0 or 1, scale range: 0 to 60). Higher scores indicate higher levels of stimulation and support in the home environment (Caldwell BM, Bradley RH, 2003). Danish norms for 7-year-old children are available (Gantriis et al., 2019) with a clinical cut-off < 40 indicating an inadequate home environment.

Client Satisfaction Questionnaire (CSQ8): Self-report questionnaire (8 items, score: 1 to 4, scale range: 8 to 32) of user satisfaction covering self-perceived acceptability and effectiveness of the intervention (Attkisson, 1996). ***Negative Effects Questionnaire*** (NeQ20): self-report questionnaire (20 items, score: yes/no, if yes then scores: 0 to 4, scale range: 0 to 100) on negative effects. The scale includes an additional score for each negative effect on whether it was caused by the allocated treatment or by other circumstances(Rozental et al., 2019).

Exploratory outcomes

Parental Stress Scale (PSS): Self-report questionnaire (18 items, score: 1 to 5, scale range: 18 to 90) on perceived stress related to parenting. Higher scores indicate higher levels of parental stress (Berry & Jones, 1995). ***Personal and Social Performance Scale*** (PSP): Semi-structured interview on parental daily

functioning (scale range: 0-100). Higher scores indicate better daily functioning (Michalos, 2014). ***Social Provision Scale*** (SPS): Self-report questionnaire (24 items, score: 1 to 4, scale range: 24 to 96) on social support covering domains such as the experience of belonging to a group of friends, access to advice, and assurance that others can be counted on in periods of stress. Higher scores indicate better social functioning (Cutrona CE, Russell D, 1987). ***Parenting and Family Adjustment Scales*** (PAFAS): Self-report inventory consisting of the PAFAS Parenting Scale (18 items, score: 0 to 3, scale range: 0 to 54) measuring parenting practices and the parent–child relationship. PAFAS Family Scale (12-items, score: 0 to 3, scale range: 0 to 36) on parental emotional adjustment and partner and family support in parenting. Higher scores indicate more impairment in domains (Sanders et al., 2014). ***Parenting scale*** (PS): Self-report questionnaire (30 items, score: 1 to 7, scale range: 1 to 7) on parenting behaviours. Higher scores indicate more problematic parenting behaviours (Arnold et al., 1993).

Training of assessors and expert clinical conferences

All assessors were accredited to perform the HOME-MC/EA (Caldwell BM, Bradley RH, 2003), SCAN (Wing, 1990) and K-SADS (Kaufman et al., 1997) interviews. At weekly expert clinical conferences (MM, AT), assessor-rated interviews were supervised (PSP, SCAN and K-SADS, and HOME-MC/EA with scores <40).

Statistical Analyses

Statistical analyses were carried out according to the published study protocol (Müller et al., 2019). Analyses were performed in the intention-to-treat population. Treatment effects on outcomes were evaluated using analysis of covariance including the outcome measured at baseline, stratum, and participant gender as baseline covariates. Missing data was handled by multiple imputations targeting an efficacy estimand under the assumption that missing data are missing at random. P-values were not adjusted for multiple testing, hence spurious findings cannot be ruled out.

A random effect of familiarity was included in analyses involving data from siblings (outcomes: HOME-MC/EA, PS and PAFAS). In cases where both parents met the criteria for SMI, the parent first listed in our register-based cohort was defined as the parent with SMI in statistical analyses, and the second listed parent defined as the co-parent.

Sensitivity analyses were performed to test the robustness of the findings and to explore the impact of missing data. Sensitivity analyses included complete case analysis, analysis without outliers defined as residuals greater than three standard deviations, per protocol analysis excluding participating families with less than one contact with VIA Family, and a per-protocol analysis excluding participating families with less than 15 contacts with VIA Family. No criteria of minimum or maximum use of services in TAU were considered a violation of the protocol. Changes to protocol are listed in **Supplementary**.

Analyses were performed in R studio, version 4.2.0 (R studio, version 4.2.0) using the LMMstar-package (Ozenne, B. and Forman, J., 2021). Multiple imputations were performed using the MICE package (Buuren & Groothuis-Oudshoorn, 2011) with 100 imputations and 20 iterations for each outcome. Data were analysed from June 2022 through April 2023.

Role of funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Characteristics of study sample

Recruitment took place from October 1, 2017, to March 31, 2019, with final data collected on April 30, 2021. **Figure 1** illustrates the flow of participants from the register-based cohort of 1090 families to the 95 (8.7%) families randomised. All families referred from mental health or social services (n=7) simultaneously appeared in the register-based cohort (1090). 47 families (47 parents with SMI, 44 co-parents, and 58 children) were randomly allocated to VIA Family and 48 families (48 parents with SMI, 40 co-parents, and 55 children) to usual treatment. Of parents with SMI (mean age 42 [SD 6.08]), mostly women (71 [74.7%]; 24 [25.3%] men) participated. The distribution of parents with SMI in the three diagnostic groups (12 [12.6%] schizophrenia spectrum disorder, 25 [26.3%] bipolar affective disorder, and 58 [61.1%] recurrent major depressive disorder) reasonably represents the distribution of the diagnostic groups in the register-based cohort.

Family structure varied between a single parent with one child to two parents with three children in the eligible age (6-12 years at inclusion). In nearly half of families (43 [45.3%]) parents lived together as a couple. In most families, the primary caregiver (n=95) was currently employed or studying (69 [72.6%]), with upper secondary or higher educational attainment (82 [86.3%]). Approximately 6% of parents with SMI and nearly 5% of co-parents fulfilled the ICD-10 criteria for misuse of alcohol (F10-12) within the previous two months. Three (1.7%) parents reported substance use disorder (alcohol, cannabis and/or cocaine) within the previous two months. Baseline daily functioning (PSP) for parents with SMI varied (range: 20 to 90) with broad (15-point) standard deviations illustrating a span in daily functioning from hospitalization to full recovery. The two intervention groups were balanced across baseline characteristics (**Table 1**).

In the full study sample of 95 families, trial assessors sent reports to child protection or social services in 8 (8.4%) families at baseline (0 months) and 10 (12.1%) at follow-up (18 months). During the 18-month intervention, case managers wrote similar reports in ten (21.3%) out of 47 families allocated to VIA Family.

VIA Family

- All families allocated to VIA Family (n=47 [100%]) were assigned a case manager and 44 (93.6 %) completed the introduction modules
- 41 (87.2%) families of which 16 (39.0%) completed three or more sessions of Triple P/Stepping-Stones
- 22 (46.8%) families completed psychoeducation about mental illness or emotions
- 22 (46.8%) families took on financial counselling
- 20 (42.6%) families took on sessions of support on collaboration between parents (in some cases on reducing conflicts and arranging holiday schedules for children in families of parents separated or divorced).
- 20 (42.6%) families engaged in sessions with case managers on the optimization of parents' treatments and lifestyles

Less than 30% of families chose practical support in homes, e.g., structuring daily activities. Only 6 (12.8%) families took up the offer of a structured safety plan concerning future relapse and/or hospitalizations. However, case managers pointed out that crisis management was part of other sessions with most families. For further information see **Supplementary**.

A total of 20 (42.6 %) families in VIA Family (n=47 families) had their 18-month intervention take place during the societal lockdown due to the Covid-19 pandemic. VIA Family was allowed early opening so that

lockdown only affected VIA Family from March 12, 2020, until May 9, 2020. A total of 18 out of 20 (90.0%) families maintained digital, including video, contact during this period.

Usual treatment

Use of services was balanced between VIA Family and usual treatment groups, both at baseline and at 18-month follow-up. Only contact with a private psychiatrist or psychologist at 18 months of assessment was significantly different across the two groups. For further information see **Supplementary**.

Estimated treatment effects

Table 2 summarises treatment effects on family functioning and the home environment. Self-reported family functioning did not differ between VIA Family and usual treatment; neither for parents with SMI (0.11 [95% CI -0.10 to 0.31], *P* =.296) nor for co-parents (-0.07 [-0.27 to 0.13], *P* =.482). Assessor-rated levels of stimulation and support in the home environment increased in VIA Family; however, not significantly compared with usual treatment (1.79 [95% CI -0.37 to 3.95], *P* =.104).

Table 3 summarises user satisfaction and negative effects. Parents with SMI reported better user satisfaction with VIA Family (3.58 [0.79 to 6.37], *P* =.013) compared with usual treatment. User satisfaction reported by co-parents did not differ significantly between the two groups (2.48 [-1.20 to 6.16], *P* =.179). Negative effects due to treatment did not differ between the two groups, either for parents with SMI (-0.03 [-1.28 to 1.22], *P*=.960) or for co-parents (-0.02 [-0.32 to 0.29], *P*=.901. Also, the reported negative impact of any negative effects due to allocated treatment did not differ between the two groups. Further, we found that negative effects due to other causes were significantly lower for parents with SMI in VIA Family (-1.33 [-2.44 to -0.22], *P*=.019) compared with the usual treatment. On the contrary, negative effects due to other causes were significantly higher for co-parents allocated to VIA Family (0.86 [0.20 to 1.53], *P*=.012).

Table 4 summarises the effects on exploratory outcomes. For parents with SMI, there were no significant group differences in exploratory outcomes. For co-parents, no significant group differences were found, except for family adjustment (-2.46 [-4.04 to -0.87], *P* =.002).

Sensitivity analyses

Sensitivity analysis listed in the **Supplementary** confirmed our main findings. **eFigure 1** visualises sensitivity analyses of HOME-MC/EA and illustrates the skewness of the confidence intervals favouring VIA Family over usual treatment.

Discussion

We conducted a randomised controlled trial investigating the effect of a preventive family-based intervention for school-aged children of parents with SMI. Effects on family functioning and the home environment did not differ significantly between VIA Family and usual treatment. Exploratory outcomes regarding parental stress, parenting skills, family adjustment, and parental daily functioning did not differ between the two groups for parents with SMI. Similarly for co-parents, exploratory outcomes did not differ between the two groups except for family adjustment in favour of VIA Family. However, since we did not adjust for multiple testing, this could be a chance finding. Sensitivity analyses confirmed our main findings. Underpowered analysis on HOME-MC/EA showed wide and skewed confidence intervals suggesting potential effects on levels of stimulation and support in the home environment of VIA Family.

There is no established evidence regarding preventive interventions for children of parents with psychotic disorders (Lannes et al., 2021). A scoping review of interventions appropriate for parents with psychotic disorders, identified 34 interventions from which seven were characterised as Long-Term Tailored Support for the Whole Family defined as a minimum one year duration (Radley et al., 2022). One intervention (besides VIA Family) was studied in an RCT. This RCT of 99 families of parents with depressive, anxiety, or personality disorders, found significant improvement in parenting skills after 2-years Preventive Basic Care Management. However, similar to our findings, they did not find effects measured with HOME (Wansink et al., 2014, 2015).

Meta-analyses have established evidence regarding child outcomes of various interventions for parents with mood disorders (Havinga et al., 2021; Loechner et al., 2018), but to our knowledge no meta-analyses have established evidence regarding effects on family functioning or home environment. To contextualize our findings, we searched trials of family-based interventions supporting parents with SMI. The family-group cognitive-behavioural intervention (FGCB) in the American context for parents with major depressive disorder and in its German adaption GuG-Auf for parents with mental disorders are found to effectively improve child outcomes (Compas et al., 2009, 2015; Löchner et al., 2021, 2023). However, irrespectively of targeting communication between family members there were no measures of family functioning applied in these trials, which makes it difficult to compare FGCB and GuG-Auf with VIA Family. A Chinese RCT of a multiple-family-therapy for parents recovering from depression found significant decrease in psychological distress in parents compared with usual treatment, but similar to our study they did not find effects on family functioning measured with FAD (Ma et al., 2023). In a Greek RCT, the Family Talk (6-8 sessions) intervention and its briefer adaption Let's Talk about Children were both found to effectively improve family functioning measured with FAD (Giannakopoulos et al., 2021).

The differences in effects on FAD between the VIA Family, the multiple-family-therapy and Family Talk/Let's Talk about Children can be attributed to the active treatment components provided but can also be understood considering sample characteristics. In Ma et. al (2023) it was found that at subgroup of families, of parents with depression who were not treated with medication, had improvement in family functioning, which the authors suggest is due milder depression and better daily functioning at baseline (Ma et al., 2023). We suggest this indicate families with less complex needs benefitted, and we hypothesise that families with complex needs (e.g., families with multiple family members having a mental illness) require long-term tailored support.

Families of parents with psychosis are found to be at highest risk of inadequate home environments (Gantriis et al., 2019), and are often characterized by complex needs. A qualitative study examining Family Talk for parents with psychosis concluded that parents need continued support in talking to their children about their mental illness (Strand & Meyersson, 2020), which we would translate into a need for long-term support. Further studies are needed to better conceptualise subgroups of families and to understand which families profit from which interventions.

Strengths and limitations

The main strength of our study is the rigorous RCT design including successful blinding of assessors and researchers. Further, we verified parental diagnosis at expert clinical conferences based on SCAN interviews. Another strength of our study is the recruitment of participants from a register-based cohort of mothers and fathers with SMI, increasing representativity in our sample. Fathers are often overlooked and under-studied considering parental mental illness (Leijdesdorff et al., 2017; Scarlett et al., 2023). A further strength is that we did not compare VIA Family to an exceptionally low use of usual treatment. This was ensured by our thorough baseline assessments and feedback to parents on their children's mental health

status combined with manualised information on available services. This have helped not to overestimate effects of VIA Family; however, it might have increased the risk of a type II error.

The main limitation of our findings is that the VIA Family trial was not powered to assess effects on HOME-MC/EA, nor to perform subgroup analyses. Further studies with adequate power could establish whether VIA Family effectively improves levels of stimulation and support in the home environment. And whether subgroups of families benefitted from VIA Family.

A further limitation of our study is that the Danish versions of the FAD and the HOME-MC/EA are not validated, which may bias our findings.

Challenging representability of our sample, due to lack of funding non-Danish speaking parents and their families could not participate. Further, our recruitment procedure caused sampling bias, since parents who did not read their emails or paper mails, and parents with secret telephone numbers were not recruited. Further, parents with secret addresses would not appear in the register-based cohort, and only seven families (7.4%) were recruited directly from mental health or social services. Altogether, this challenges the generalizability of our findings.

Interpretation of findings

VIA Family might be equally beneficial or unbeneficial compared with usual treatment. Some circumstances must be considered when interpreting our findings. First, the lockdown during the Covid-19 pandemic affected our study and may challenge the ecological validity of our findings since the pandemic involved a massive impact on vocational, educational, social, and personal life for families in Denmark. All physical

meetings were postponed in both treatment groups during the lockdown and use of telephone and video calls was applied. We decided not to adjust for time effects since the lockdown affected both treatment groups.

Second, most families had high educational attainment status and our recruitment process may have caused a sampling bias towards better functioning parents and families. We hypothesise that vulnerable families (e.g., with higher rates of relapse, poorer daily functioning, more poverty, more social marginalization etc.) were less likely to participate due to experiences of stigma and parental overburden. Parental overburden, shame and stigma have previously been reported as challenges in recruiting participants in preventive intervention programmes (Havinga et al., 2021). And as a selective preventive intervention, we applied no criteria of *indication* of a need for intervention as eligibility criteria, which meant that some families, parents, and children had very good functioning at baseline. However, we found a large heterogeneity in parental daily functioning (from being hospitalized to being in full recovery) making it difficult to interpret our findings regarding this heterogeneity in sample characteristics and response to outcome measurements. Further, our study sample was characterised by one in ten of families having referrals sent to child protection or social services by assessors. Further, a group of families were characterized by multiple family members having a mental illness (7% of co-parents met criteria of lifetime SMI and 32% of children met criteria for a DSM-IV or DSM-5 diagnosis) suggesting complex problems and needs in these families. Unfortunately, sample size did not allow subgroup analyses.

Finally, parents with SMI reported superior user satisfaction (self-perceived effectiveness and acceptability) with VIA Family. No differences were found on self-reported negative effects in relation to allocated treatment. Negative effects due to other causes than allocated treatment differed between the two treatment groups. Parents with SMI allocated to the usual treatment group reported more negative effects

due to other causes than treatment. On the contrary, co-parents allocated to VIA Family reported more negative effects due to other causes than treatment. These findings must be interpreted with caution, since we do not know what these other causes were. Future studies are recommended to apply qualitative interviews to explore the positive as well as negative effects experienced by parents and by children.

When planning future studies, it is important to consider that some parents got upset or angry when contacted by phone based on information from health registers. We hypothesise that this relates to stigma in relation to mental illness and fear of involvement from professionals such as ultimately having one's child placed in out-of-home care since such themes are central to parenting and SMI (Harries et al., 2023; Havinga et al., 2021). Finding ways to approach the most vulnerable families demand careful ethical consideration and respectful engagement with parents and children.

In conclusion, we did not find superiority of VIA Family on family functioning or levels of stimulation and support in the home environment compared with usual treatment. Our study was underpowered regarding effects on levels of stimulation and support in the home environment, and we found wide confidence intervals suggesting clinically relevant effects of VIA Family. Parents with SMI reported superior user satisfaction with VIA Family. All in all, our findings indicate that VIA Family is acceptable, and we propose that future trials investigate stepped-care interventions powered to enable subgroup analyses. Long-term follow-up is needed to investigate preventive effects.

Future perspectives

The long-term aim of VIA Family is preventing mental illness in familial-high-risk children by improving family functioning and the home environment during childhood. Three years follow-up interviews and long-term follow-up in registers will investigate preventive effects of VIA Family.

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Contributions

AT and MN together with Merete Bonne and Helle Busck designed the trial and obtained the funding. IG, AM, MM, SC, LM and SN collected data, interviewed participants, and managed the trial. NH taught and

supervised assessors. SI managed data in VIA Family. MM worked as a consultant. IG and AM cleaned and managed data. CH supervised power calculations and statistical analyses. JF supervised the statistical analyses. IG wrote the manuscript draft. All authors reviewed and provided revisions for the manuscript. All authors can access to data through IG, AM, and AT.

Data sharing

Deidentified participant data can be shared in anonymised form from the project leader (AT) on reasonable request after review by the PI group, e.g., assessment of study outline, aims and objectives.

Declaration of interest

All authors declare no competing interests.

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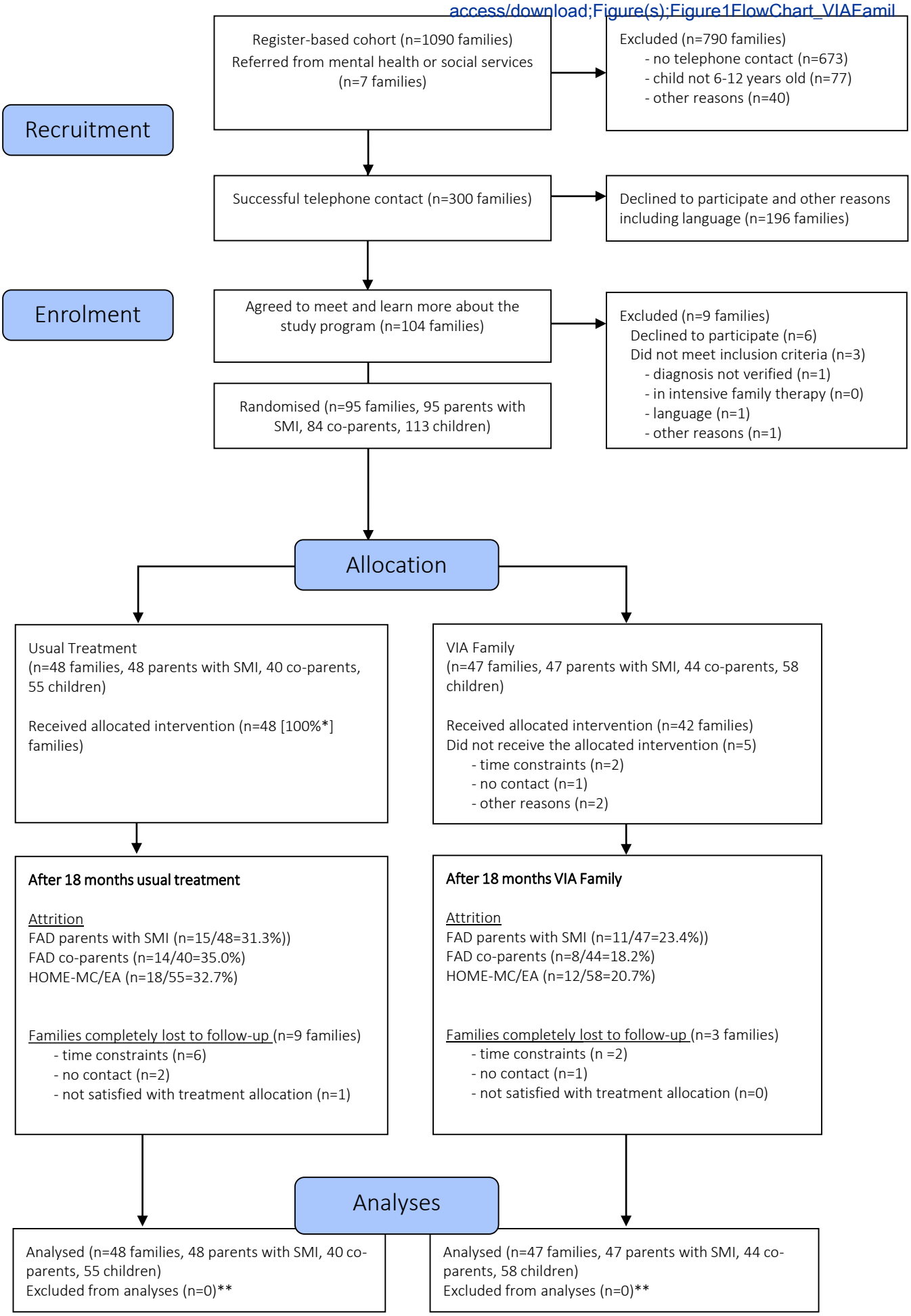
Figure 1



Data are observed n (%). *Note:* FAD=McMaster Family Assessment Device. HOME-MC/EA=Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence. SMI=severe mental illness.
*Since no fidelity criteria were applied to usual treatment, it could not be characterised as discontinued. **Analyses were performed in the intention-to-treat population with missing data handled by multiple imputations, see *Methods* for further information.

Figure 1. Flowchart of participants

Table 1. Baseline characteristics of participants

Parents with severe mental illness		Usual treatment (n=48)	VIA Family (n=47)	All parents with severe mental illness (n=95)
Age	Years	42.05 (6.55)	42.56 (5.63)	42.30 (6.08)
Gender	Female	35 (72.9%)	36 (76.6%)	71 (74.7%)
	Male	13 (27.1%)	11 (23.4%)	24 (25.3%)
Diagnostic group[1]	SZ	6 (12.5%)	6 (12.8%)	12 (12.6%)
	BP	12 (25.0%)	13 (27.7%)	25 (26.3%)
	rMDD	30 (62.5%)	28 (59.6%)	58 (61.1%)
Comorbidities[2]		18 (37.5%)	17 (36.2%)	35 (36.8%)
Substance misuse[1]	Alcohol	3 (6.3%)	3 (6.4%)	6 (6.3%)
	Cannabis, cocaine	..	..	≤ 2
Daily functioning	PSP	60.94 (16.28)	59.60 (14.79)	60.27 (15.48)
Participated as primary caregivers[3]		33 (68.8%)	32 (68.1%)	65 (68.4%)
Co-parents		(n=40)	(n=44)	All co-parents (n=84)
Age	Years	42.31 (5.84)	42.56 (5.18)	42.44 (5.47)
Gender	Female	13 (32.5%)	11 (25.0%)	24 (28.6%)
	Male	27 (67.5%)	33 (75.0%)	60 (71.4%)
Severe mental illness[1]	SZ/BP/rMDD	> 3	< 3	6 (7.1%)
Substance misuse[1]	Alcohol misuse	2 (5.0%)	2 (4.5%)	4 (4.8%)
	Cannabis, cocaine	..	..	≤ 2
Daily functioning	PSP	77.56 (10.81)	77.50 (11.11)	77.53 (10.90)
Participated as primary caregivers[3]		15 (37.5%)	15 (34.1%)	30 (35.7%)
Children		Usual treatment (n=55)	VIA Family (n=58)	All children (n=113)
Age	Years	9.70 (2.02)	9.78 (1.92)	9.74 (1.96)
Gender	Girls	28 (50.9%)	25 (43.1%)	53 (46.9%)
	Boys	27 (49.1%)	33 (56.9%)	60 (53.1%)
Mental disorders	DSM-IV or DSM-5[4]	21 (38.2%)	15 (25.9%)	36 (31.9%)
Families		(n=48)	(n=47)	All families (n=95)
Parents living together		18 (37.5%)	25 (53.2%)	43 (45.3%)
Education[5]	Primary or lower secondary	4 (8.3%)	9 (19.1%)	13 (13.7%)
	Upper secondary, vocational, or short-cycle tertiary	13 (27.1%)	12 (25.5%)	25 (26.3%)

	Bachelor's degree, or higher	31 (64.6%)	26 (55.3%)	57 (60.0%)
Employment[5,6]		35 (72.9%)	34 (72.3%)	69 (72.6%)

Data are mean (SD) or n (%) unless otherwise specified. *Note*: BP=bipolar disorder. DSM= Diagnostic and Statistical Manual of Mental Disorders. PSP=Personal and Social Performance Scale. rMDD=recurrent major depressive disorder. SZ=schizophrenia spectrum disorder.

[1] Diagnoses were concluded at expert clinical conferences based on interviews with the Schedules for Clinical Assessment in Neuropsychiatry and classified according to the International Classification of Diseases tenth revision.

[2] Self-reported diagnosis verified by hospital journals: substance misuse, eating disorder, ADHD, PTSD, or personality disorders.

[3] The primary caregiver was the parent who gave information about the child with the criteria of knowing the child well and living with the child minimum 50% of the time.

[4] Criteria were met within the past 8 weeks. Diagnoses were concluded at expert clinical conferences based on interviews with the Kiddie Schedule for Affective Disorders and Schizophrenia for school-aged children. Excl. elimination disorder, simple phobia, and tics/Tourette's syndrome.

[5] Self-reported by the primary caregivers (n=95).

[6] Any form of employment with no minimum working hours. Studying and absence from work (e.g., sick leave, maternity/paternity leave) was defined as employment.

Table 2. Estimated treatment effects on family functioning and levels of stimulation and support in the home environment

FAD general family functioning[1]				
Parents with severe mental illness (n=95)	Usual treatment (n=48)	VIA Family (n=47)	Adjusted mean difference[2] (95% CI)	*P*-value
0 months	2.08 (0.50); n=44 (91.7%)	1.91 (0.51); n=42 (89.4%)	-	
18 months	1.77 (0.46); n=33 (68.8%)	1.82 (0.53); n=36 (76.6%)	0.11 (-0.10 to 0.31)	.296
Co-parents (n=84)	(n=40)	(n=44)		
0 months	1.91 (0.38); n=37 (92.5%)	1.89 (0.48); n=38 (86.4%)	-	
18 months	1.67 (0.36); n=26 (65.0%)	1.62 (0.47); n=36 (81.8%)	-0.07 (-0.27 to 0.13)	.482
HOME-MC/EA Levels of stimulation of support in the home environment[3]				
Children (n=113)	Usual treatment (n=55)	VIA Family (n=58)	Adjusted mean difference[4] (95% CI)	*P*-value
0 months	46.74 (5.85); n=53 (96.4%)	46.42 (6.07); n=55 (94.8%)	-	
18 months	45.86 (5.31); n=37 (67.3%)	47.17 (5.58); n=46 (79.3%)	1.79 (-0.37 to 3.95)	.104

Data are observed unadjusted mean (SD) or n (%) unless otherwise specified. *Note:* FAD=McMaster Family Assessment Device. HOME-MC/EA=Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence.

[1] FAD: lower scores, better family functioning.

[2] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, with missing data handled by multiple imputations.

[3] HOME-MC/EA: higher scores, higher levels of stimulation of support in the home environment.

[4] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and child's gender, and including a random effect of family. Missing data handled by multiple imputations.

Table 3. User satisfaction and negative effects

CSQ User satisfaction[1]			Adjusted mean difference[2] (95% CI)	*P*-value
Parents with severe mental illness (n=95)	(n=48)	(n=47)		
18 months	23.55 (6.11); n=31 (64.5%)	27.19 (4.14); n=37 (78.7%)	3.58 (0.79 to 6.37)	**.013**
Co-parents (n=84)	(n=40)	(n=44)		
18 months	24.07 (5.27); n=14 (35.0%)	26.55 (3.59); n=33 (75.0%)	2.48 (-1.20 to 6.16)	.179
NeQ Negative effects				
Parents with severe mental illness (n=95)	(n=48)	(n=47)		
Negative effects due to allocated treatment	1.80 (2.71); n=35 (72.9%)	1.78 (2.75); n=37 (78.7%)	-0.03 (-1.28 to 1.22)	.960
Impact of negative effects due to allocated treatment	2.10 (0.64); n=18 (37.5%)	1.77 (0.98); n=20 (42.6%)	-0.12 (-0.96 to 0.73)	.777
Negative effects due to other causes	2.77 (2.94); n=35 (72.9%)	1.46 (1.98); n=37 (78.7%)	-1.33 (-2.44 to -0.22)	**.019**
Impact of negative effects due to other causes	2.25 (0.91); n=23 (47.9%)	2.12 (0.79); n=21 (44.7%)	-0.12 (-0.80 to 0.55)	.710
Co-parents (n=84)	(n=40)	(n=44)		
Negative effects due to allocated treatment	0.22 (0.64); n=27 (67.5%)	0.23 (0.60); n=35 (79.5%)	-0.02 (-0.32 to 0.29)	.901
Impact of negative effects due to allocated treatment	0.75 (0.96); n=4 (10.0%)	0.60 (0.55); n=5 (11.4%)	0.87 (-0.91 to 2.65)	.329
Negative effects due to other causes	0.11 (0.32); n=27 (67.5%)	0.89 (1.95); n=35 (79.5%)	0.86 (0.20 to 1.53)	**.012**
Impact of negative effects due to other causes	0.33 (0.58); n=3 (7.5%)	1.18 (0.80); n=11 (25.0%)	0.87 (-0.91 to 2.65)	.329

Data are observed unadjusted mean (SD) or n (%) unless otherwise specified. *Note:* CSQ=Client Satisfaction Questionnaire. NeQ=Negative Effects Questionnaire.

[1] CSQ: higher scores, better user satisfaction

[2] Analysis of covariance performed in the intention-to-treat population with adjustment for baseline score, stratum (severe mental illness diagnostic group), and gender, and with missing data handled by multiple imputations.

[3] NeQ: higher scores, more negative effects

Supplementary materials

Contents

Diagnostic codes

- Schizophrenia spectrum disorder:
    - ICD-10: F20, F21, F22, or F25.
    - ICD-8: 295, 297, 298.29, 298.39, 298.89, 298.99, or 301.83.
- Bipolar affective disorder:
    - ICD-10: F30 or F31
    - ICD-8: 296.19 or 296.39.
- Recurrent major depressive disorder:
    - ICD-10: F 33.1, F33.2, or F 33.3
    - ICD-8: 296.0, 298.0 or 300.4.

Changes to protocol

We made three changes to the published protocol[1].

- First, our predefined secondary per-protocol analysis (attending a minimum of 50 % intended personal meetings) was not considered meaningful by VIA Family case managers. They did not find it meaningful to establish a universal criterion of intended personal meetings, whereby we pragmatically decided it changed to a cut-off of a minimum of 15 sessions.
- Second, concerning fidelity, psychoeducation was reported with a minimum cut-off of 3 sessions instead of 1 session since case managers found this an adequate estimate of minimum use of psychoeducation.
- Third, concerning fidelity with VIA Family. A minimum of 15 sessions with a family's case manager was our initial definition of compliance with treatment. However, case managers found a cut-off of combined 15 sessions VIA Family (not selectively with case manager) meaningful and became the definition of fidelity with VIA Family.

[1] 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). https://doi.org/10.1186/s13063-019-3191-0

VIA Family

eTable 1. Families' use of VIA Family

Basic treatment components	Families (n = 47)
Assigned a case manager	47 (100 %)
Introduction sessions with case manager completed (cut-off 2 sessions)	44 (93.62 %)
Parenting intervention. Either Triple-P level 2 (seminar), Triple-P level 3 (1-3 sessions), or parenting support (1-3 sessions).	41 (87.23 %)
Psychoeducation about mental illness or emotions (cut-off 3 sessions)	22 (46.81 %)
Support on collaboration between parents (cut-off 1 session)	20 (42.55 %)
Triple-P level 4-5 /Stepping-stones (3 or more sessions). Individual sessions for parents (involving children in sessions, where parenting is practiced with focus on the learned positive parenting strategies)	16 (34.04 %)
Practical support on parenting (cut-off 1 session). E.g., structuring daily activities.	13 (27.66 %)
Safety plan (cut-off 2 session)	6 (12.77 %)
Additional Elements in VIA Family	
Counselling and guidance regarding financial, social, or practical support from the municipality (cut-off 1 meeting)	22 (46.81 %)
Optimization of the ill parent's treatment and lifestyle (cut-off 1 session)	20 (42.55 %)
Case manager participated in meeting with public job centres or social services (cut-off 1 meeting)	12 (25.53 %)
Specialized treatment for the child's (transient or sub-threshold) mental health difficulties. Including psychoeducation of parents on how to structure everyday life at home to support the child (cut-off 1 session)	19 (40.43 %)
Case manager participated in meeting with schools and/or other institutions (cut-off 1 meeting)	13 (13/47 = 27.66 %)
Peer support groups incl. group psychoeducation led by one/two case managers	
Children's groups Families, n = 47 Children aged 6-12-years at baseline, n = 58	32 (32/47 = 68.09 %) 36 (36/58 = 62.70 %)
Parent's groups (one or both parents in families participated) Families, n = 47	31 (31/47 = 65.96 %)
Teenage Children's Groups Families, n = 47 Siblings 13-20-years, n = 11	 4 (4/47 = 8.51 %) 5 (5/11 = 45.45 %)

Usual treatment

eTable 2. Usual treatment 6 months before baseline assessments

Families (n=95)	Usual treatment (n=48)	VIA Family (n=47)	Chi-square, Risk Ratio (95% CI); *P*-value)
Families interviewed about use of services (n=86 [90.1%])	(n=44 [91.7%])	(n=42 [89.4%])	
Child and Adolescent Mental Health Services (CAMHS)	7 (15.9%)	3 (7.1%)	0.45 (0.12 to 1.62); p=0.315
Parents' Use of Services in Mental Health Services (MHS)[2]	13 (29.5%)	15 (35.7%)	1.21 (0.66 to 2.23); p=0.647
Next-of-kin support in MHS	4 (9.1%)	2 (4.7%)	0.52 (0.10 to 2.71); p=0.677
Contact with Municipality	8 (18.2%)	6 (14.3%)	0.79 (0.30 to 2.07); p=0.772
School or Day-care Psychological Support for Children (Municipality)	6 (13.6%)	8 (19.0%)	1.40 (0.53 to 3.69); p=0.567
Contact with Social Worker in Social Services (Municipality)	11 (25.0%)	10 (23.8%)	0.95 (0.45 to 2.01); p=1
Medical doctor appointments incl. prescription on psychotropics (Free of Charge, General Practitioner)	6 (13.6 %)	7 (16.7%)	1.22 (0.45 to 3.34); p=0.769
Public Job Centres	0 (0.0%)	2 (4.8%)	..
Private Psychologist or primary sector public free-of-charge Psychiatrist	16 (36.4%)	19 (45.2%)	1.24 (0.74 to 2.08); p=0.511
Services at non-for-profit organizations	5 (11.4%)	3 (7.1%)	0.63 (0.16 to 2.47); p=0.714
Contact with Social Services	1 (2.3%)	3 (7.1 %)	3.14 (0.34 to 29.03); p=0.355

[2] including psychiatric hospitalization, psychotherapy, medical appointments with psychiatrist etc.

eTable 3. Usual treatment 6 months before the 18-month assessments

Families (n=95)	Usual treatment (n=48)	VIA Family (n=47)	Chi-square, Risk Ratio (95% CI); *P*-value)
Families interviewed about use of services (n=84 [88.4%])	(n=40 [83.3%])	(n=44 [93.6%])	
Child and Adolescent Mental Health Services (CAMHS)	4 (10.0%)	2 (4.5%)	0.45 (0.09 to 2.35); p=0.418
Parents' Use of Services in Mental Health Services (MHS)[3]	15 (31.3%)	14 (29.8%)	0.85 (0.47 to 1.53); p=0.649
Next-of-kin support in MHS	2 (5.0%)	1 (2.3%)	0.45 (0.04 to 4.82); p=0.603
Contact with Municipality	5 (12.5%)	3 (6.8%)	0.55 (0.14 to 2.14); p=0.469
School or Day-care Psychological Support for Children (Municipality)	6 (15 %)	4 (9.1%)	0.61 (0.18 to 1.99); p=0.508
Contact with Social Worker in Social Services (Municipality)	9 (22.5%)	10 (22.7%)	1.01 (0.56 to 2.23); p=1
Medical doctor appointments incl. prescription on psychotropics (Free of Charge, General Practitioner)	5 (12.5%)	8 (18.2%)	1.45 (0.52 to 4.08); p=0.555
Public Job Centres	4 (10.0%)	7 (15.9%)	1.59 (0.50 to 5.03); p=0.53
Private Psychologist or primary sector public free-of-charge Psychiatrist	8 (20.0%)	22 (50.0%)	2.50 (1.26 to 4.97); **p=0.006**
Services at non-for-profit organizations	3 (7.5%)	5 (11.4%)	1.52 (0.39 to 5.94); p=0.715
Contact with Social Services	0 (0.0%)	0 (0.0%)	..

[3] including psychiatric hospitalization, psychotherapy, medical appointments with psychiatrist etc.

Sensitivity analyses

Summary of sensitivity analyses

Findings from complete case analyses did not differ from our primary analyses. Analysis of the removal of outliers could not be performed regarding family functioning since no cases were identified by the criteria of scores greater than three residuals from the mean. Our first predefined per-protocol analysis (defined as participants not having a single contact with VIA Family) could not be performed since no cases were identified by this criterion. Our second per-protocol analysis, defined by having a minimum of 15 contacts or sessions at VIA Family, did not differ from our main findings.

McMaster Family Assessment Device; FAD

Higher scores indicate more impairment in family functioning

Primary analysis: parents with severe mental illness

Parents with severe mental illness (n=95)	Usual Treatment (n=48)		VIA Family (n=47)		Adjusted difference* (95% CI); p-value
Assessment timepoint	0	18	0	18	
General family functioning (FAD)	2·1 (0·5); n=44 (92%)	1·8 (0·5); n=33 (69%)	1·9 (0·5); n=42 (89%)	1·8 (0·5); n=36 (77 %)	0·11 (-0·10 to 0·31); p=0·296
Data are observed unadjusted mean (SD) or n (%) unless otherwise specified. *Note:* FAD=McMaster Family Assessment Device. *Adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), and parent's gender.					

Complete case analysis: parents with severe mental illness

Parents with severe mental illness (n=66 [69%])	Usual Treatment (n=31 [65%])		VIA Family (n=35 [77%])		Adjusted difference* (95% CI); p-value
Assessment timepoint	0	18	0	18	
General family functioning (FAD)	1·93 (0·42)	1·73 (0·44)	1·93 (0·51)	1·82 (0·54)	0·08 (-0·10 to 0·26); p=0·391
Data are observed unadjusted mean (SD) and estimates of complete cases n (% of the full sample). *Note:* FAD=McMaster Family Assessment Device. *Analyses adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), and parent's gender.					

Per protocol analysis: parents with severe mental illness

Parents with severe mental illness (n=90 [95%*])	Usual Treatment (n=48 [100%*])		VIA Family (n=42 [89%*])		Adjusted difference*** (95% CI); p-value
Assessment timepoint	0	18	0	18	
General family functioning (FAD)	2.08 (0.50); n=44 (92%**)	1.77 (0.46); n=33 (69%**)	1.98 (0.50); n=37 (88%**)	1.85 (0.52); n=35 (83%**)	0.11 (-0.09 to 0.31); p=0.272
Data are observed and unadjusted mean (SD). *Note:* FAD=McMaster Family Assessment Device. * n (% of the full sample). **n (% of the per-protocol sample). ***Analysis set-up as main analysis handling missing data by multiple imputations and adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), and parent's gender. The per protocol criteria for VIA Family was defined as a minimum of 15 contacts or sessions with case managers. No minimum or maximum criteria were applied to define the use of services in usual treatment, hence, the per-protocol population allocated to usual treatment is identical to the intention-to-treat population allocated to usual treatment.					

Main analysis: co-parents

Co-parents (n=84)	Usual Treatment (n=40)		VIA Family (n=44)		Adjusted difference** (95% CI); p-value
Assessment timepoint	0	18	0	18	
General family functioning (FAD)	1·9 (0·4); n=37 (93%)	1·7 (0·4); n=26 (65%)	1·9 (0·5); n=38 (86%)	1·6 (0·5); n=36 (82%)	-0·07 (-0·27 to 0·13); p=0·482
Data are observed unadjusted mean (SD) or n (%), unless otherwise specified. *Note:* FAD=McMaster Family Assessment Device. *Adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), and parent's gender.					

Complete case analysis: co-parents

Co-parents (n=56 [67%])	Treatment as Usual (n=24 [60%])		VIA Family (n=32 [73%])		Adjusted difference* (95% CI); p-value
Assessment timepoint	0	18	0	18	
General family functioning (FAD)	1.85 (0.33)	1.65 (0.37)	1.87 (0.46)	1.67 (0.47)	0.01 (-0.19 to 0.21); p=0.914

Data are observed unadjusted mean (SD) and estimates of complete cases n (% of full sample). *Note:* FAD=McMaster Family Assessment Device. *Analyses adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), and parent's gender.

Per protocol analysis: co-parents

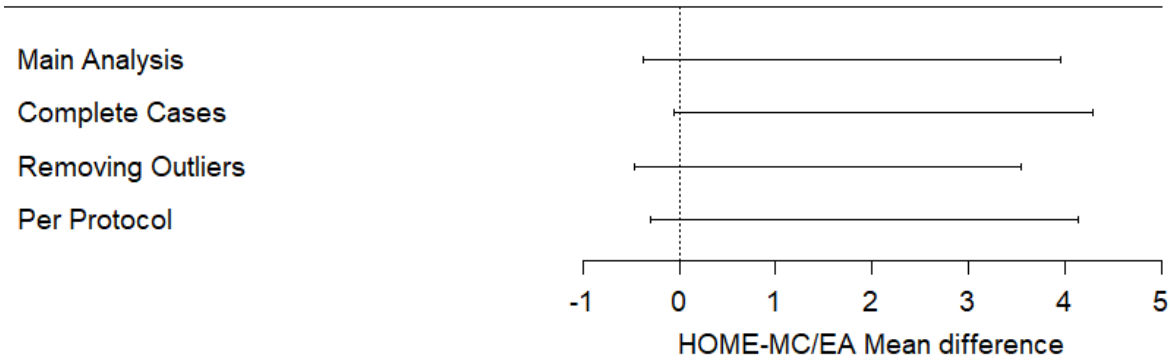
Co-parents (n=79 [94%*])	Treatment as Usual (n=40 [100%*])		VIA Family (n=39 [89%*])		Adjusted difference* (95% CI); p value
Assessment timepoint	0	18	0	18	
General family functioning (FAD)	1.91 (0.38); n=37 (93%**)	1.67 (0.36); n=26 (65%**)	1.97 (0.47); n=33 (85%**)	1.66 (0.46); n=34 (87%**)	-0.05 (-0.25 to 0.16); p=0.628

Data are observed and unadjusted mean (SD). *Note:* FAD=McMaster Family Assessment Device. *n (% of the full sample). **n (% of the per-protocol sample). ***Analysis set-up as main analysis handling missing data by multiple imputations and adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), and parent's gender.

Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence; HOME-MC/EA

Higher scores indicate higher levels of stimulation and support in the home environment

eFigure 1. Forest plot of HOME-MC/EA sensitivity analysis



The forest plot illustrates sensitivity analyses of estimated treatment effects on the home environment measured with the HOME Inventory (HOME-MC/EA) of VIA Family compared with usual treatment.

Main analysis: HOME-MC/EA children in families

Children (n=113); Families (n=95)	Treatment as Usual (n=55 children)		VIA Family (n=58 children)		Adjusted difference* (95% CI); p-value
Assessment timepoint	0	18	0	18	
Quality of home environment (HOME-MC/EA)	46.74 (5.85); n=53 (96%)	45.86 (5.31); n=37 (67%)	46.42 (6.07); n=55 (95%)	47.17 (5.58); n=46 (79%)	1.79 (-0.37 to 3.95); p=0.104
Data are observed unadjusted mean (SD) or n (%) unless otherwise specified. *Note:* HOME-MC/EA= Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence.*Adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), child's gender, and random effect of children nested in families.					

Complete case analysis: HOME-MC/EA children in families

Children (n=78 [69%]); Families (n=65 [68%])	Treatment as Usual: Children (n=35 [64%]); Families (n=31 [65%]) families)		VIA Family (n=43 [74%]) children, (n=34 [72%]) families)		Adjusted difference* (95% CI); p-value
Assessment timepoint	0	18	0	18	
Quality of home environment (HOME-MC/EA)	47.51 (4.55)	45.77 (5.34)	47.26 (5.77)	47.63 (5.35)	2.12 (-0.06 to 4.29); p=0.056
Data are observed unadjusted mean (SD) and estimates of complete cases n (% of the full sample). *Note:* HOME-MC/EA= Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence. *Adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), child's gender, and random effect of children nested in families.					

Removing outliers analysis: HOME-MC/EA children in families

Children (n=111 [%*]); Families (n=93 [%*])	Treatment as Usual: Children (n=54 [%*]); Families (n=47 [%*])		VIA Family: Children (n=57 [%*]); Families (n=46 [%*])		Adjusted difference*** (95% CI); p-value
Assessment timepoint	0	18	0	18	
Quality of home environment (HOME-MC/EA)	47.21 (4.77); n=	45.86 (5.31)	46.81 (5.36)	47.31 (5.57)	1.45 (-0.64 to 3.54); p= 0.173
Data are observed and unadjusted mean (SD). *Note:* HOME-MC/EA= Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence. *n (% of the full sample). ** n (% of the sample after removal					

of outliers, +-3SD). ***Analyses adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), child's gender, and random effect of children nested in families. Outliers are defined as exceeding +-3 standard deviations.

Per protocol analysis: HOME-MC/EA children in families

Children (n=108 [96%] *); Families (n=90 [95%*])	Treatment as Usual: Children (n=55 [100%*]); Families (n=48 [100%*])		VIA Family: Children (n=52 [90%*]); Families (n=42 [89%*])		Adjusted difference*** (95% CI); p-value
Assessment timepoint	0	18	0	18	
Quality of home environment (HOME-MC/EA)	46.74 (5.85); n=53 (96%**)	45.86 (5.31); n=37 (67%**)	46.63 (6.22); n=49 (94%**)	47.20 (5.71); n=44 (85%**)	1.92 (-0.29 to 4.13); p=0.089

Data are observed and unadjusted mean (SD). *Note:* HOME-MC/EA= Home Observation Measurement of the Environment Middle-Childhood or Early-Adolescence.
* n (% of the full sample). ** n (% of per protocol sample). ***Analysis set-up as main analysis handling missing data by multiple imputations and adjusted for baseline score, allocated treatment group, stratum variable (parent with severe mental illness diagnostic group), child's gender, and random effect of children nested in families.

The per protocol criteria for VIA Family was defined as a minimum of 15 contacts or sessions with case managers. No minimum or maximum criteria were applied to define use of services in usual treatment, hence, the per protocol population allocated to usual treatment is identical to the intention-to-treat population allocated to usual treatment.

Att. Editors-in-Chief:

Kenneth S. Kendler, *Virginia Institute for Psychiatric and Behavioral Genetics,Dept of Psychiatry, Virginia Commonwealth University, P O Box 980710, Richmond, VA 23298-0710, USA,* and

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Please consider our manuscript entitled *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* for publication in *Psychological Medicine.* Our manuscript presents unique data from an innovative study and is not considered for publication elsewhere.

We are the first to report on the effects of a preventive intervention for children of parents with severe mental illness including psychotic disorders. We did not find superior treatment effects of the experimental family-based intervention (VIA Family) compared with usual treatment. However, we cannot rule out a clinically relevant effect on blinded assessor-rated levels of stimulation and support in the home environments. And parents with severe mental illness reported superior effectiveness and acceptability with VIA Family compared with usual treatment.

We provide valuable findings for future evidence-synthesis of preventive interventions targeting the harmful cascading consequences of intergenerational transmission of severe mental illness. We hope you will find our manuscript of interest to the readers of *Psychological Medicine*.

On behalf of all authors,

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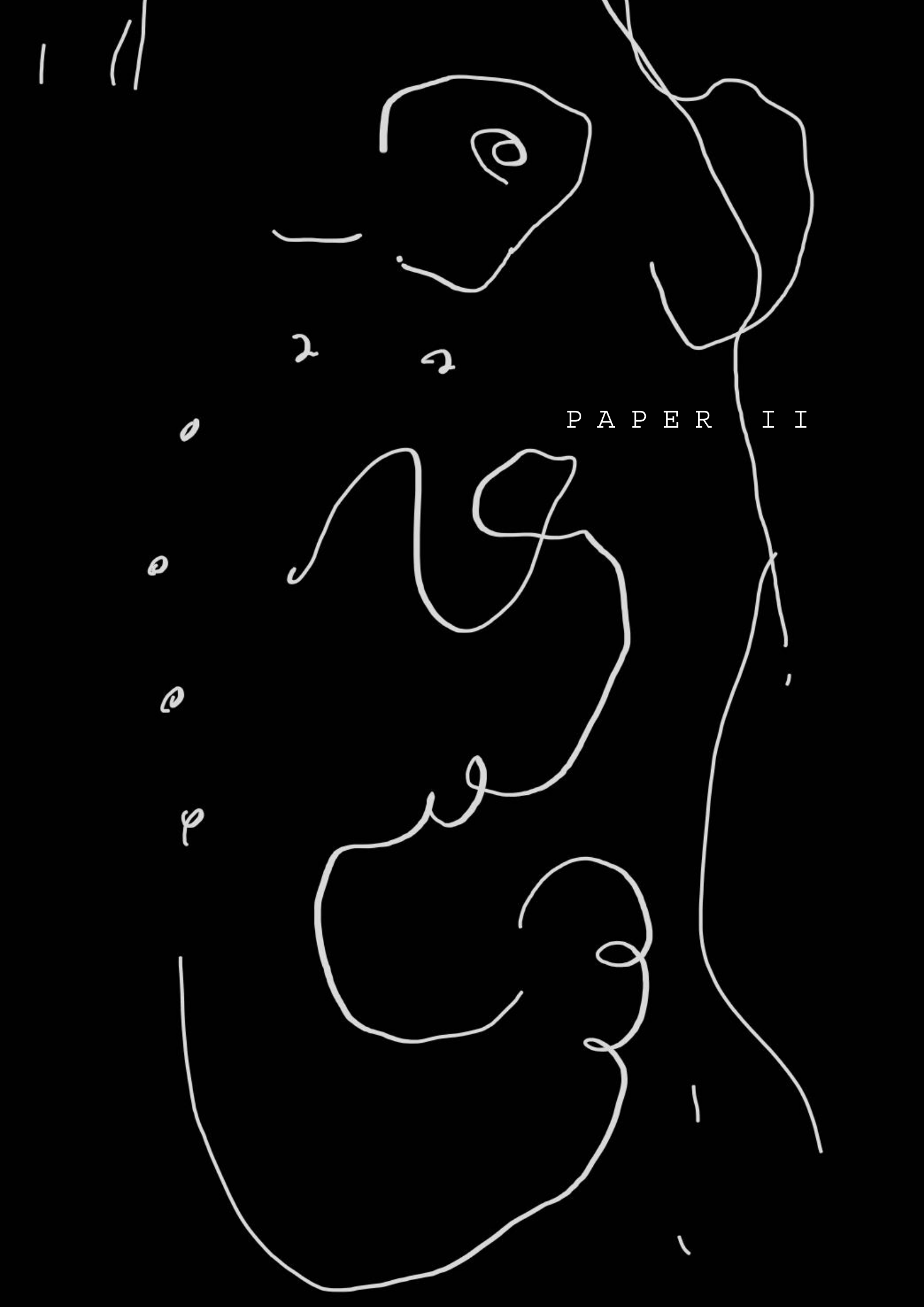
PAPER II

1. Title page

Title

Association of Maternal and Paternal Personality Disorders With Risk of Mental Disorders in Children. A Nationwide, Register-Based Cohort Study of 1,406,965 Children

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Key Points

Question*:* Are children of parents with personality disorders at an increased risk of developing mental disorders compared with nonexposed children?

Findings*:* In this cohort study of 1,406,965 children, parental personality disorders was associated with 2 to 3.5 times higher risk of mental disorders in offspring. Absolute risk (34.1%) at age 18 was more than double the absolute risk in nonexposed children (15.2%).

Meaning*:* Parental personality disorders were associated with risk of mental disorders in children comparable to risk of mental disorders in children of parents with schizophrenia, bipolar disorder, and major depressive disorder.

2. Abstract

Importance: Knowledge of the association between parental personality disorders and mental disorders in children is limited.

Objectives: To examine the association between parental personality disorders and risk of mental disorders in offspring.

Design, Setting, and Participants: We linked Danish health registers to create a cohort of children born from January 1, 1995, to December 31, 2016. Children were followed until 18th birthday, diagnosis set, emigration, death, or December 31, 2016.

Exposures: Parental personality disorders according to the International Classification of Diseases (ICD) Eighth or 10th Revision.

Main Outcomes and Measures: Poisson regression analyses were used to estimate incidence risk ratio (IRR) and cumulative incidence of ICD 10th mental disorders in offspring (age 0-17).

Results: The study cohort included 1,406,965 children. For girls, maternal or paternal personality disorder (MPD/PPD) was associated with mental disorders: MPD girls (IRR, 2.74; 95% CI, 2.59-2.89) and PPD girls (IRR, 2.10; 95% CI, 1.94-2.27). Likewise, risk was increased for both MPD boys (IRR, 2.44; 95% CI, 2.33-2.56) and PPD boys (IRR, 2.04; 95% CI, 1.91-2.18). For girls and boys combined, exposure to two parents with a personality disorder was associated with the highest risk (IRR, 3.69; 95% CI, 3.15-4.33). At age 18 cumulative incidence of any mental disorder in children of one or two parents with a personality disorder was 34.1% (95% CI, 33.0-35.1) which was twice the cumulative incidence of mental disorders in nonexposed children (15.2% [95% CI, 15.1-15.3]).

Conclusion and Relevance: Children of parents with a personality disorder were at a 2 to 3.5 times higher risk of mental disorders compared with nonexposed offspring. Possible mechanisms of transmission of mental disorders from parent to child involve genetic, environmental, and gene-environment pathways. More research into these mechanism and research into preventive interventions is warranted.

Keywords borderline, dissocial, antisocial, children of parents with a mental illness

3. Text

Introduction

Children of parents with a mental disorder are at increased risk of developing a mental disorder[1–6]; however, knowledge of the association of parental personality disorder with mental disorder in offspring is limited. Personality disorders are characterized by pervasive difficulties in interpersonal relationships across contexts including family, workplace, friendships and parent-child relationships[7–11]. Personality disorders are further associated with substance use disorders, reduced quality of life, poor health, self-harm, suicide and premature mortality[7,8], which are known risk factors for family disruptions, unstable parenting behavior, and ill mental health in offspring.

Parents with personality disorders are more likely to engage in problematic parenting behaviors than controls[9,11–14]. A central aspect of parenting is the ability to manage negative emotions in oneself and in others, and to respond adequately to the distress in children without hostility, panic, or neglect[9]. A core feature in cluster B personality disorders is emotion dysregulation[15–18], which is associated with negative parenting and with emotional and behavioral problems in offspring[18–23]. Observational studies have found that parental cluster B personality disorder symptoms are associated with ill mental health in pre-school offspring[24,25], and further predict decreased social skills in school-aged offspring[26].

The first aim of this study was to investigate if there was an association between parental personality disorders and mental disorders in offspring during childhood and adolescence (age 0-

17). The second aim was to investigate whether the risk of mental disorders in offspring was highest among parents with cluster B personality disorders: emotionally unstable personality disorder (EUPD) and dissocial personality disorder (DPD) when compared to other parental personality disorder subtypes.

Methods

To create our study cohort, we linked information across the Danish Civil Registration System[27], Danish Psychiatric Central Research Register[28] , The Danish National Patient Registry[29], and Statistics Denmark[30]. Information was linked completely de-identifed on an individual level by use of personal identification numbers, which individuals in Denmark are assigned at birth or at immigration[27,31]. The Danish Civil Registration System contains information on date of birth, sex, marital status, parental status, death, and emigration, which enables linkage of children to their legal parents[27,31]. Mental disorder diagnoses registered in the Danish Psychiatric Central Research Register and the Danish National Patient Register were concluded by psychiatrists in the free of charge mental health services. Results are reported following the Strengthening the Reporting of Observational Studies in Epidemiology guideline.

Study Population

Our study cohort consisted of all children born in Denmark from January 1, 1995, until December 31, 2016. Children were followed from birth until 18th birthday, date of emigration, death, being diagnosed with a mental disorder in the *International Classification of Diseases (ICD), 10th Revision*, or until December 31, 2016. Information on race or ethnicity was not obtained.

Exposure

Exposure was defined as parental personality disorders diagnosed before the child's birth. Diagnostic codes: ICD-10: F60.xx + F61.x (excluding F62-69). ICD-8: 301.0-301.9, 301.x9 (not 301.19), 301.80, 301.81, 301.82, 301.84 (eTable 1 in **Supplement**). From 1969 to 1993, ICD-8, and from 1995 until 2016 ICD-10 was used in Denmark[32]. We further estimated incidence risk ratios of all subtypes of ICD-10 personality disorders. ICD-8 are excluded from the secondary analysis since subgroups in the two versions of ICD are not sufficiently compatible. To avoid the same parent to count in multiple diagnostic categories we applied a hierarchy in which F60.0 overrules F60.1-9 and F61, and F60.1 overrules F60.2-9 and F61, etc. Thus F61.0 is overruled by all other personality disorder subtypes. To study interaction with parental comorbidity with substance use disorder we used the following ICD-10 codes: F1x, and ICD8: 303, 304, 291, 5711, 57109.

Outcomes

Outcomes were defined as the full spectrum of ICD-10 mental disorders: F00-99 (eTable 2 in **Supplement**).

Statistical Analysis

Poisson regression analysis was performed to provide estimates of relative risk as incidence risk ratios. We used the GENMOD procedure in SAS software, release 9.4 (SAS Institute, Inc), to perform the Poisson regression analysis with the logarithm of person-years as an offset. This

method approximates a Cox Regression model[33]. The 95% confidence intervals were based on Wald's test statistics. We considered two-sided p-values less than 5% to be significant. We further estimated cumulative incidence curves (CIFs) using the Nelson-Aalen estimator with adjustments for competing risks from death and emigration. Analyses were adjusted for child age, sex, and calendar period. Child's age and calendar year were grouped in year groups. For each outcome, follow-up of a child ended when a diagnosis was registered. That is, if child x was registered with ADHD at age 7, then child x was excluded at age 7 in the analysis with ADHD as outcome. Child x remained in analyses of other outcomes. In the analysis with *any mental disorder* as outcome, child x was excluded at first registered diagnosis. We evaluated 95% confidence intervals to investigate differences in risk of mental disorder in children across different parental personality subtypes. Further, we investigated interaction between parental personality disorder and comorbid parental substance use disorder on the association with offspring mental disorders. Sensitivity analyses were performed adjusting main analyses for parental socio-economic status to investigate robustness of our findings. Forest plots were created with R studio, version 4.2.0[34]. Data was analyzed from December 2019 through April 2020. Draft was prepared from December 2022 through May 2023.

Results

This study cohort consisted of 1,406,965 children of whom 35,484 (2.5%) were born to one or two parents with a personality disorder before birth of the child. The total number of follow-up years varied and depended on the frequency of the outcome. The maximum number of follow-up years was 15,057,110 person-years, producing 10.7 years-at-risk. Out of the full cohort (1,406,965

children) a total of 108,853 (7.7%) children (44,933 [6.6%] girls and 63,920 [8.9%] boys) developed a mental disorder during follow-up.

Table 1 shows adjusted IRRs of mental disorders in children exposed to maternal personality disorder (MPD) and/or paternal personality disorder (PPD) compared with nonexposed children. Having two parents with personality disorder was associated with highest IRR, 3.69, (95% CI: 3.15-4.33), followed by MPD alone: IRR, 2.61 (95% CI: 2.52-2.71), and PPD: IRR, 2.17 (95% CI: 2.06-2.28). Sensitivity analyses showed that a higher level of parental education at child's birth was associated with lower risk of mental disorders compared with lower levels of parental education (eTable 3 in **Supplement**), however, risk was still increased in the context of high levels of education and as a proxy for socioeconomic status these findings confirm robustness of the association between MPD and PPD with mental disorders in offspring.

Figure 1 and **Figure 2** show risk of mental disorder in boys vs girls in the context of MPD and PPD respectively. Risk was increased for both boys and girls when compared with nonexposed children, and risk was increased for both boys and for girls in the context of both MPD and PPD. Across the full spectrum of the ICD-10 diagnoses of mental disorders, IRRs were significantly increased in offspring exposed to either MPD or PPD with few exceptions: MDD boys sleep disorders (IRR, 1.12 [95% CI, 0.74-1.70]; PPD girls sleep disorders (IRR, 1.12 [95% CI, 0.60-2.10]); PPD boys sleep disorders (IRR, 1.05 [95% CI, 0.63-1.75]); and PPD boys eating disorders (IRR, 1.19 [95% CI, 0.79-1.79]).

Figure 3 visualizes cumulative incidence of mental disorder in children exposed to one or two parents with a personality disorder. Absolute risk at age 18 was 34.1% (95% CI, 33.0-35.1) which is twice the risk in nonexposed children: 15.2% (95% CI, 15.1 to 15.3). Absolute risk in exposed girls at age 18 was 33.0% (95% CI, 31.5 to 34.6) and for nonexposed girls was 14.7% (95% CI, 14.5 to 14.8). Absolute risk in exposed boys at age 18 was 35.1% (95% CI, 33.7 to 36.5) and for nonexposed boys was 15.7% (95% CI, 15.5 to 15.8). Cumulative incidence respectively for girls and boys is visualized in eFigure 1 in **Supplement**.

Table 2 shows adjusted IRRs of mental disorders in children across MPD and/or PPD subtypes. Children of mothers with EUPD an increased risk of having been diagnosed with any mental disorder before age 18 compared with nonexposed children (IRR, 2.89 [95% CI, 2.73-3.05]). The following MPD subtypes were associated with lower risk than maternal EUPD: F60.6 Anxious-avoidant personality disorder (IRR, 2.00 [95% CI, 1.75-2.28]), F60.7 Dependent personality disorder (IRR, 2.29 [1.94-2.71]), and F60.9 Disorder of personality structure, combined and other type (IRR, 2.33 [2.15-2.53]). Children of mothers with DPD had an increased risk of having been diagnosed with any mental disorder before age 18 compared with nonexposed children (IRR, 3.39 [95% CI: 2.52-4.56]). Across ICD-10 personality disorder subtypes exclusively maternal F60.6 Anxious-avoidant personality disorder was associated with a lower risk of mental disorders in offspring compared with maternal DPD.

Children of fathers with EUPD had an increased risk of having been diagnosed with any mental disorder before age 18 compared with nonexposed children (IRR, 2.42 [95% CI, 2.16-2.72]). Across

ICD-10 personality disorder subtypes exclusively paternal F60.6 Anxious-avoidant personality disorder was associated with a lower risk (IRR, 1.59 [95% CI, 1.23-2.05]) of mental disorders in offspring compared with paternal EUPD. Children of fathers with DPD had an increased risk of having been diagnosed with any mental disorder before age 18 compared with nonexposed children (IRR, 2.31 [95% CI, 1.99-2.69]), which was comparable to all other ICD-10 personality disorder subtypes in fathers (**Table 2**).

With a reference point of no personality disorder and no substance use disorder, parental substance use disorder modified the association between parental personality disorder and mental disorder in children. PPD with comorbid substance use disorder: IRR, 2.23 (95% CI: 2.07-2.40); PPD with no substance use disorder: IRR, 1.91 (95% CI: 1.79-2.04). MPD and comorbid substance use disorder: IRR, 2.97 (95% CI: 2.76-3.19); MPD with no comorbid substance use disorder: IRR, 2.42 (95% CI: 2.33-2.52) (eTable 4 **in Supplement)**.

Discussion

MPD and PPD were independently associated with 2 to 2.5-times higher risk of mental disorders in offspring (age 0-17) compared with nonexposed children, and both girls and boys were at elevated risk. Having two parents with a personality disorder was associated with 3.5 times higher risk of mental disorders in offspring. Absolute risk of mental disorders at age 18 in children of parents with personality disorders were 34%, which is more than 2 times higher the risk in nonexposed offspring (15%). The estimated absolute risk of mental disorders at age 18 in the Danish

population (15%) aligns with previous register-based studies of incidence of child and adolescent mental disorders in the Danish population[35].

Risk of mental disorders was 3.5 times higher in offspring where both parents had a personality disorder, which support findings from other studies that having two parents with a mental disorder is associated with higher risk of mental disorders and other adverse outcomes in offspring compared with offspring with one parent with a mental disorder[36,37]. Our findings of an association of PPD with offspring mental disorders aligns with findings from a longitudinal study of father-mother-child triads that have found strong associations between paternal borderline personality disorder and offspring internalizing and externalizing symptoms[17].

Risk estimates of mental disorders in children of parents with personality disorders were comparable to risk of mental disorders in children of parents with schizophrenia, bipolar disorder, and major depressive disorder, which has been estimated to 2.5 times higher in register-based studies and 3 times higher in clinical cohort studies compared with controls[38–42]. This resonates research suggesting heritability in borderline personality disorder[43] and findings from a large-scale genome-wide association study suggesting shared genetic overlap between borderline personality disorder and schizophrenia, bipolar disorder, and major depressive disorder[44].

Risk of mental disorders in offspring were increased in relation to all parental ICD-10 personality disorder subtypes. Our findings did not support our secondary hypothesis that children born to parents with either EUPD or DPD would be at increased risk of mental disorder compared with other personality disorder subtypes. However, risk was lower in the context of parental anxious avoidant personality disorder. To our knowledge, no other study has compared risk of mental disorders in children across parental personality disorder subtypes.

Strengths and Limitations

Strengths of our study include the large sample size due to the unique Danish registers, and minimal bias in analysis since both exposed and nonexposed children were followed similarly. Further, no recall-bias is implicated since diagnoses were registered and assessed at time of symptom presence and contact with mental health professionals. Further, selection-bias did not influence our findings since the Danish nationwide registers are administratively driven with juridical regulations ensuring complete registrations[31]. Additionally, we ensured not to overestimate risk in exposed children by allowing parental comorbid mental disorders in the control group and thereby not comparing with an ultra-healthy control group.

A limitation of our study is the lack of evidence on the validity of the personality disorder diagnosis in the Danish health care system. However, in Sweden, a comparable Scandinavian welfare state, a validation study confirmed good construct validity[45]. Another limitation of our study is that our definition of exposure is parental personality disorder diagnosis at child's birth. This means that diagnoses registered after birth of the child were not included in our analyses, and our results may

have underestimated the true values. This limitation was chosen to enable the statistical analysis which provided absolute risk estimates.

A further limitation was that in analysis of risk across parental personality disorder subtypes, parents with ICD-8 diagnosed personality disorders were included in the reference group. Thereby our results potentially were drawn towards the null hypothesis. However, absolute estimates of incidence did not differ greatly between the main analysis and the secondary analysis based only on ICD-10 subgroups. As a final limitation, we did not extract data from prisons whereby parental DPD diagnosed in this societal institution is missing from our analysis. Consequently, our analysis on parental DPD potentially were drawn towards the null hypothesis.

All limitations described pose a challenge to the generalizability of our findings. However, none of the limitations described may have caused us to overestimate risk.

Interpretation of Findings

Development of mental disorders during childhood and adolescence is caused by complex genetic, environmental, and gene-environment interactions[46–50]. To interpret our findings, first direct genetic transmission from parent to child is a plausible cause underlying the strong association between parental personality disorders and mental disorders in offspring. To interpret the increased risk across full spectrum ICD-10 mental disorders in offspring, beside pleiotropy due to shared genetic liability across mental disorders[50,51], also environmental factors such as parenting

and family environment must be considered which include gene-by-environment pathways (shared genetics between parent and offspring)[43,49,52,53]. Environmental factors further include exposure to substance, toxins, infections, and nutritional deprivation in the intrauterine environment[46]. After birth the quality of attachment in the first three years of life with both mothers and fathers as primay caregivers is a critical environmental factor, that is associated with child mental health development[54–56]. Further, wider social environments such as school and peer relationships in early and middle childhood are important domains of protective versus risk factors. The combined environmental factors mentioned represent mediators it was not possible to adjust for in the current study. Finally, to fully interpret our findings, we must consider potential detection bias since it is possible that children of parents with personality disorders are more likely to receive attention and assessments in the Danish free-of-charge welfare system including social services and child protection services.

We, the authors consider it important to reflect upon our responsibility not to re-produce stigma central to the discourse on personality disorders[7] which affects experiences of living with personality disorders as a parent[57]. Considering the impact of genetic factors as well as wider socio-cultural factors and not solely focusing on mechanism related to parenting is important to not reproduce stigma.

Conclusion

The risk of mental disorder in children of parents with personality disorders was 2 to 3.5 times higher than in nonexposed children. The risk was increased for both boys and girls and associated independently with MPD and PPD. Parental EUPD and DPD were not associated with higher risk of

mental disorders in children compared with other parental personality disorder subtypes. Sensitivity analysis confirmed the robustness of our findings. The findings in this study suggest a substantial increased risk of mental illness in children of parents with personality disorder; however, more research is needed to understand the mechanism at play in the transmission of personality disorders in parents to mental disorders in offspring.

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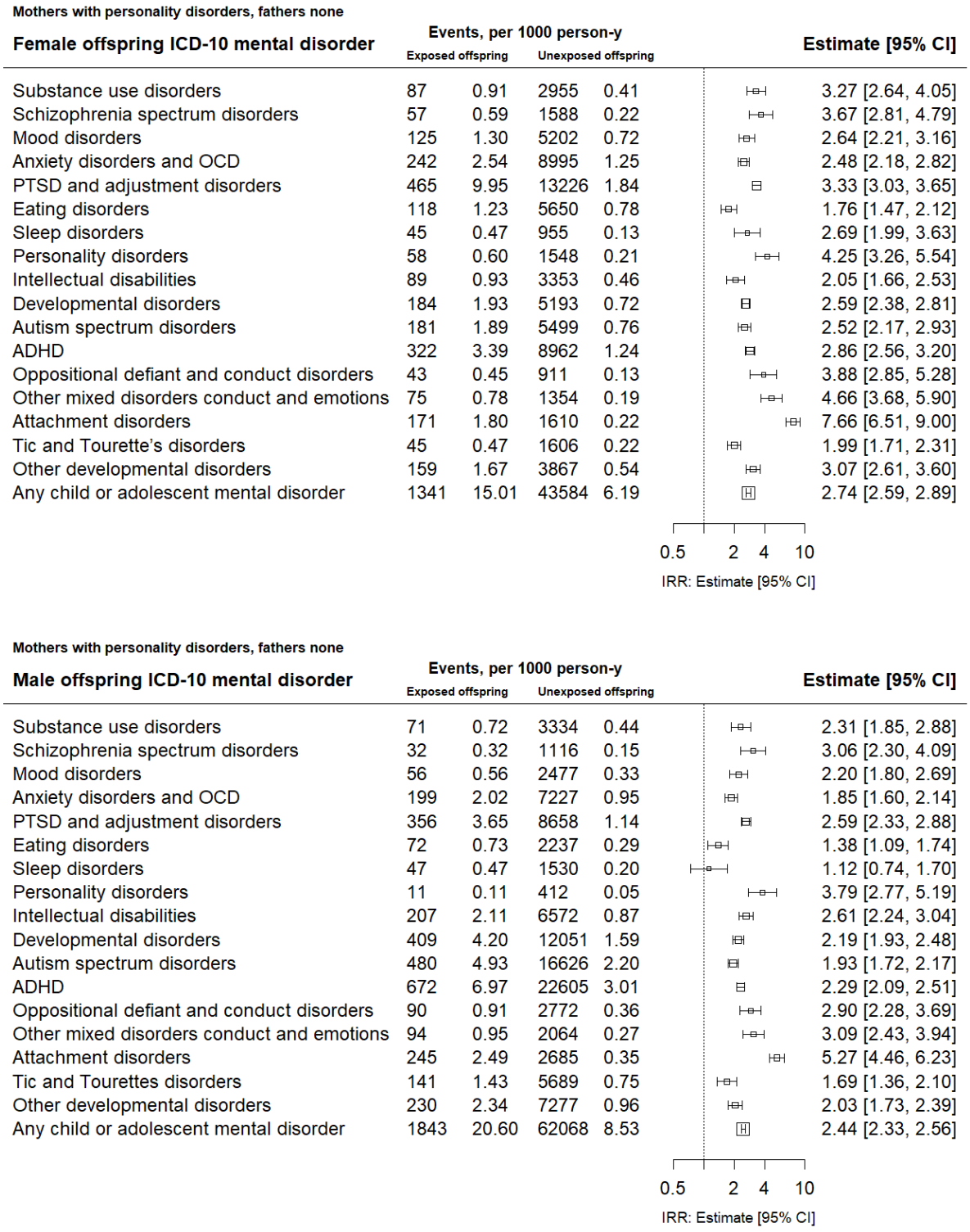
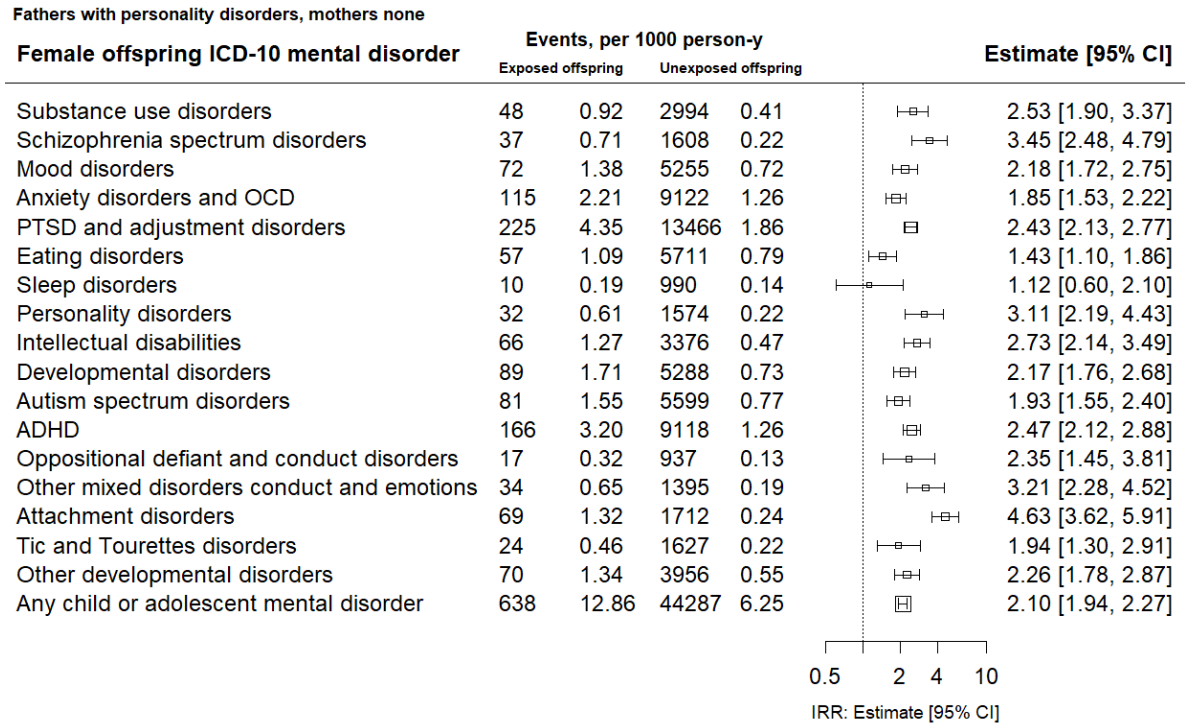
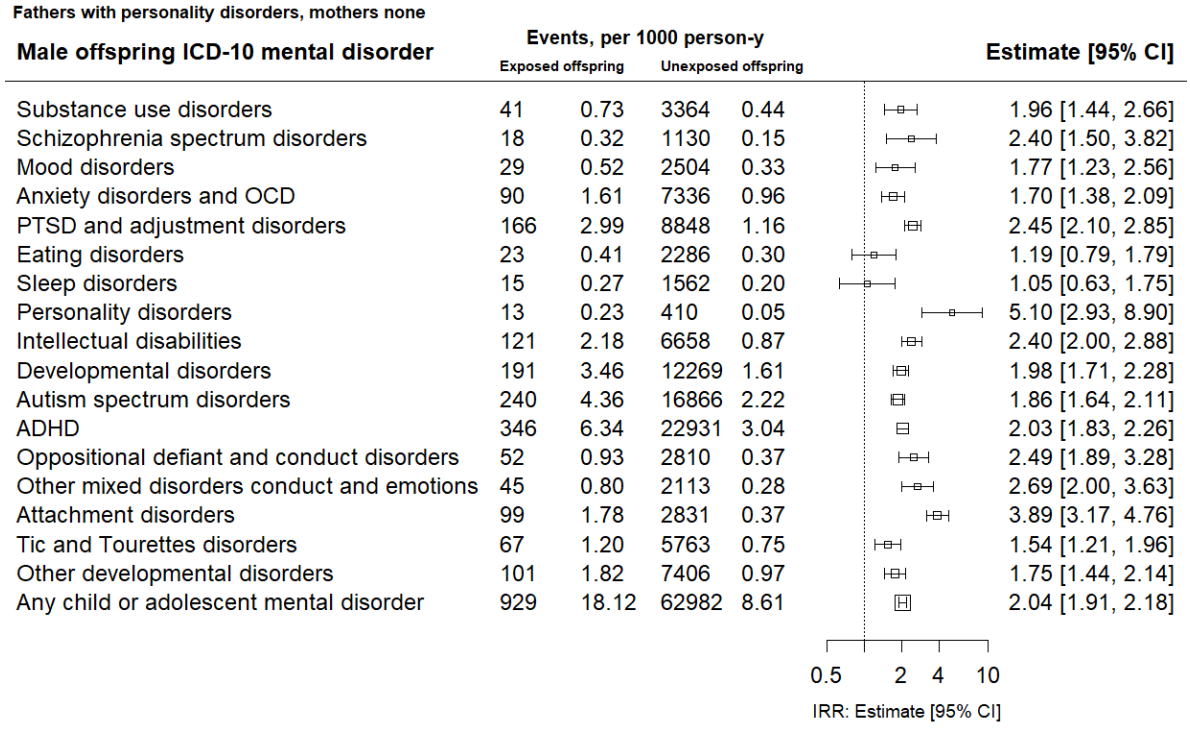
Figure 1. Associations of Any Maternal Personality Disorder With Mental Disorders in Female and Male Offspring



Incidence rate ratios (IRR) are analyzed by Poisson regression analysis with the logarithm of perions-years as an offset. Analyses were adjusted for offspring age and sex, and calender period. Estimates are visualized on a log scale. Square markers represents IRR, and horizontal lines represents 95 % confidence intervals. Size of square markers indicate size of combined events: combined numbers of offspring diagnosed with specific mental disorders. ADHD, Attention-deficit/hyperactivity-disorders; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder.

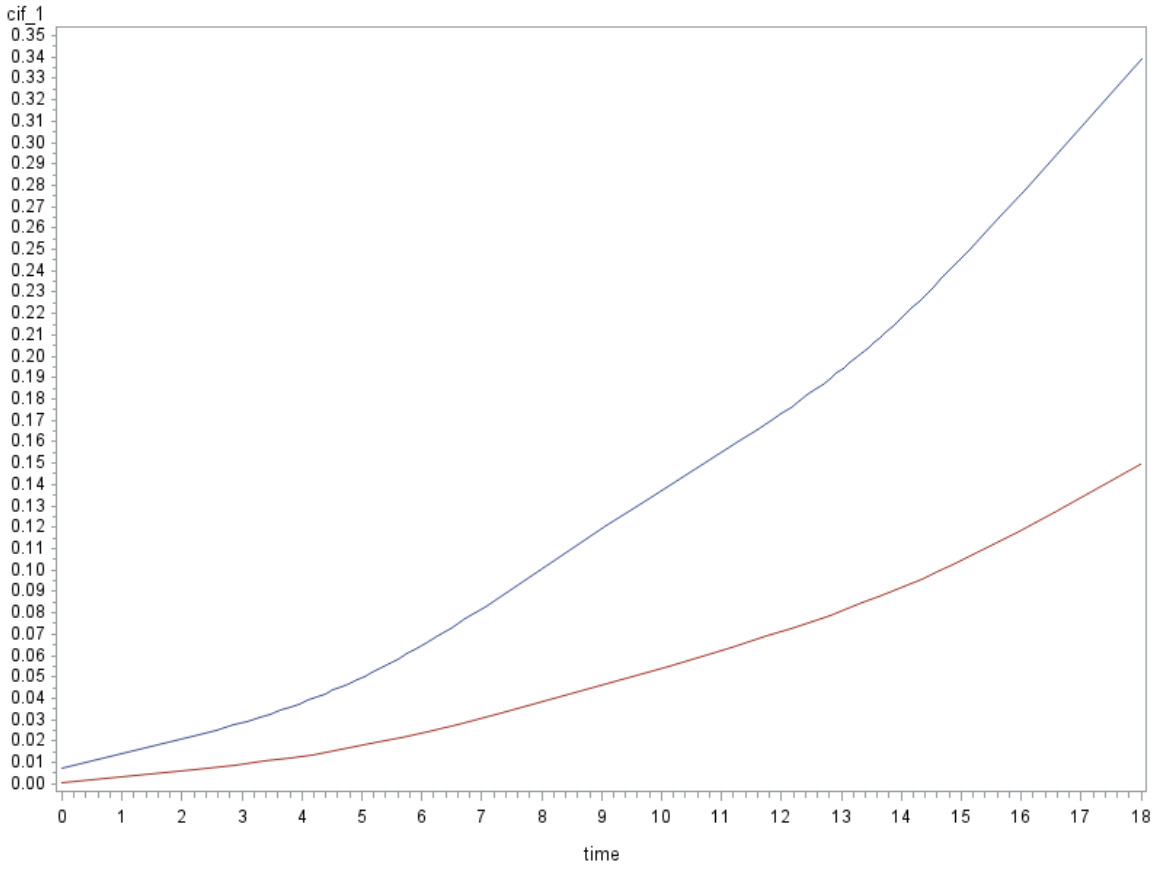
Figure 2. Associations of Any Paternal Personality Disorder With Mental Disorders in Female and Male Offspring





Incidence rate ratios (IRR) are analyzed by Poisson regression analysis with the logarithm of perions-years as an offset. Analyses were adjusted for offspring age and sex, and calender period. Estimates are visualized on a log scale. Square markers represents IRR, and horizontal lines represents 95 % confidence intervals. Size of square markers indicate size of combined events: combined numbers of offspring diagnosed with specific mental disorders. ADHD, Attention-deficit/hyperactivity-disorders; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder.

Figure 3. Absolute Risk of Any Mental Disorder in Offspring (age 0 to 18)



Visualized cumulative incidence of any mental disorder in a Danish nationwide cohort of children born to parents with a diagnosed personality disorder according to the International Classification of Diseases 8th or 10th edition (**blue**). Compared to children in the general Danish population (**red**). All children were followed from birth until either 18th birthday, diagnosis of any mental disorder was registered, or until death, immigration, disappearance or until December 31st, 2016.

Table 1. Associations of Offspring's Risk of Specific Mental Disorders With Any Parental Personality Disorder

N, IRR (95% CI)	Maternal personality disorder	Paternal personality disorder	Both parents have a personality disorder	Reference group: *no* parental personality disorder
Any child or adolescent mental disorder	3030 2.61 (2.52-2.71)	1413 2.17 (2.06-2.28)	154 3.69 (3.15-4.33)	104239 1
Organic mental disorders	≤5	15 1.75 (0.72-4.23) *	≤5	458 1
Mental and behavioral disorders due to substance use	149 2.89 (2.46-3.40)	80 2.31 (1.85-2.88)	9 4.84 (2.52-9.31)	6209 1
Schizophrenia spectrum disorders and acute psychoses	81 3.39 (2.72-4.23)	47 3.06 (2.30-4.09)	8 9.23 (4.61-18.47)	2657 1
Mood disorders	175 2.64 (2.28-3.07)	95 2.20 (1.80-2.69)	6 2.45 (1.10-5.45)	7584 1
Anxiety and OCD	421 2.47 (2.24-2.72)	185 1.85 (1.60-2.14)	20 3.16 (2.04-4.90)	16037 1
PTSD and adjustment disorders	773 3.42 (3.18-3.68)	343 2.59 (2.33-2.88)	48 5.76 (4.34-7.64)	21541 1
Eating Disorders	182 1.88 (1.62-2.18)	72 1.38 (1.09-1.74)	8 2.18 (1.09-4.37)	7815 1
Sleep disorders	89 2.12 (1.71-2.62)	20-30 1.12 (0.74-1.70)	<=5	2463 1
Personality disorders	64 4.09 (3.19-5.25	~ 40 3.79 (2.77-5.19)	<=5	1920 1
Mental retardation	277 2.35 (2.09-2.65)	168 2.61 (2.24-3.04)	19 4.32 (2.75-6.78)	9757 1
Developmental disorders	568 2.59 (2.38-2.81)	255 2.19 (1.93-2.48)	25 2.97 (2.01-4.40)	16989 1
Autism spectrum disorders	626 2.27 (2.09-2.45)	286 1.93 (1.72-2.17)	35 3.38 (2.42-4.71)	21839 1
ADHD	947 2.59 (2.43-2.77)	465 2.29 (2.09-2.51)	47 3.44 (2.59-4.58)	31102 1
Oppositional defiant and conduct disorder	132 3.18 (2.67-3.79)	60-70 2.90 (2.28-3.69)	<=5	3615 1
Other mixed disorders of conduct and emotions	157 4.07 (3.47-4.78)	67 3.09 (2.43-3.94)	12 8.40 (4.76-14.80)	3351 1
Attachment disorder	391 7.66 (6.90-8.51)	143 5.27 (4.46-6.23)	25 13.53 (9.13-20.05)	4152 1
Tic and Tourette's disorder	178 1.99 (1.71-2.31)	83 1.69 (1.36-2.10)	8 2.32 (1.16-4.63)	7212 1

Other developmental disorders incl. enuresis, encopresis	370 2.68 (2.41-2.97)	152 2.03 (1.73-2.39)	19 3.61 (2.30-5.66)	10992 1

Incidence (N) of mental disorders at age 0-17. Incidence rate ratios (IRR) in offspring born to parents with personality disorder. Estimates are adjusted for age, sex and calendar period, p=<.00001, * p=0.00010. Outcomes for mental disorders with five or less cases are not shown. ADHD, Attention-deficit/hyperactivity-disorders; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder.

Table 2. Associations of Offspring's Risk of Specific Mental Disorders With Parental Personality Disorders Subtypes

n, IRR 95% CI	Mother	Father
Reference group No personality disorder	106,205 1	107,770 1
F60.0 Paranoid personality disorder	27 2.78 (1.90-4.05)	26 1.50 (1.02-2.20)
F60.1 Schizoid personality disorder	25 2.00 (1.35-2.97)	31 1.61 (1.13-2.29)
F60.2 Dissocial personality disorder	44 3.39 (2.52-4.56)	173 2.31 (1.99-2.69)
F60.3 Emotionally unstable personality disorder	1291 2.89 (2.73-3.05)	284 2.42 (2.16-2.72)
F60.4 Histrionic personality disorder	29 1.95 (1.36-2.81)	22 2.02 (1.33-3.07)
F60.5 Obsessive personality disorder	37 2.55 (1.85-3.52)	
F60.6 Anxious-avoidant personality disorder	224 2.00 (1.75-2.28)	59 1.59 (1.23-2.05)
F60.7 Dependent personality disorder	137 2.29 (1.94-2.71)	30 1.62 (1.13-2.32)
F60.8 Other specific disorder of personality structure*	106 2.42 (2.00-2.93)	96 1.99 (1.63-2.43)
F60.9 Disorder of personality structure, unspecified	589 2.33 (2.15-2.53)	284 1.96 (1.74-2.20)
F61.0 Disorder of personality structure, combined and other type	125 2.41 (2.02-2.87)	64 2.22 (1.73-2.83)

Incidence rate ratios (IRR) of psychiatric disorders in offspring born to parents diagnosed personality disorder subtypes. Parental subtypes of personality disorders according to the International Classifications of Diseases 10th edition. All children were born between January 1st, 1995- December 31st, 2016. Estimates of IRR and 95 % CIs were obtained with Poisson regression models adjusted for child's age and sex and calendar time. Since our cohort consist of less than 5 cases of fathers with diagnosed F60.4 and F60.5 they are combined in this table. ADHD, Attention-deficit/hyperactivity-disorders; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder. * Incl. Narcissistic and passive-aggressive personality disorder

Supplement

Association of Parental Personality Disorder With Risk of Mental Disorder in Children

eTable 1. Exposure: Parental personality disorders, ICD-10 diagnosis (and corresponding ICD-8 diagnoses)

ICD-10	ICD-8
F60 + F61 (excl. F62-69).	301.x9 (not 301.19), 301.80, 301.81, 301.82, 301.84
F60.0 Paranoid personality disorder F60.1 Schizoid personality disorder F60.2 Dissocial personality disorder F60.3 Emotionally unstable personality disorder F60.4 Histrionic personality disorder F60.5 Obsessive personality disorder F60.6 Anxious-avoidant personality disorder F60.7 Dependent personality disorder F60.8 Other specific disorder of personality structure Incl. Narcissistic and passive-aggressive personality disorder F60.9 Disorder of personality structure, unspecified F61.0 Disorder of personality structure, combined and other type	301.09, 301.29, 301.39, 301.49, 301.59, 301.69, 301.79, 301.89, 301.99, 301.80, 301.81, 301.82, 301.84.

eTable 2. Diagnostic codes for all outcomes: ICD-10 diagnoses in offspring throughout childhood and adolescence.

Child and adolescent mental disorders	ICD-10
Any child or adolescent mental disorder	F00–99
Organic mental disorders	F00-09
Mental and behavioral disorders due to substance use	F10-19
Schizophrenia spectrum disorders and acute psychoses	F20-29
Mood disorders	F3, F92.0
Anxiety disorders and OCD	F40-F42 F44-F49, F93, F94.0
PTSD and adjustment disorders	F43
Eating disorders	F50, F98.2
Sleep disorders	F51
Personality disorders	F60, F61 (excl. F62-69)
Intellectual disability	F70-79
Developmental disorders	F80, F81, F82, F83
Autism spectrum disorders	F84.0, F84.1, F84.5-84.9
Attention-deficit/hyperactivity-disorder	F90 + 98.8
Oppositional defiant disorders and conduct disorders	F91
Other mixed disorders of conduct and emotions	F92.8, F92.9
Attachment disorders	F94.1, F94.2, F94.8, F94.9
Tic and Tourette's disorders	F95
Other developmental disorders incl. enuresis, encopresis	F98.0, F98.1, F98.3-F98.7, F98.9

eTable 3. Parental socio-economic status: Mothers' and fathers' level of education at child's birth

Mothers' level of education at child's birth	Child's risk of any psychiatric disorder before age 18. IRR (95% CI)
Elementary school	1.48 (1.35 - 1.63)
Higher secondary examination, *General upper secondary education*	1.10 (1.00 - 1.21)
Higher commercial examination, *General upper secondary education*	1.02 (0.92 - 1.13)
Vocational education and training, preparation for academy profession programmes	1.14 (1.04 - 1.25)
Academy profession programmes, such as electrician, chef's school etc.	1.04 (0.94 - 1.14)
Professional bachelor's programmes. Medium cycle programs, such as nurses, social workers etc.	1.00 (0.91 - 1.11)
University bachelor's (BA, B.Sc.) degree: long cycle programs, such as BA English	1.05 (0.94 - 1.16)
University master's (MA, M.Sc.) degree: long cycle programs, such as MA English	0.94 (0.85 - 1.03)
Unknown	1.24 (1.13 - 1.38)
Research degree, such as a Ph.D.	1
Fathers' level of education at child's birth	Child's risk of any psychiatric disorder before age 18. IRR (95% CI)
Elementary school	2.22 (1.89 - 2.61)
Higher secondary examination, *General upper secondary education*	1.56 (1.33 - 1.84)
Higher commercial examination, *General upper secondary education:*	1.40 (1.19 - 1.66)
Vocational education and training, preparation for academy profession programmes	1.60 (1.36 - 1.88)
Academy profession programmes, such as electrician, chef's school etc.	1.35 (1.15 - 1.59)
Professional bachelor's programmes. Medium cycle programs, such as nurses, social workers etc.	1.37 (1.17 - 1.61)
University bachelor's (BA, B.Sc.) degree: long cycle programs, such as BA English	1.37 (1.16 - 1.61)
University master's (MA, M.Sc.) degree: long cycle programs, such as MA English	1.21 (1.03 - 1.42)
Unknown	1.35 (1.14 - 1.59)
Research degree, such as a Ph.D.	1

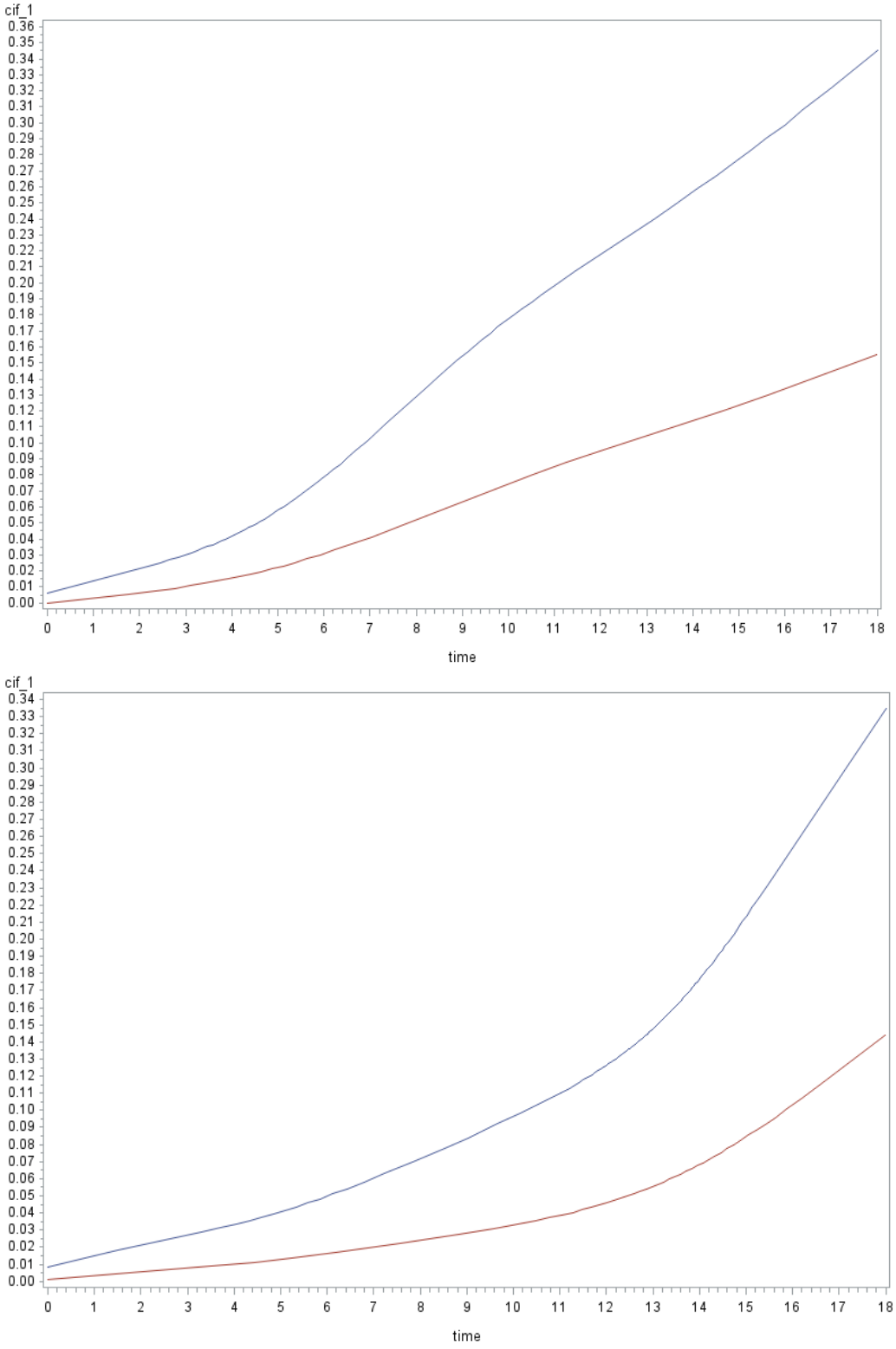
Model was adjusted for sex, age, calendar-period, father unknown and either father or mother highest education at child's birth. Estimated incidence rate ratios (IRRs) and 95% CI, p-value <.00001.

eTable 4. Mental Disorder Comorbidity: Substance Use Disorders

	Offspring any mental disorder before age 18. IRR (95% CI)
Paternal personality disorder (PPD) and substance use disorder	
PPD and substance use disorder	2.23 (2.07 - 2.40)
PPD, no substance use disorder	1.91 (1.79 - 2.04)
No PPD, substance use disorder	1.60 (1.55 - 1.65)
No PPD, no substance use disorder	1
Maternal personality disorder (MPD)	
MPD and substance use disorder	2.97 (2.76 - 3.19)
MPD, no substance use disorder	2.42 (2.33 - 2.52)
No MPD, substance use disorder	1.84 (1.77 - 1.91)
No MPD, no substance use disorder	1

Incidence Risk Ratios (IRR) for any psychiatric disorder in offspring with a parent with substance misuse and a diagnosed personality disorder diagnosed before birth of the child. Parents were diagnosed before birth of the child. Children were followed age 0-18 in the period of 1995 to ultimo 2016. Substance use disorders diagnostic codes: ICD10 = F1; ICD8 = '303', '304', '291', '5711', '57109'. Any parental psychiatric disorder: ICD8 = 290-315; ICD10 = F. Our model was adjusted for sex, age, calendar time and father unknown.

eFigure 1



Visualized cumulative incidence of any mental disorder. Top graph (female offspring) and bottom graph (male offspring) illustrates incidence of mental disorders in offspring. Personality disorders **blue line**, and unexposed children **red line**. All children were followed from birth until either 18th birthday, diagnosis of any mental disorder was registered, or until death, immigration, disappearance or until December 31st, 2016.

Att. Editor-in-Chief Ida Hageman, Copenhagen, Denmark

Dear Editorial Board,

Please consider our manuscript entitled *Association of Maternal and Paternal Personality Disorders With Risk of Mental Disorders in Children. A Nationwide, Register-Based Cohort Study of 1,406,965 Children* for publication in *Acta Psychiatrica Scandinavica*.

We are the first to report on risk of mental disorders in children of parents with personality disorders based on nationwide data. Risk of any mental disorder was 2 to 3.5 times higher in children of parents with personality disorders compared with nonexposed children. Interestingly, risk was comparable to risk in children of parents with schizophrenia, bipolar disorder, and major depressive disorder. Possible mechanism of transmission of mental disorders across generations is discussed.

We hope you will find our paper of interest to the readers of *Acta Psychiatrica Scandinavica*.

On behalf of all authors,

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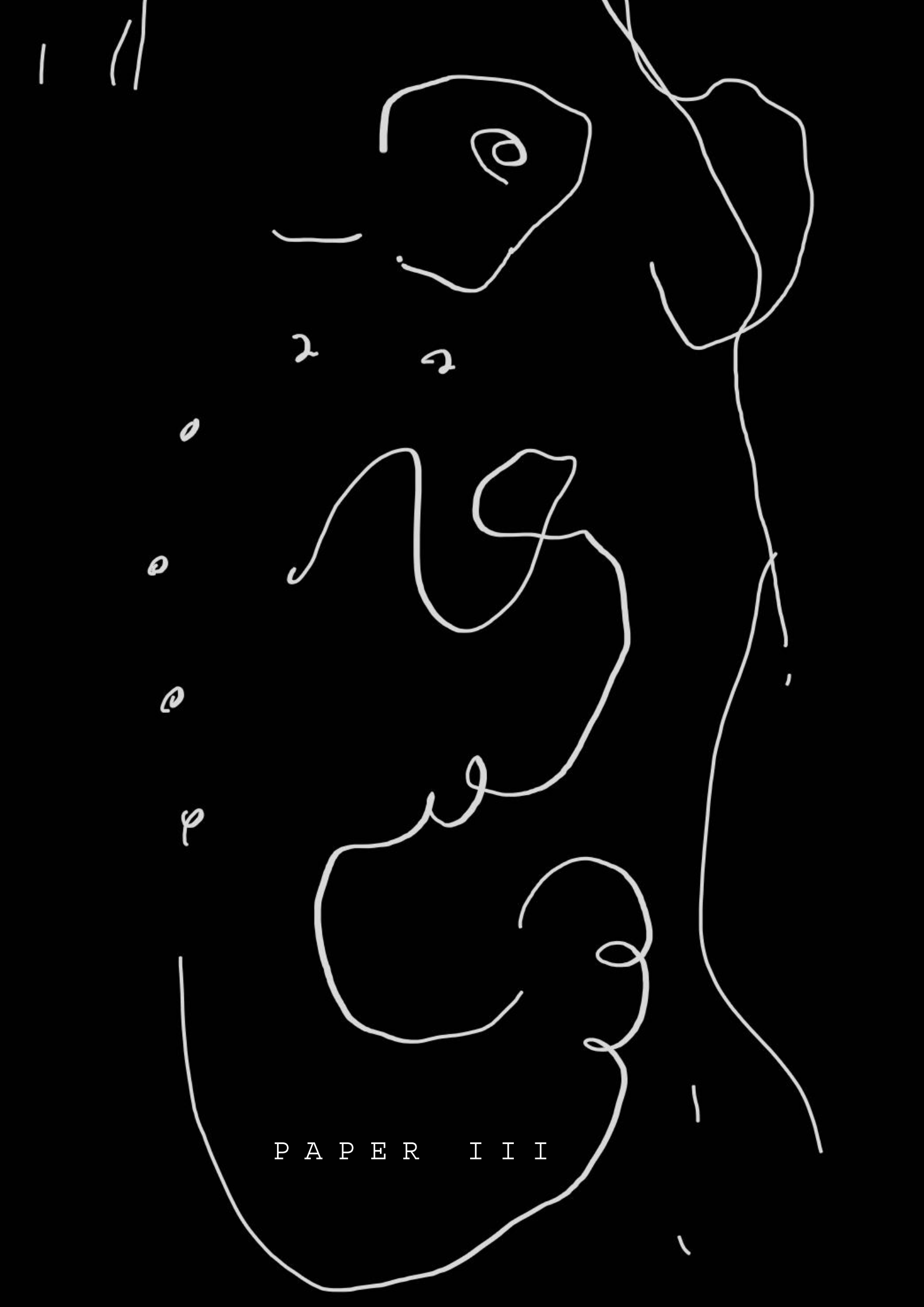
PAPER III

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Trials

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

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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. 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

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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'

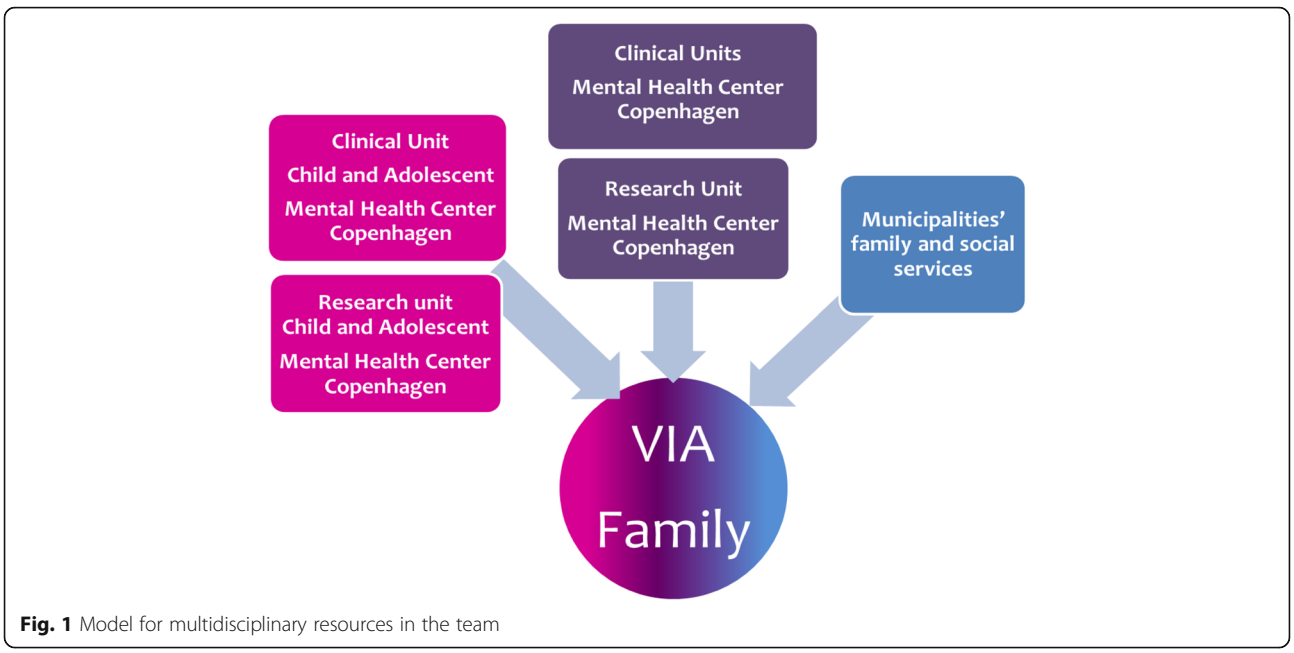

Fig. 1 Model for multidisciplinary resources in the team

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

- a child and adolescent psychiatrist or physician who has experience with providingchild 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[3]*	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 Lability 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.

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.
- *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.

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

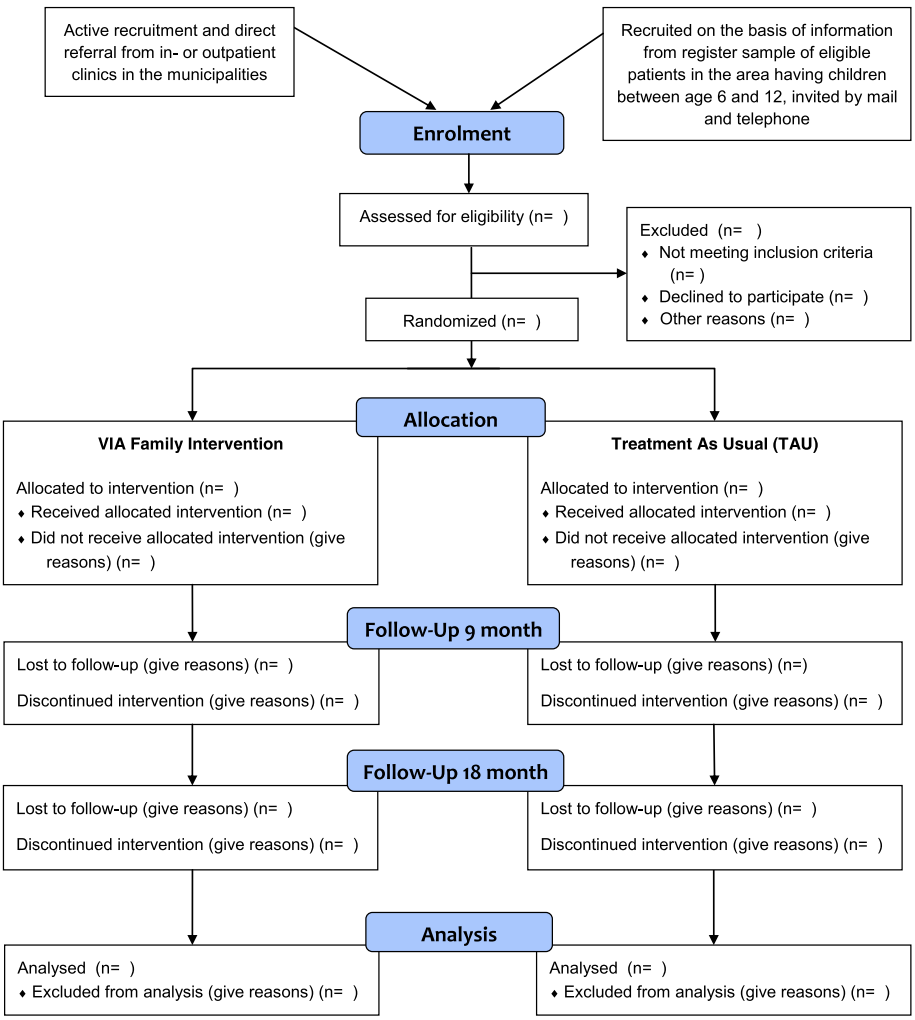

Fig. 3 CONSORT flowchart for participants in the VIA Family study. TAU treatment as usual

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 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; 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

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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.

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