Stress and family dysfunction: Examining their influence on mental health outcomes and service use in the offspring of parents with affective disorders

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ABSTRACT

Stress and family dysfunction: Examining their influence on mental health outcomes and service use in the offspring of parents with affective disorders

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Offspring of parents with affective disorders (OAD) are at risk of developing a wide range of mental disorders. Deficits in the rearing environment and exposure to adverse events are well known risk factors for negative outcomes in OAD. Building on prior research, this thesis aimed to examine the longitudinal relationships between familial dysfunction, exposure to adverse events, emotional and behavioural well-being, and mental health service utilization in OAD and control offspring of parents with no affective disorder. Studies 1 and 2 in the thesis used data from the TRacking Adolescents' Individual Lives Survey, a longitudinal study of youth in the Netherlands. 2230 participants (51% female, Mage= 11.1 years, SD = 0.6, at baseline) and their parents completed questionnaires across 6 time points, spanning 15 years. Mental health and behavioural data were measured using standardized questionnaires, while adverse life events and health service utilization were assessed using structured interviews. In the first study, multi-group structured equation modelling revealed that family dysfunction was linked to internalizing and externalizing problems in the OAD (B = 0.05, SD = 0.02, p = .008), but not in controls (B = 0.06, SD = 0.01, p = .636), and that this relationship was stable from middle childhood to adulthood. In the second study, we expanded the scope of investigation from family functioning to cumulative environmental risk, referring to the assessment of multiple risk factors in families, and mental health service utilization. Results from moderated mediation analyses revealed that the OAD were more likely to seek out more intensive mental health services as adults than

controls (CI = [0.01, 0.15]), as a function of their cumulative environmental risk and subsequent significant mental health need. Study 3 examined whether a preventative intervention to improve family functioning in OAD might improve offspring's internalizing and externalizing symptoms through changes in parenting stress. In this study, we compared the offspring of a parent having bipolar disorder (OBD), who underwent the *Reducing Unwanted Stress in the Home (RUSH)* intervention program, with control offspring. Designed as a quasi-experiment, in which the control group underwent an assessment-only condition, families of both groups completed assessments pre- and post-intervention, as well as at 3- and 6-month follow-ups. Mixed-modeling analyses revealed that improvements in parenting stress mediated the relationship between participation in the RUSH program and reduced offspring internalizing and externalizing symptoms at a six-month follow-up. Taken together, the results show that the OAD may be especially sensitive to stress in the rearing environment as compared to offspring of parents with no affective disorders. Adversity and dysfunction in the home environment might be a particularly salient risk factor for OAD, leading to the development of emotional and behavioural problems, as well as costly mental health interventions. Interventions aimed at improving the rearing environment during childhood may therefore improve developmental outcomes in the OAD and decrease the cost-of-care for these high risk families, as evidenced by the findings of this thesis.

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Contribution of Authors

This thesis consists of three manuscripts, and contributing authors as well as their role for each manuscript is outlined below.

Study 1: Resendes, T., Ellenbogen, M. A., & Oldehinkel, A. J. (2024). Family dysfunction, stressful life events, and mental health problems across development in the offspring of parents with an affective disorder. *Journal of Child Psychology and Psychiatry.* Advance Online Publication. http://doi.org/10.1111/jcpp.13991

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Vanessa Iacono and Mark Ellenbogen designed the study. Lisa Serravalle and Vanessa Iacono collected the data and conducted the clinical interventions. Tiffany Resendes conducted the statistical analyses and wrote the first draft of the manuscript. Tiffany Resendes and Mark Ellenbogen edited subsequent versions of the manuscript. All authors approved the final manuscript.

Table of Contents

List of Figures

List of Tables

Chapter 1: General Introduction

The offspring of parents with affective disorders (OAD) are a well-studied population at risk of mental disorders and negative psychosocial outcomes across development (Henin et al., 2005; Vandeleur et al., 2012). Although the pathways to negative outcomes are not fully known, one hypothesis is that inherited vulnerabilities interact with a stressful rearing environment, characteristic of families where one or both parents have an affective disorder, leading to the development of psychopathology and adjustment difficulties (Bella et al., 2011; Ellenbogen & Hodgins, 2004; Lau et al., 2018; Mesman et al., 2013; Nijjar et al., 2014; Vandeleur et al., 2012). Building on recent research aiming to elucidate key environmental risk factors for the OAD, by which to uncover viable foci of intervention, this thesis aims to (1) provide evidence of the OAD's sensitivity to dysfunction in the family environment, (2) delineate pathways from family dysfunction to mental disorders and mental health service use among the OAD, and (3) present preliminary support for a viable preventative intervention for the OAD. This thesis builds upon prior research on the OAD (Ellenbogen & Hodgins, 2004; Iacono et al., 2018; Maciejewski et al., 2018; Remes et al., 2021; Serravalle et al., 2021), as well as theoretical frameworks such as the diathesis-stress model (Rosenthal, 1963; Zuckerman, 1999) and the transactional model of psychopathology (Cicchetti & Toth, 1997). This rich foundation of literature highlights the interplay of genetic predispositions and stress in the rearing environment of families having a parent with an affective disorder, both leading to the development of psychopathology in the OAD. In turn, this introduction aims to delineate risk factors for maladaptive outcomes and the use of mental health care resources among the OAD, as well as a review of current trends in interventions for the OAD.

Affective disorders and psychosocial dysfunction in the OAD

Affective disorders are the most common category of psychiatric disorder and, consequentially, have been at the center of many research studies. Affective disorders refer to both depressive disorders, such as major depressive disorder, and bipolar spectrum disorders, such as bipolar disorder type I and type II, as well as related disorders of persisting mood difficulties and accompanying dysfunction. Individuals meeting criteria for major depressive disorder will often report more than one discreet period lasting a minimum of two weeks, characterized by persistent low mood, such as sadness, irritability, or boredom, loss of pleasure associated to previously pleasurable activities, changes to quality or need for sleep, changes in appetite, motivation, energy, or concentration, changes in weight or psychomotor functioning, increased feelings of guilt, and increased thoughts of death or dying (American Psychiatric Association, 2022). Bipolar spectrum disorders, however, are characterized by cycles of major depression and (hypo)mania, which refer to periods of unexplained elevated mood lasting up to several days, that can be accompanied by increased impulsivity, increased goal-directed behaviour, perceived flight of ideas, noticeable pressured speech, or delusions of grandeur (American Psychiatric Association, 2022). Recent epidemiological efforts estimate that 12.6% of Canadians over the age of 15 will meet criteria for an affective disorder in their lifetime, while rates of incidence of affective disorders for any one year was 5.4% (Canada, 2016). Cross-national epidemiological studies have reported an average lifetime prevalence of major depressive disorder of 14.6% in high-income countries (Bromet et al., 2011). The cross-national prevalence rate of bipolar spectrum disorders was 2.6% (Merikangas et al., 2011). Overall, affective disorders are known for their significant impairment on cognitive, emotional, occupational, economic, and interpersonal functioning (Baune & Renger, 2014; Copeland et al., 2013; Léda-Rêgo et al., 2020; Wittchen et al., 2010), and consequentially burden individuals,

families, and society. Understanding the high rates of familial aggregation of affective disorders has gained traction within the field of developmental psychopathology, leading to a newfound appreciation of the OAD as an at-risk population.

Studies show that on average, one third of OAD, as compared to offspring of parents with no mental disorders, develop an affective disorder within their lifetime (Nijjar et al., 2014; Sandstrom et al., 2020; Vandeleur et al., 2012). In fact, the OAD are up to four times as likely to develop a major depressive disorder compared to offspring of parents with no history of depression (Weissman et al., 2016), while offspring of parents with bipolar spectrum disorders are up to 15 times more likely to develop bipolar disorder when compared to offspring of parents with other types of psychiatric disorders (Birmaher et al., 2021; Mesman et al., 2013; Vandeleur et al., 2012). Risk of the OAD developing an affective disorder doubles when both biological parents have an affective disorder (Vandeleur et al., 2012), which is relevant given research highlighting that individuals living with affective disorders tend to seek out partners with similar psychopathology (Serravalle et al., 2020). Beyond affective disorders, the OAD are at greater risk of developing a wide range of mental disorders (Henin et al., 2005). Studies assessing lifetime prevalence of mental disorders in the OAD found that half met criteria for an anxiety disorder (between 42% and 58% of probands) – rates which are more than double that of offspring of parents with no mental disorders (Vandeleur et al., 2012). Further, children of depressed parents are more likely to struggle with substance use and poor interpersonal functioning than children of non-depressed parents (Weissman et al., 2006), while children of parents having a bipolar disorder are two-to-four times more likely to develop neurodevelopmental disorders, such as attention-deficit/hyperactivity disorders, or other behavioural problems as compared to children of parents without affective disorders (Birmaher

et al., 2021; Propper et al., 2023; Singh et al., 2007). These developmental trends continue well into adulthood, as evidenced by the OAD's high rates of interpersonal difficulties, sexual risk behaviors, and occupational difficulties later in life (Bella et al., 2011; Duffy et al., 2014a; Nijjar et al., 2014; Ostiguy et al., 2009, 2012; Shaw et al., 2005; Weissman et al., 2006).

The intergenerational transmission of affective disorders by gene*environment interactions and heightened sensitivity to stress

Genetic predispositions are a primary vulnerability factor reported in twin and adoption studies, with heritability estimates for affective disorders ranging between 40% and 93% (Fernandez-Pujals et al., 2015; Kieseppä et al., 2004; McGuffin et al., 2003). Large studies exploring associations between specific genes and the development of affective disorders led to the conclusion that the genetic transmission of multiple genes and their subsequent interaction may increase one's risk of developing major depressive disorder and bipolar spectrum disorders (Ferreira et al., 2008; Howard et al., 2019). Importantly, twin studies have repeatedly highlighted that genes cannot independently predict the development of psychopathology (Kieseppä et al., 2004; McGuffin et al., 2003; Sullivan et al., 2000). The diathesis-stress model therefore posits that genetic underpinnings and selective inherited personality traits together create a vulnerability to stress, which combines with exposure to stressful life events to explain the development of mental disorders (Zuckerman, 1999). Empirical findings have highlighted the role of the gene*environment interaction in explaining the development of major depressive disorder (Starr et al., 2014; Vrshek-Schallhorn et al., 2014). Specifically, Vrshek-Schallhorn and colleagues provided evidence that carriers of the short-allele serotonin transporter–linked polymorphism (5-HTTLPR) were more likely to develop a clinically significant major depressive episode following chronic family stress or major interpersonal stressful life events, as

compared to non-carriers. This significant moderation effect supported the key roles of both inherited vulnerability and exposure to stress in the development of depression.

Anchored in the diathesis-stress literature of affective disorders, the stress-sensitivity hypothesis was developed in an effort to explain the interplay of heightened sensitivity to stress and exposure to chronic family stress observed in OAD (Ellenbogen & Hodgins, 2004; Harold et al., 2011; Stapp et al., 2020). While the underlying cause of stress-sensitivity in the OAD is not yet known, evidence suggests that it may reflect risk factors beyond inherited traits, such as both pre- and perinatal events, and exposure to early adversity including post-partum depression (Flouri et al., 2020; LeMoult et al., 2020; Vrshek-Schallhorn et al., 2014). Additionally, researchers have posited that inherited traits which increase one's vulnerability to negative environmental factors may also partially explain the heritability of affective disorders (Nilsson et al., 2015). Of interest, trait neuroticism has been extensively studied as a mechanism of familial transmission of affective disorders, given its role as both a genetic and environmental risk-factor (Ask et al., 2021; McAdams et al., 2014; Ostiguy et al., 2012). Neuroticism, defined as a high level of emotional instability and susceptibility to negative emotions, predisposes individuals to react negatively to stress (Clark et al., 1994), and may therefore underlie the development of psychopathology when exposed to adverse events.

Cumulative exposure to early risk factors may alter certain stress-sensitive systems and sensitize youth to the later exposure of stressful life events, which makes it especially pertinent in the study of OAD (Blair et al., 2011; Dich et al., 2015). Studies have shown that early adversity, including having a parent with major depressive disorder, may alter neuroendocrine stress reactivity, further explaining future sensitivity to stressful events (Halligan et al., 2004; Laurent et al., 2015). In a Danish cohort study by Dich and colleagues (2015), adverse childhood

experiences such as prolonged familial conflict, parental illness or death, and financial problems predicted poor cardiovascular, immune, and metabolic regulation in adult men. An earlier study by Appleyard and colleagues (2005) quantified early exposure to risk factors, including childhood maltreatment, exposure to marital conflict and violence, family dysfunction, and stressful life events, to predict both internalizing and externalizing problems across middle childhood and adolescence. The evidence robustly suggests that negative outcomes in youth and adulthood, in terms of mental health (Appleyard et al., 2005), physiological regulation (Dich et al., 2015), and stress physiology (Evans & Cassells, 2014), are better predicted by cumulative exposure to adversity in childhood than single risk factors (Shonkoff et al., 2012). Taken together, recent research has laid foundation for efforts dedicated to investigating key elements within the OAD's environment which may predict the development of psychopathology, and provide viable intervention targets.

Understanding the rearing environment as a risk-factor for the OAD

Dysfunctional family environments are known to predict numerous maladaptive psychosocial outcomes (Scully et al., 2020). Children of high functioning families report fewer mental health difficulties than those of dysfunctional families, which can be partially explained by the fact that dysfunctional families experience both a higher incidence of poor parent-child interactions and higher levels of conflict than functional families (Infurna et al., 2016; Katz & Low, 2004; Scully et al., 2020). In fact, the quality of the parent-child relationship as well as parenting styles adopted within families are particularly salient facets of family functioning. Children typically acquire many of the skills associated to positive socio-emotional outcomes, such as effective and adaptive coping strategies, through the parent-child relationship (Bornstein, 2002; Liga et al., 2020; Morgan et al., 2012). Evidence also suggests that effective parenting

styles balancing both emotional responsiveness (i.e., warmth, emotional expression, and emotional involvement) and structure (i.e., organization, expectations, control, and monitoring) are linked to secure parent-child relationships and well-being in children (Doinita & Maria, 2015; Larzelere et al., 2013). Thus, ineffectual parenting styles and poor parent-child interactions together represent facets of familial dysfunction with both unique individual and cumulative effects on offspring development.

An additional factor influencing family functioning is parenting stress, which is a unique type of stress stemming from perceptions of one's role as a parent and cumulative daily hassles surrounding the role (Bögels et al., 2010; Crnic et al., 2005). Parenting stress is shown to have adverse effects on offspring emotional and behavioural functioning, as it significantly impacts the parent-child relationship as well as parenting skills independently from adverse life events (Bögels et al., 2010; Holly et al., 2019; Louie et al., 2017). In fact, studies have shown a direct link between parenting stress and offspring behaviour problems (Neece et al., 2012; Verkleij et al., 2015), while others suggest that parenting stress may increase familial conflict and neglectful parenting practices, explaining its detrimental effect on at-risk youths (Gerdes et al., 2007; Repetti et al., 2002). Parenting stress may, in fact, mediate the relationship between affective disorders in parents and socio-emotional functioning and language development in offspring (Fredriksen et al., 2019).

Familial risk factors highlighted in the previous section are particularly salient in understanding the transmission of risk from parents to offspring in families with a parent having an affective disorder (Ellenbogen & Hodgins, 2004; Halligan et al., 2004; Laurent et al., 2015; Ostiguy et al., 2012; Starr et al., 2014). Parents with affective disorders are less supportive of their children, provide less warmth and nurturance, and display less affection than parents

without affective disorders. Additionally, they report low levels emotional sensitivity, expressed emotions, and emotional responsiveness (Cummings et al., 2005; Iacono et al., 2018; Lau et al., 2018; Wilson & Durbin, 2010). This low emotional engagement may lead to dysfunctional parent-child interactions and contribute to persistent deficits in interpersonal functioning in the OAD due to the development of sub-optimal attachment styles (Cummings & Cummings, 2002). Parents with affective disorders also engage in nonoptimal parenting strategies. For example, studies show that mothers living with an affective disorder display high levels of negativity, criticism, and disapproval towards their children (Cummings et al., 2005; Inoff-Germain et al., 1992; Suppes et al., 2017). Ineffectual parenting practices and poor parent-child relationships further contribute to family dysfunction (Calam et al., 2012; Lovejoy et al., 2000a).

Finally, research has documented markedly higher levels of parenting stress in parents with bipolar spectrum disorders as compared to parents with no affective disorders (Jones et al., 2017). In addition, parents experiencing depressive symptoms also report higher levels of parenting stress, compared to healthy parents (Fang et al., 2022). Cardinal traits underlying parental psychopathology, such as neuroticism, may predispose parents to develop ineffective stress-coping strategies (Belsky & Barends, 2002; Ellenbogen & Hodgins, 2004). In the face of cumulative parenting daily hassles, parents experiencing high levels of poorly managed parenting stress may struggle to remain warm and understanding towards their children, and may become excessively rejecting, controlling, and reactive (Belsky & Barends, 2002; Bögels et al., 2010). Parents living with affective disorders are therefore more susceptible to struggle with high levels of parenting stress, which may adversely impact the parent-child relationship and family functioning and have downstream effects on offspring's emotional and behavioural well-being.

Dysfunction in the rearing environment is a well-known risk-factor for poor developmental outcomes in the OAD (Iacono et al., 2018; Ostiguy et al., 2012). Studies looking at cross-sectional data have shown that families having one or more parents living with an affective disorder report worse functioning than families having healthy parents (Barron et al., 2014; Romero et al., 2005; Weinstock et al., 2006; Wiegand-Grefe et al., 2019). In the literature, there is evidence that the relationship between affective disorders in parents and illness onset in offspring may be mediated by poor family functioning (Beardslee et al., 2013; Iacono et al., 2018; Ostiguy et al., 2012; Serravalle et al., 2021). However, there are some inconsistencies, as recent research failed to provide evidence of an association between familial environment risk factors and the onset of depressive or bipolar disorders in the OAD (Moulin et al., 2022).

Overall, the literature presents evidence that family functioning, as well as early exposure to stress, are key mechanisms in understanding the OAD's developmental trajectories to negative outcomes. However, there is limited research on the longitudinal associations between family dysfunction and mental health in the OAD, especially in comparison to offspring of parents with no affective disorders (i.e., controls). The investigation of the long-term association between family dysfunction and mental health outcomes in the OAD may be pertinent in providing evidence that the OAD display heightened stress-sensitivity, especially to stress within the rearing environment.

Exploring cost-of-care and predictors of mental health care use in the OAD

It is known that individuals living with mental illness are more likely to use inpatient, emergency, and primary physical and mental health care services, as compared to individuals without mental health problems (Ronaldson et al., 2020). Comorbid physical and mental illness are associated with longer hospital stays, higher readmission rates, and higher medical costs than

individuals using health care services without comorbid mental disorders (Jansen et al., 2018). In addition, healthcare disparities, associated to the pervasive stigma towards mental illness and the separation of physical and mental health services, place individuals living with mental disorders at higher risk of poorer overall health outcomes than individuals without mental disorders (Lawrence & Kisely, 2010). Barriers to effectual or optimal care not only pose risk to individuals' health, but are also tied to long-term increases in expenses, as highlighted by frequency of use and readmission rates in those living with mental illness. Further exploration of pathways to care and overall expenditures for individuals living with mental illness stands to promote the adoption of interventions to offset costs and optimize access to care.

The economic burden of mental disorders is well represented by the high costs they entail. The annual cost of health care services for mental disorders, from a small proportion of the population, can be upwards of twice the expenditure of individuals without mental health disorders (de Oliveira et al., 2016; Larrañaga et al., 2023). More specifically, the economic burden attributed to the affective disorders is tied to both the direct costs of medical interventions as well as downstream impacts of the associated disability (Dembek et al., 2023; Greenberg et al., 2021). Recent studies in the United States estimate that yearly direct and indirect costs associated to depressive disorders increased by almost 40% from 2010 to 2018, to $333.7 billion, while healthcare costs for bipolar spectrum disorders are approximately $25 billion higher than that for the general population (Dembek et al., 2023; Greenberg et al., 2021). It thus seems that economic and societal burdens associated to affective disorders are best understood through both service use and level of psychosocial dysfunction experienced by the individual.

As it pertains to the OAD, children of parents with mental disorders have been documented to use significantly more health and social services, as well as school-based

resources, than children of healthy parents (Waldmann et al., 2021). More specifically, children of parents living with major depressive disorder report higher service use rates and expenditures than children of healthy parents (Olfson et al., 2003; Stalujanis et al., 2019). Similarly to the adult population, costs of care associated to the OAD also spread beyond direct health service use, and include costs of psychosocial support such as school accommodations and occupational therapy (Waldmann et al., 2021). Importantly for the OAD, psychopathology in parents and familial well-being are possible predictors of mental health service use, and may even be associated with more ineffectual pathways to care as compared to children of parent without affective disorders (Stalujanis et al., 2019). Understanding specific risk factors for mental health service utilization in the OAD may help identify optimal cost-benefit ratios of preventative interventions, while providing viable opportunities to offset long-term costs of care.

Experiencing high levels of conflict in the home, parental separation, and emotional neglect are the strongest predictors of mental health service use when compared to other adverse early experiences (van Duin et al., 2019). In addition, family dysfunction more generally, as well as internalizing problems in parents and high levels of stress also predict which children go on to using services (Ezpeleta et al., 2002; Jansen et al., 2013). Lastly, ineffectual parenting styles and high levels of disorganization in the home are additional documented risk factors for children's mental health service use (Oltean et al., 2020). Despite the fact that families of parents with an affective disorder are characterized by low cohesion, high levels of conflict and stress, and poor parent-child relationships (Beardslee et al., 2013; Iacono et al., 2018; Moulin et al., 2022; Stapp et al., 2020), there is a paucity of research exploring service use rates and types of service used by the OAD. Thus, we aim to move beyond assessing mental health outcomes in the OAD by exploring their mental health service use.

Preventative interventions to offset risk in the OAD

The goal of prevention science is to prevent the development of various problems or disorders (Mendelson & Eaton, 2018). Prevention science builds on epidemiological research which identifies structural, intermediate (i.e., the family or peer circles), and individual risk factors for disorders, while simultaneously understanding factors which may mediate or moderate exposure to risk, or increase resiliency more generally (Catalano et al., 2012; O'Connell et al., 2009). Preventative interventions are thus administered prior to the onset of disorders, and aim to reduce the presence of risk factors and foster protective factors, to promote emotional and behavioural well-being.

There are three types of preventative interventions as proposed by the Institute of Medicine: universal programs, indicated programs, and selective programs (Mendelson & Eaton, 2018). Universal programs are typically administered to the general population and do not rely on identifying risk, such as school-wide health promotion efforts. Meta-analyses have highlighted that universal school-based efforts aiming to reduce maladaptive behaviours (i.e., substance use or bullying) are associated with high costs and often lead to marginal changes in behaviour or mood symptoms, given the lack of engagement from participants and generalizability of presented information (Baffsky et al., 2022; Tanner-Smith et al., 2018). Thus, universal programs may not be appropriate for targeting complex risk factors associated to the transmission of affective disorders.

While indicated preventative programs target prodromal individuals, experiencing symptoms of a disorder without meeting full criteria, selective programs are created for unaffected individuals presenting with known biological, psychological, and environmental risk factors tied to disorders of interest (Mendelson & Eaton, 2018). Researchers in the field have

thus suggested that selective preventative interventions are invaluable in the study of the OAD, who can be easily identified as at-risk by their positive family history of affective disorders (Gotlib et al., 2020; Loechner et al., 2018). Furthermore, selective preventative program studies may reduce the risk of maladaptive outcomes in the OAD, while simultaneously providing evidence for key environmental mechanisms of transmission.

Stemming from the OAD's well-documented vulnerability to psychopathology (Henin et al., 2005; Vandeleur et al., 2012), studies spanning the last four decades have aimed to identify malleable environmental and psychological risk factors from selective preventative programs. A review by Loechner and colleagues (2018) explored the effectiveness of different types of preventative interventions which each aimed to reduce symptoms of depression in unaffected OAD. Interventions typically presented psychoeducation about major depressive disorder and targeted stress-coping, yet varied on the theoretical approach and subsequent intervention targets. Preventative programs anchored in psychoeducation or cognitive-behavioural principles, such as the Coping with Depression program (Cuijpers et al., 2009), are designed for youths aged 8-to-15 years and their families. These programs focus on teaching youths how to restructure their negative or unhelpful thoughts, and develop efficacious problem-solving skills to more adaptively manage stressors which arise from having a depressed parent. These programs are shown to yield immediate improvements on internalizing symptoms; however, evidence of long-term gains is weaker (Loechner et al., 2018). In their review, Loechner and colleagues (2018) could not evaluate, at the meta-analytic level, whether parent involvement mediated the effect of interventions.

Recently, Löchner and colleagues (2023) published a randomized-controlled trial aiming to elucidate the added role of parent involvement within preventative efforts. Results from their

study demonstrated that Family-Group cognitive-behavioural therapy, which focused on improving family communication and stress resilience, while also targeting parenting difficulties common to parents with affective disorders, significantly reduced depression risk as compared to control OAD receiving no intervention. In fact, evidence suggested that the intervention led to a decrease in negative parenting, which partially explained to relationship between taking part in the family-based intervention and reductions in depressive symptoms (Löchner et al., 2023). These findings are in line with a review by Wirehag-Nord and colleagues (2023), which highlight that family-based interventions yielded larger decreases in child mental health symptoms than interventions which do not focus on the family (Wirehag-Nord et al., 2023). At the focus of their review were the Family Talk Intervention (Beardslee et al., 2003) and the Let's Talk about Children intervention (Solantaus and Toikka, 2006), which were identified as exemplary preventative intervention programs. These programs both focus on psychoeducation about depression in parents, its impact on the family, and teach effective parenting strategies for optimal child development.

Regarding the offspring of parents with bipolar spectrum disorders, current programs are anchored in Adapted Family-Focused Therapy, which targets youths between 9 and 17 years of age presenting with symptoms of the bipolar spectrum, but not a full disorder (Miklowitz et al., 2006). The program was found to improve the course of bipolar spectrum disorder in adulthood and even delay the onset of the disorder altogether (Miklowitz et al., 2006, 2011, 2014). More recently, a multisite randomized controlled trial demonstrated that offspring who took part in Adapted Family-Focused Therapy had longer intervals between recovery and onset of depressive episodes as compared to those who underwent 6 sessions of enhanced usual care (Miklowitz et

al., 2020). Together, these studies highlight promising avenues of family-based preventative interventions for the OAD.

Building on this literature, we have developed a family-based preventative intervention program entitled *Reducing Unwanted Stress in the Home* (RUSH) to target families having unaffected 6-11 year-old offspring of parents with bipolar disorders (OBD; i.e., who have not yet developed symptoms of an affective disorder). The RUSH program targets the stressful and chaotic family environment of the OBD, with a particular focus on improving organization, consistency, stress-coping, and parenting practices, and aims to prevent the early development of internalizing and externalizing symptoms in OBD. Although there are no randomized controlled trials of the RUSH program, a proof-of concept study has been completed, comparing OBD to offspring of parents with no affective disorders (i.e., control offspring). The RUSH program was found to significantly reduce externalizing symptoms, but not internalizing symptoms in OBD (Serravalle et al., in preparation). Secondary analyses found RUSH to be associated with significant improvements in parental positivity (i.e., positive emotions and control) and dyadic mutuality (i.e., interactive reciprocity, cooperation, and co-responsiveness), and reductions in parental negativity (i.e., negative emotions and control). Several mediating variables, including parental negativity, and family functioning, were found to influence the impact of RUSH on offspring internalizing and externalizing symptoms (Serravalle et al., 2021), as well as diurnal cortisol levels (Yong Ping et al., in preparation). Such markers of hypothalamic-pituitary-adrenal (HPA) axis function have been shown to predict the development of affective disorders in youth and adult populations (Halligan et al., 2007; Ellenbogen et al., 2011), highlighting a potential pathway by which preventative interventions decrease risk in OBD. These findings fall in line with literature suggesting that the success of early interventions is dependent on actual changes

in children's environment (Sameroff & Fiese, 2000). Chapter 4 will cover the RUSH intervention program in more detail.

Rationale for the three presented studies, and overarching goals of the thesis

The three primary goals of this thesis are to determine: 1) whether the OAD exhibit heightened sensitivity to stress in the home environment (i.e., family dysfunction), 2) whether the OAD, in response to stress in the family, use high levels of mental health services and require more intense services, and 3) if a preventative intervention might improve chronic interpersonal stress in families, parenting stress in families, and child outcomes.

In **Chapter 2** (study 1), we explored the concurrent association between family dysfunction and both internalizing and externalizing problems across time, and compared the associations across timepoints and between groups (i.e., OAD and controls). Our primary aim was to determine whether OAD's mental health was more strongly linked to their family's dysfunction as compared to controls across time. We also investigated whether risk-status moderates the mediating effect of family dysfunction on the relationship between stressful life events and psychosocial outcomes. As part of the TRacking Adolescents' Individual Lives Survey (TRAILS), 2230 participants and their parents completed questionnaires across 6 time points, spanning 15 years.

In **Chapter 3** (study 2), as a follow-up study using the TRAILS data, we sought to investigate the relationship between early cumulative environmental risk, subsequent mental health need, and mental health care utilization in adulthood between the OAD and controls. To better account for the different adverse events children are exposed to, we created a cumulative risk score representing the aggregating effect of repeated exposure to stressors. We then explored whether poor mental health in youth mediated the relationship between cumulative

environmental risk and intensiveness of mental health interventions used by the OAD in adulthood. Finally, we assessed whether relationships between cumulative stress and later health care use might be stronger in the OAD than controls. Cumulative risk scores were compiled using known environmental risk factors, including SES, parenting styles, familial dysfunction, and parenting stress, assessed at the first timepoint. Understanding pathways to intensive and costly care stemming from exposure to adverse events highlights the societal and economic benefits to providing preventative interventions for the OAD.

In **Chapter 4** (study 3), we evaluate the efficacy of the RUSH preventative intervention program, which targeted family functioning, parenting styles, and stress-coping in an effort to improve children's emotional and behavioural outcomes. The program consists of parent and child groups that aim to provide psychoeducation and tangible skills to improve family functioning and stress-coping. The proof-of-concept study was conducted with families where one parent met criteria for a bipolar disorder, and had at least one child between the ages of 6 and 11 years. Offspring of parents with bipolar disorder were compared to age-matched controls who underwent all assessments but did not participate in the RUSH program. We investigated whether improvements in parenting stress mediated the relationship between participation in the RUSH program and offspring internalizing and externalizing symptoms following the end of the intervention and six months later. Providing evidence of the mediation would further support the family environment as a key factor in the determining mental health outcomes in high risk youth.

Chapter 2: Family dysfunction, stressful life events, and mental health problems across development in the offspring of parents with an affective disorder

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Abstract

The offspring of parents with affective disorders (OAD) are at risk of developing a wide range of mental disorders. Deficits in the rearing environment and high levels of stress are well known risk factors for negative outcomes in the OAD. Building on prior research, we aim to examine the longitudinal relationships between family dysfunction, stressful life events, and mental health in the OAD and control offspring of parents with no affective disorder. In the present study, we hypothesized that high levels of family dysfunction would be associated to more internalizing and externalizing problems in the OAD across time than in controls, and that family dysfunction would mediate the relationship between stressful life events in adolescence and poor mental health in adulthood, particularly in the OAD. As part of the TRacking Adolescents' Lives Survey (TRAILS), 2230 participants (51% female, M_{age}= 11.1 years, SD = 0.6, at baseline) and their parents completed questionnaires across 6 time points, spanning 15 years. Mental health, family dysfunction, and stressful life events were assessed with the *Youth and Adult Self-Report*, *Family Assessment Device*, and an in-house measure, respectively. Multi-group structured equation modelling revealed that poor family dysfunction was linked to internalizing and externalizing problems in the OAD, but not the controls, across time. Risk-status did not moderate family dysfunction's mediation of the relationship between stressful life events and negative outcomes in adulthood. The OAD show high sensitivity to dysfunction in the rearing environment across childhood and adolescence, which supports the use of family-based interventions to prevent the development of mental disorders in high-risk youth.

Introduction

The offspring of parents with affective disorders (OAD) are at risk of developing a wide range of psychiatric disorders (Henin et al., 2005). Studies show that on average, one third of OAD children develop an affective disorder, while almost half report having an anxiety disorder (Lau et al., 2018; Stapp et al., 2020; Vandeleur et al., 2012). These developmental trends continue well into adulthood, as evidenced by the OAD's high rates of interpersonal difficulties, sexual risk behaviors, and poor occupational outcomes (Bella et al., 2011; Duffy et al., 2014a; Nijjar et al., 2014; Ostiguy et al., 2009; Shaw et al., 2005; Weissman et al., 2006). Research on the familial transmission of affective disorders has highlighted the interplay of both genetic and environmental risk factors (Ellenbogen & Hodgins, 2004; Harold et al., 2011; Stapp et al., 2020). Beyond heritability, some studies, but not all (Moulin et al., 2022), have shown that a dysfunctional rearing environment may mediate the relationship between psychopathology in parents and offspring mental health (Harold et al., 2011; Iacono et al., 2018). In particular, the OAD are at-risk of experiencing high levels of stress, stemming from both their rearing environment and frequent negative life events, which together exacerbate their likelihood of developing mental disorders (Amone-P'Olak et al., 2010; Hillegers et al., 2004; Ostiguy et al., 2009). This study aims to further explore the association between family dysfunction and offspring mental health across time, as well as examine family dysfunction as a potential mediator of the relationship between children's exposure to stressful life events and functioning in adulthood for the OAD.

A dysfunctional rearing environment is a well-known risk factor for poor developmental outcomes in the OAD (Iacono et al., 2018; Ostiguy et al., 2012; Serravalle et al., 2021). Parents with affective disorders are less supportive of their children and provide less warmth and

nurturance than parents without affective disorders (Cummings et al., 2005; Iacono et al., 2018; Lau et al., 2018; Serravalle et al., 2021). Additionally, they report lower emotional sensitivity, fewer expressed emotions, and more blunted emotional responsiveness compared to parents with no affective disorders (Cummings et al., 2005; Iacono et al., 2018; Serravalle et al., 2021; Wilson & Durbin, 2010). Low emotional engagement from caregivers may lead to dysfunctional parent-child interactions and insecure attachment styles, thus contributing to persistent deficits in interpersonal functioning in the OAD. Parents with affective disorders were also found to frequently engage in non-optimal parenting strategies. For example, mothers with major depressive disorder or bipolar disorder display high levels of negativity and criticism towards their children (Cummings et al., 2005; Inoff-Germain et al., 1992; Suppes et al., 2017). While reliance on ineffective parenting practices may stem from one's own stress-coping deficits as a parent (Belsky & Barends, 2002; Clark et al., 1994; Ellenbogen & Hodgins, 2004), these techniques further contribute to poor family functioning (Calam et al., 2012; Lovejoy et al., 2000b) and could place the OAD at further risk of poor developmental outcomes.

Cross-sectional studies have shown that families including a parent with an affective disorder report worse functioning than families with healthy parents (Barron et al., 2014; Romero et al., 2005; Weinstock et al., 2006; Wiegand-Grefe et al., 2019). In fact, poor family functioning may explain, in part, the development of mental health problems in the OAD. Studies have shown that the relationship between affective disorders in parents and illness onset in offspring may be mediated by problems in the rearing environment (Beardslee et al., 2013; Iacono et al., 2018; Ostiguy et al., 2012; Serravalle et al., 2021). One longitudinal study, for example, identified that links between postnatal depression in mothers and later depression in their adolescent offspring were partially explained by the fact that depressed mothers are less

supportive of their children than non-depressed mothers (Murray et al., 2011). However, some studies have not replicated this effect (Bouma et al., 2008; Moulin et al., 2022). A study by Bouma and colleagues found that, although children of depressed mothers were more likely to report depressive symptoms of their own following stressful life events, this relationship was not mediated by family functioning. Problems in the rearing environment and high exposure to stress may thus both contribute to the OAD's risk status.

Overall, the literature presents robust evidence that the rearing environment, as well as early exposure to stress, are key mechanisms in understanding the OAD's developmental trajectories to negative outcomes. However, there is limited research on the longitudinal associations between family dysfunction and mental health in the OAD, especially in comparison to offspring of parents with no affective disorders (i.e., controls). Despite recent research failing to provide evidence of familial environment factors being associated to the onset of depressive or bipolar disorders in the OAD (Moulin et al., 2022), we aim to investigate the long-term association between family dysfunction and mental health outcomes in the OAD across a 15-year period spanning from childhood to early adulthood. Therefore, our primary aim is to determine whether the OAD's mental health is more strongly linked to their family's dysfunction as compared to controls across time. We hypothesize that internalizing and externalizing problems across early development will be more strongly associated to family dysfunction for the OAD than controls, when statistically accounting for both variables' changes over time.

A second aim of this study is to investigate whether risk-status moderates the mediating effect of family dysfunction on the relationship between stressful life events and psychosocial outcomes. For clarity, we present our goals and hypotheses in steps. Firstly, we hypothesize that the OAD will report higher levels of exposure to stressful life events in childhood, higher levels

of family dysfunction in adolescence, and worse outcomes on internalizing, externalizing, and sexual risk behaviours in young adulthood as compared to controls. We then hypothesize that family dysfunction will worsen as a function of stressful life events, which will consequently lead to an increase in internalizing symptoms, externalizing symptoms, and sexual risk behaviours. Finally, we hypothesize that risk-status will moderate all three of the proposed paths. Mediation paths are expected to be stronger for the OAD than controls, in that early family dysfunction will predict higher levels of future internalizing problems, externalizing problems, and sexual risk behaviours. We included sexual risk behaviours as an adult outcome of interest in this study as they were previously identified as a key outcome measure distinguishing the offspring of parents with bipolar disorder in late adolescence from controls (Nijjar et al., 2014).

Methods

Participants

The participants were recruited as part of the TRacking Adolescents' Individual Lives Survey (TRAILS). TRAILS is an ongoing, multidisciplinary study exploring the psychological, social, and physical development of adolescents and young adults in the Netherlands. The data used in the present study was collected at 6 time points, once every 2-3 years, over the span of 15 years. The sampling procedure was as follows. The TRAILS research team identified 135 primary schools across five municipalities in the North of the Netherlands within which they could run their data collection efforts. Within the 122 schools which agreed to participate in the TRAILS project, brochures explaining the study aims, procedure, and confidentiality were distributed to both parents and children. Finally, families were contacted by telephone to extend a direct invitation to participate in the study (Huisman et al., 2008). The first data collection time point was in 2000/2001 and consisted of 2230 participants between 10 and 12 years old (51%

female, Mage= 11.1 years, SD = 0.6). At the second time point, there were 2149 participants (96% retention rate, 51% female, Mage= 13.6, SD = 0 .5). At time point 3, there were 1816 participants (81% retention rate, 52% female, Mage= 16.3, SD = 0.7). At time point 4, there were 1881 participants (84% retention rate, 52% female, Mage= 19.1, SD = 0.6). At time point 5, there were 1778 participants (80% retention rate, 53% female, Mage= 22.3, SD = 0.6). At time point 6, 1618 participants remained (73% retention rate, 54.5% female, Mage = 25.6, SD = 0.6; for more details see Oldehinkel et al., 2015). The population cohort includes participants born between October 1989 and September 1991, living in the north of the Netherlands at the time of the baseline assessment. School attendance was required for study eligibility, as was Dutch fluency, as data collection occurred in schools and in Dutch. The majority of participants were from middle or high socio-economic classes, as measured by maternal education and parental work status. About one third (32.6%) of the parents did not complete high school at a level that would give access to higher vocational or university education. Exclusion criteria included severe intellectual disabilities, as well as serious physical illness or handicap, in either offspring or parent. The study was approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO) and was conducted according to the principles of the Declaration of Helsinki; informed consent was obtained from all participants.

Measures

Family dysfunction

The Family Assessment Device (FAD) assesses family dysfunction in the areas of communication, roles, behaviour control, affective responsiveness, affective involvement, and problem-solving. It is theoretically anchored in the McMaster Model of Family Functioning (Epstein et al., 1993). The current study used the 12-item General Functioning short-form of the

FAD (Epstein et al., 1983a). The 12 items assess functioning in each of the areas mentioned above. Each item is scored on a 4-point scale (strongly agree to strongly disagree), with higher scores indicating higher levels of dysfunction. The 12-item short-form presents with adequate reliability and validity (Byles et al., 1988). Parent-reported data from this measure was collected at every time point.

Internalizing and externalizing problems

The Youth Self-Report (YSR) questionnaire was designed for 11- to 18-year-olds. Its 112 items assess various strengths and difficulties in youths' functioning (Achenbach, 2001). The Adult Self-Report (ASR) was designed for individuals aged 18-59 years, and includes 126 items assessing psychopathology and aspects of adaptive functioning (Rescorla & Achenbach, 2004). Composite scores are derived from subscales on both the YSR and ASR representing internalizing (emotional) and externalizing (behavioural) symptoms. The YSR's and ASR's psychometric properties are well-known and conveniently summarized (Achenbach, 2001; Rescorla & Achenbach, 2004). Items are rated on a 3-point scale (0=absent/not true, 1=occurs sometimes/somewhat true, 2=occurs often/very true). Higher scores represent more dysfunction. Data from the YSR was collected across time points 1 to 3, while data from the ASR was collected across time points 4 to 6.

Sociodemographic information

A sociodemographic questionnaire was created by the TRAILS research team and administered at time 1. The in-house measures assessed the participants' sex, age, ethnicity, and living conditions, as well as their parents' educational and work status. Participants' socioeconomic status (SES) was obtained by analyzing both parental educational attainment,

work status, and income. Three SES categories were constructed based on the data's distribution: the lowest 25%, the middle 50%, and the highest 25%.

Affective disorders in parents

The presence of an affective disorder in parents was assessed at time point 1. Parents were asked about their own experiences with mental health problems as part of the Family History Interview. The interview assesses five domains of psychopathology: depression (including mania), anxiety, substance use, antisocial behaviours, and psychosis. One parent per family was presented with vignettes that described the DSM-IV criteria of each domain (available upon request), with specific questions targeting lifetime occurrence, professional treatment, and medication use. Extensively trained interviewers then coded responses provided by parents on a 4-point Likert scale, consisting of "0 = no", "1 = probably not", "2 = probably yes", and "3 = yes". The lifetime prevalence rates of disorders obtained from the Family History Interview were comparable to the CIDI–DSM-IV lifetime rates obtained by direct clinical interviews in a large epidemiological study conducted in the Netherlands prior to TRAILS, in which 19% of respondents reported a mood disorder (NEMESIS; Bijl et al., 1998). Rates for mothers and fathers, respectively, in the TRAILS sample were as follows for depression: 27% and 15%; for anxiety: 16% and 6%; for substance dependence: 3% and 7%; and for antisocial behaviour: 3% and 7% (Ormel et al., 2005). Responses higher than or equal to 2 on questions pertaining to lifetime depressive and manic episodes were used to categorically represent the data as having or not having an affective disorder in a parent (0=no/probably not, 1=probably yes/yes). Adolescents were identified as offspring of parents with affective disorders (i.e., OAD; n = 761), or as offspring of parents with no affective disorders (i.e., controls; n = 1468). A high

probability of a lifetime affective disorder was reported for 601 mothers and 319 fathers, whereas for 159 participants lifetime affective disorders were reported for both parents.

Long-term difficulties questionnaire

The long-term difficulties questionnaire is a parent-reported questionnaire developed by the TRAILS team. Parents categorically (0=no, 1=yes) reported the presence of longstanding stressors in their adolescents' lives, including interpersonal (i.e., bullying, lack of friends, or persistent conflict) and non-interpersonal (i.e., academic pressure, housing or neighbourhood difficulties, or family financial problems) problems. Data on this measure was collected from time point 2. Participants received one point for each stressor that was reported by their parents. Higher scores represent higher levels of stress in early adolescence.

Sexual risk behaviours

A questionnaire assessing adolescents' sexuality was developed by the TRAILS team. Participants were asked the age at which they first experienced sexual intercourse, from time points 2 to 6. Sexual intercourse prior to the age of 16 was considered a sexual risk behaviour. Additional data was collected at time points 4 to 6 regarding participants' sexual experiences and pregnancies. Participants were asked to rate how often they engaged in safe sex (i.e., use of contraception), and responses were given on a four-point Likert scale (1=always to 4=never). Scores higher than 1 were considered a sexual risk behaviour. Participants were also asked whether they or their partners had an abortion in the last 2 to 5 years (0=no, 1=yes); a response of "yes" was considered a sexual risk behaviour. Participants were assigned a score based on the presence of one of the three sexual risk behaviours, or the absence of all behaviours.

Data Analysis

All analyses were run on MPlus version 8 (Muthen et al., 2017). To test our first hypothesis, we modeled changes in offspring internalizing and externalizing symptoms using latent curve modelling . Curve modelling can be applied to repeated measures data in order to account for within-subject longitudinal trajectories on the outcomes of interest, as well as for between-person variations in the shape of these trajectories (Bollen & Curran, 2006). Curves estimated changes in internalizing and externalizing symptoms across all six time points, as well as changes in family dysfunction across time. The relationship between family dysfunction and offspring mental health was estimated at each time point separately. A conceptual diagram representing this model can be found in Figure 1.

The first step was to identify the optimal solutions for these longitudinal trajectories, contrasting intercept-only (no change), linear, and quadratic representations of the data (see Tables S1 and S5 in Supplemental Material). Following the identification of this latent curve, time-invariant factors, also known as between-person factors, assessed at time 1 (i.e., sex and SES) were added to the solutions to statistically account for their impact on both initial levels and rates of change of outcomes (see Tables S2 and S6). Changes on the FAD were then modelled across all six time points to identify the best representation of this data (see Tables S3 and S7), before it was entered as a time-varying factors, or within-person factors, to assess its time-specific effects on the trajectories of the outcome (see Tables S4 and S8). Multi-group curve models then allowed us to analyze the invariance of the models between the OAD and controls, and to compare differences in parameter estimates between groups (see Results). Risk-status thus served as a moderator of the relationship between family dysfunction and mental health. Models were estimated using full information maximum likelihood (FIML; Allison, 2012), and a maximum-likelihood estimator with robust standard errors was used.

To assess our second hypothesis, we ran a series of moderated mediation analyses. A diagram representation of all three proposed moderated mediation models can be seen in Figure 2. Long-term difficulty scores representing stress in early adolescence served as the independent variable. The mediator variable used was the FAD scores averaged across time points 3 and 4, to represent family dysfunction in adolescence. Outcome variables consisted of internalizing and externalizing symptoms averaged across time points 5 and 6, and sexual risk behaviours assessed at time points 4 to 6, respectively. A multi-group approach was used to assess the hypothesized moderation effect, and allowed us to test whether pre-defined data groups (i.e., OAD vs. controls) showed differences in group-specific parameter estimates (i.e., regression slopes). Regression models were estimated using full information maximum likelihood (FIML; Allison, 2012). Baseline levels of family dysfunction and internalizing and externalizing problems were added to the models to account for their impact on estimated relationships.

Results

The effect of family dysfunction on offspring mental health across time and risk group

Plotted curves representing changes over time in internalizing problems, externalizing problems, and family dysfunction between groups can be found in Figure 3. A multi-group approach was used to investigate whether the effect of family dysfunction on internalizing problems differed between OAD and controls. First, using the identified baseline model (Model 10; Table S3), effects were allowed to vary freely between groups, thus accounting for hypothesized differences between OAD and controls. Then, effects were constrained to equality between groups, to better understand how data fit the alternate hypothesis that effects are equal between groups (see Model 11 and 12; Table S3). A significant worsening of model fit when groups were estimated to be equal thus supports the hypothesis that significant differences exist

between OAD and controls. The effects discussed below are therefore allowed to vary between groups.

As seen in Table 1, the average standardized *M(SD)* baseline level of internalizing problems was 0.29(0.04) for the OAD, and 0.34(0.02) for controls. The OAD improved on internalizing symptoms at an average rate of -0.011(0.02) per time point, and this rate of change was non-linear. The relationship between family dysfunction and internalizing problems was statistically significant for the OAD group ($B = 0.05$, $SD = 0.02$, $p = .008$). This effect was deemed comparable, or invariant, across all 6 time points (see Table S3). In other words, more family dysfunction was associated to more internalizing problems for the OAD at each specific time point, but not for the controls ($B = 0.06$, $SD = 0.01$, $p = .636$), and the effect was comparable across all 6 time points. Across the whole sample, girls reported more internalizing problems than boys at baseline (see Table 1).

In estimating multi-group curves for externalizing problems, we began with the identified baselines model (Model 22; Table S7), and allowed effects to vary between groups. Effects were then constrained to equality across groups and model fit significantly worsened (see Model 23 and 24 in Table S7), supporting the hypothesized differences between groups. As seen in Table 2, the average *M(SD)* baseline level of externalizing problems was 0.21 (0.03) for the OAD, and 0.25 (0.02) for controls. The OAD improved on externalizing symptoms at an average rate of -0.07 (0.03) per time point, while this rate of change was slightly non-linear. More family dysfunction was associated to more externalizing problems for the OAD ($B = 0.04$, $SD = 0.02$, $p = .004$) at each specific time point, but not for the controls ($B = 0.01$, $SD = 0.01$, $p = .550$). Across groups, boys reported more externalizing problems than girls at baseline (see Table 2).

There were also significant SES effects on family dysfunction (across Tables 1 and 2). Across groups, families of lower SES reported higher baseline levels of both internalizing and externalizing problems. Within the control groups, families of higher SES reported improvements in family dysfunction over time which followed non-linear curves, as opposed to more linear changes in families of lower SES. Families of male participants also reported changes in family dysfunction over time which followed less linear curves than families of female participants.

Family dysfunction as a mediator of the relationship between stressful life events and mental health in adulthood

A multi-group approach was used to investigate differences in mediation models between the OAD and the controls. The mediation models investigated both the direct and indirect effect of stressful life events in early adolescence on offspring mental health in adulthood, via family dysfunction as mediator (see Figure 2). Offspring outcomes of interest included internalizing problems, externalizing problems, and sexual risk behaviours in adulthood. Models also took into account baseline levels of family dysfunction, internalizing symptoms, and externalizing symptoms. Parameter estimates of the relationship between predictor and mediator (paths a), the mediator and outcomes (paths b), and the predictor and outcomes (paths c) are found in Table 3.

The standardized mean internalizing score (± *SD*), averaged across T5 and T6, for controls was 0.29 (0.24), while for the OAD it was 0.33 (0.26). The standardized mean externalizing score, averaged across T5 and T6, for controls was 0.19 (0.16), while for the OAD it was 0.21 (0.17). In terms of sexual risk behaviours, the standardized mean score (± *SD*) was 0.43 (0.49) for controls, and 0.44 (0.50) for the OAD; however, the proportion of individuals who had ever engaged in at least one sexual risk behaviour was identical across groups (35%).

The standardized mean family dysfunction scores (± *SD*), averaged across T3 and T4, were 1.63 (0.33) for controls, and 1.73 (0.36) for the OAD. Finally, the stressful life event score from parental reports was 0.40 (0.77) for controls, and 0.75 (1.14) for the OAD. Group differences on the mediator variable and mental health outcomes were all significant ($p < .05$); however, groups did not differ on engagement in sexual risk behaviours.

Family dysfunction in adolescence partially mediated the relationship between exposure to stress in early adolescence and internalizing problems in adulthood for both the OAD and controls. Across groups, exposure to more stressful life events predicted more family dysfunction, which in turn predicted more internalizing problems in adulthood. The above findings were repeated for externalizing problems. Family dysfunction partially mediated the relationship between stressful life events and offspring externalizing problems in adulthood for both the OAD and controls. Lastly, family dysfunction did not mediate the relationship between stressful life events and offspring sexual risk behaviours for either group. However, the direct effect was significant across groups, in that higher levels of stress in early adolescence predicted engagement in sexual risk behaviours in adulthood.

Simple slope comparisons were run to investigate whether the two groups differed on any of the mediation paths. Analyses revealed no significant differences between groups (moderated mediation) on any paths across all mediation models (see Table S9 in Supplemental Material).

Discussion

The findings of the present study showed that the OAD, but not offspring of parents without affective disorders, experienced increases in internalizing and externalizing behaviours in response to worsening family dysfunction throughout adolescence and early adulthood. It supports the view that the OAD are generally more sensitive to family dysfunction than offspring

of parents without affective disorders. In addition, family dysfunction in adolescence partially mediated the relationship between stressful life events in adolescence and internalizing and externalizing symptoms in adulthood across groups. That is, both the OAD and the control families reported worse family dysfunction in the years following high levels of stress in early adolescence, which in turn predicted higher rates of internalizing and externalizing symptoms in adulthood. In contrast, no evidence of mediation by family dysfunction was observed for sexual risk behaviours as the outcome.

Recent findings provide evidence of the OAD's sensitivity to stress in their rearing environments, which appears to be stable across adolescence and persists well into adulthood. The OAD may in fact exhibit high stress-sensitivity, meaning that they appear to react more strongly to environmental adversity, particularly within the family, than children having healthy parents (Nijjar et al., 2016; Ostiguy et al., 2011, 2012). The underlying cause of stress sensitivity in high-risk youth is not yet known, but may reflect genetic risk, pre- and perinatal events, and exposure to early adversity including post-partum depression (Flouri et al., 2020; LeMoult et al., 2020; Vrshek-Schallhorn et al., 2014). Indeed, it is known that offspring of parents with bipolar disorder experience both high levels of stress early in life, as well as a chaotic home environment and dysfunctional family dynamics; the latter being elicited through high emotional reactivity and sensitivity to stress (i.e., neuroticism) in parents who struggle in their parenting role (Ellenbogen & Hodgins, 2004; Ostiguy et al., 2011). Moreover, there is increasing evidence that cumulative exposure to early risk factors might alter certain stress-sensitive systems and sensitize youth to the later exposure of stressful life events (Blair et al., 2011; Dich et al., 2015). Studies have shown that early adversity, including having a parent with a depressive disorder, may alter neuroendocrine stress reactivity, explaining future sensitivity to stressful events (Halligan et al.,

2004; Laurent et al., 2015; Starr et al., 2014). Thus, the OAD might evidence high sensitivity to adverse family conditions that puts them at high risk for negative outcomes. Thus, the between-group differences reported in the present study replicate findings from studies of the OAD populations, as well as studies on offspring of parents without affective disorders.

The second hypothesis proposed that family dysfunction would mediate the relationship between stressful life events in early adolescence and mental health outcomes in adulthood, and that the mediation would be stronger among the OAD than among the control offspring. Support for the hypothesis was mixed. Family dysfunction partially mediated the relationship between stressful life events and both internalizing and externalizing symptoms, but contrary to prediction, and despite observed differences within the multi-group latent curve model, there were no differences between the OAD and the controls. Exposure to stressful life events may thus strongly predict the development of future mental health problems, regardless of risk-status, while the relationship between family dysfunction and mental health at any one time point may be unique to the OAD. One explanation may be that high numbers of stressful life events in adolescence are known to predict internalizing and externalizing problems across both risk- and non-risk populations (Kessler, 1997; Low et al., 2012). Experiencing a multitude of stressful life events may therefore place individuals at risk of negative outcomes more reliably than unique risk factors such as having a parent with an affective disorder. In contrast, family dysfunction did not mediate the relationship between life stressors and sexual risk behaviours. Sexual risk behaviors may be more relevant as an outcome in the offspring of parents with bipolar disorder (Nijjar et al., 2016) than in the present sample of the OAD, where few parents had bipolar disorder. Moreover, sexual risk behaviours were relatively infrequent in the current sample, which could have contributed to our inability to detect an effect.

The results of our mediation analyses also partially replicate recent findings. While failing to support the hypothesis that familial environmental factors impacted familial transmission of affective disorders, Moulin and colleagues highlighted the importance of exposure to adverse childhood experience in explaining the onset of depression in offspring (Moulin et al., 2022). Numerous methodological factors may explain the differing results between studies. First, sample sizes vary significantly between the two studies, which may impact the power to detect an effect. The researchers ran separate mediation analyses within sub-groups of their sample based on age of onset and type of affective disorder in parents, further reducing the sample size for each analysis. Second, the methodology used between studies was vastly different. A strength of the multigroup approach to mediation analyses is the ability to use the entirety of the sample at once, while observing differences (or the lack thereof) between hypothesized groupings within the sample. Further, the outcome variables also differed. The aim of the current study was to examine the risk of developing precursors of mental disorders in youth, whereas Moulin and colleagues investigated the development of affective disorders themselves (Moulin et al., 2022). Lastly, the present study measured levels of family dysfunction as representing parental ratings of the family's communication, roles, and problem-solving, as well as parent's engagement in behaviour control, their affective responsiveness, and their affective involvement. Moulin and colleagues, in contrast, utilized offspring's perception of their parents' rearing styles. Overall, given each study's unique objectives and methodology, the differing results between studies are not surprising.

The present findings have important clinical implications. The family system is known to be an important focus of intervention for the OAD (Compas et al., 2015; Miklowitz et al., 2006). Results from randomized controlled trials have shown that family-focused therapy can delay

onset and improve the course of bipolar disorder in offspring of parents with bipolar disorder (Miklowitz et al., 2011, 2014). Family-based interventions may also lengthen recovery periods between depressive episodes in affected offspring (Miklowitz et al., 2020). Further, Compas and colleagues conducted a randomized controlled trial in which family-based group interventions had lasting positive effects on the offspring of parents with depression, reducing both their number of endorsed depressive symptoms and their incidence of depressive episodes for up to 24 months (Compas et al., 2015). In line with these findings, recent research has shown that family-based interventions decrease internalizing and externalizing symptoms in unaffected offspring of parents with bipolar disorder by both decreasing parenting stress and improving parent-child interactions (Resendes et al., 2023; Serravalle et al., 2021). Family interventions could therefore serve as prevention target for the OAD more broadly. Finally, our current findings provide further indications that family-based interventions for the OAD may be valuable across development. The relationship between family dysfunction and the OAD's mental health was comparable across the 15-year range of the study, supporting the possible utility of family-based intervention from middle childhood to early adulthood.

There are a number of study limitations that should be addressed. The study sample consisted of predominantly ethnically Dutch, Caucasian, middle-class adolescents, with two parents. The results may therefore not generalize to other, more diverse, populations. Similarly, given the measurement of internalizing and externalizing symptoms across time, as opposed to specific clinical diagnoses, we cannot determine whether participants develop certain types of disorders across time, nor can we link our conclusions to particular affective disorders. Additionally, as family dysfunction was reported by parents, this increases the risk of bias as their ratings may be influenced by their affective disorder. Finally, evidence-based structured

diagnostic interviews were not used to identify psychopathology in parents; diagnoses were probable and based on participants' endorsing of symptoms presented to them with vignette-style descriptions. Despite these limitations, there are notable strengths. Longitudinal data collection with repeated measures allowed us to study individuals across a 15-year span. Second, this study builds upon recent studies exploring within-person associations between family dysfunction and offspring mental health (Kim et al., 2022; Mastrotheodoros et al., 2020; Moulin et al., 2022), and meaningfully contributes to the literature on the development of psychopathology in the OAD.

Conclusion

In the present study, we found a significant time-concurrent association between poor family functioning and both internalizing and externalizing symptoms in the OAD, but not in control offspring. The relationships were longstanding and persisted from middle childhood to early adulthood. Additionally, family dysfunction partially mediated the predictive relationship between stressful life events in adolescence and offspring mental health in young adulthood across groups. Poor family functioning appears to contribute to heightened risk for mental disorders in the OAD. Finally, the present findings highlight the potential importance of family-based interventions for the OAD across different stages of development.

Table 1. Family dysfunction as a time-varying risk factor of internalizing problems

	Internalizing Problems			Family Dysfunction		
OAD	I	S	Q	I	S	Q
Model	0.288	-0.106	0.016	1.849	-0.189	0.020
	(0.038)**	(0.023)**	(0.005)**	(0.013)**	(0.092)*	(0.020)
Sex (0=female,	-0.091	-0.025	0.004	0.034	-0.043	0.009
1=male)	(0.017)**	(0.019)	(0.004)	(0.026)	(0.021)*	(0.004)*
SES	-0.006	-0.004	0.000	-0.085	0.009	-0.001
	(0.013)	(0.010)	(0.002)	(0.019)**	(0.017)	(0.003)
R-squared	0.098*	0.074	0.702	0.047*	0.039	0.090
Controls						
Model	0.342	-0.078	0.014	1.736	-0.171	0.021
	(0.021)**	(0.010)**	(0.002)**	(0.010)**	(0.075)*	(0.018)
Sex (0=female,	-0.057	-0.052	0.010	0.009	-0.014	0.003
1=male)	(0.012)**	(0.010)**	(0.002)**	(0.019)	(0.014)	(0.002)
SES	-0.007	-0.004	0.002	-0.075	0.027	-0.005
	(0.008)	(0.006)	(0.001)	(0.013)**	(0.011)*	(0.002)*
R-squared	0.032*	0.104*	0.133*	0.038*	0.038	0.048

Note: n_{OAD} = 761. $n_{controls}$ = 1426. I = Intercept, S = Linear change, Q = Quadratic change.

Model results refer to estimated means derived from the model, with estimated standard errors in parentheses.

Unstandardized regression coefficients are presented with their standard errors in parentheses.

$* = p < .05$, $** = p < .001$.

Table 2. Family dysfunction as a time-varying risk factor of externalizing problems

	Externalizing Problems			Family Dysfunction		
OAD	I	S	Q	I	S	Q
Model	0.210	-0.074	0.013	1.849	-0.188	0.020
	(0.028)**	(0.027)*	(0.007)	(0.013)**	(0.092)*	(0.020)
Sex (0=female,	0.052	-0.036	0.006	0.036	-0.045	0.009
1=male)	(0.014)**	(0.011)*	(0.002)*	(0.026)	(0.021)*	(0.004)*
SES	-0.002	-0.008	0.001	-0.086	0.008	-0.001
	(0.011)	(0.009)	(0.002)	(0.019)**	(0.017)	(0.003)
R-squared	0.075	0.384	0.000	0.048*	0.041	0.100
Controls						
Model	0.253	-0.058	0.012	1.736	-0.172	0.021
	(0.020)**	(0.018)*	(0.005)*	(0.010)**	(0.075)*	(0.018)
Sex (0=female,	0.059	-0.033	0.006	0.008	-0.013	0.003
1=male)	(0.010)**	(0.007)**	(0.001)**	(0.019)	(0.014)	(0.003)
SES	-0.011	-0.003	0.001	-0.074	0.027	-0.005
	(0.006)	(0.005)	(0.001)	(0.013)**	(0.011)*	(0.002)*
R-squared	0.099*	0.213	0.462	0.038*	0.038	0.047

Note: $n_{OAD} = 761$. $n_{controls} = 1426$. I = Intercept, S = Slope, Q = Quadratic.

Model results refer to estimated means derived from the model, with estimated standard errors in parentheses.

Unstandardized coefficients are presented with their standard errors in parentheses.

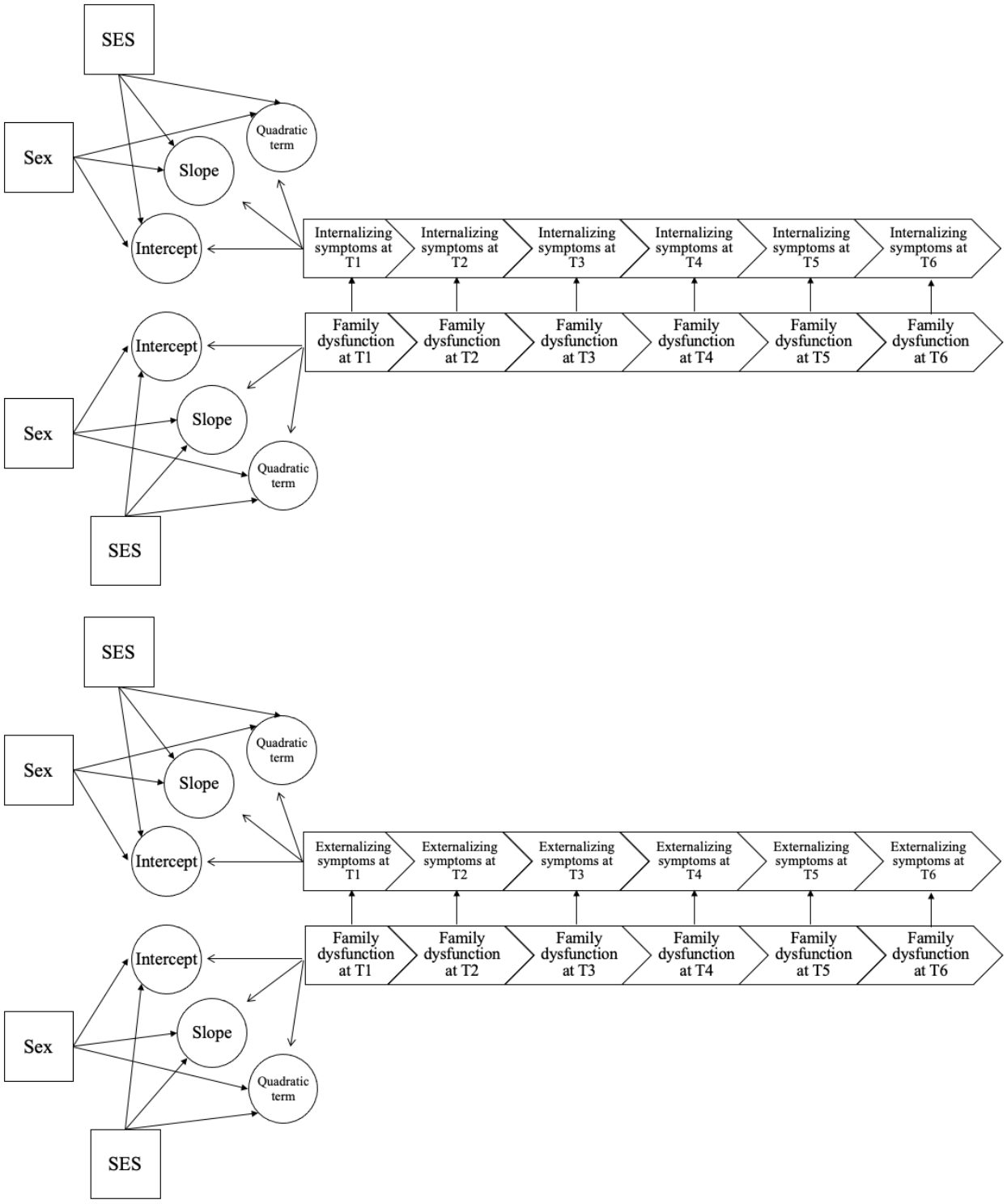
$* = p < .05$, $** = p < .001$.

Table 3. Family dysfunction in adolescence as a mediator of the relationship between stressful life events in early adolescence and outcomes in adulthood

	Internalizing Problems	Externalizing Problems	Sexual Risk Behaviours
OAD			
Effect of *IV* on mediator (*a*)	0.29 (0.03)**	0.30 (0.03)**	0.31 (0.04)**
Unique effect of mediator (*b*)	0.14 (0.06)*	0.11 (0.05)*	-0.05 (0.05)
Indirect effect (*ab*)	0.04 (0.01)**	0.03 (0.01)**	-0.01 (0.01)
Direct effect (*c*)	0.21 (0.04)**	0.14 (0.04)**	0.08 (0.03)*
Baseline outcome on mediator	0.06 (0.01)**	0.05 (0.01)**	--
Baseline mediator on mediator	0.09 (0.02)**	0.09 (0.02)**	0.09 (0.05)**
Baseline outcome on outcome	0.04 (0.01)**	0.02 (0.01)*	--
Baseline mediator on outcome	0.07 (0.02)**	0.04 (0.2)*	-0.05 (0.05)
Controls			
Effect of *IV* on mediator (*a*)	0.27 (0.03)**	0.27 (0.03)**	0.31 (0.04)**
Unique effect of mediator (*b*)	0.09 (0.04)*	0.11 (0.05)*	0.04 (0.04)
Indirect effect (*ab*)	0.02 (0.04)*	0.03 (0.01)*	0.01 (0.01)
Direct effect (*c*)	0.19 (0.03)**	0.13 (0.03)**	0.09 (0.03)*
Baseline outcome on mediator	0.08 (0.01)**	0.07 (0.01)**	--
Baseline mediator on mediator	0.13 (0.02)**	0.13 (0.02)**	0.14 (0.02)**
Baseline outcome on outcome	0.06 (0.01)**	0.04 (0.01)**	--
Baseline mediator on outcome	0.09 (0.02)**	0.07 (0.02)**	0.04 (0.04)

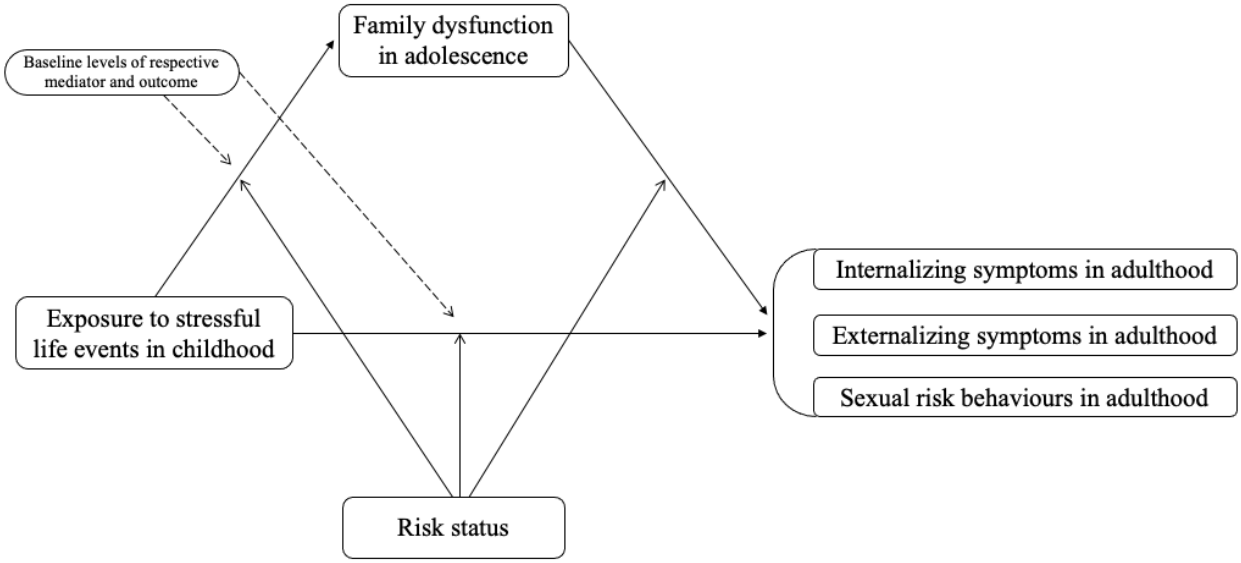
Note. Standardized results are presented. *IV* = independent variable; *$p < .05$, **$p < .001$

Figure 1.



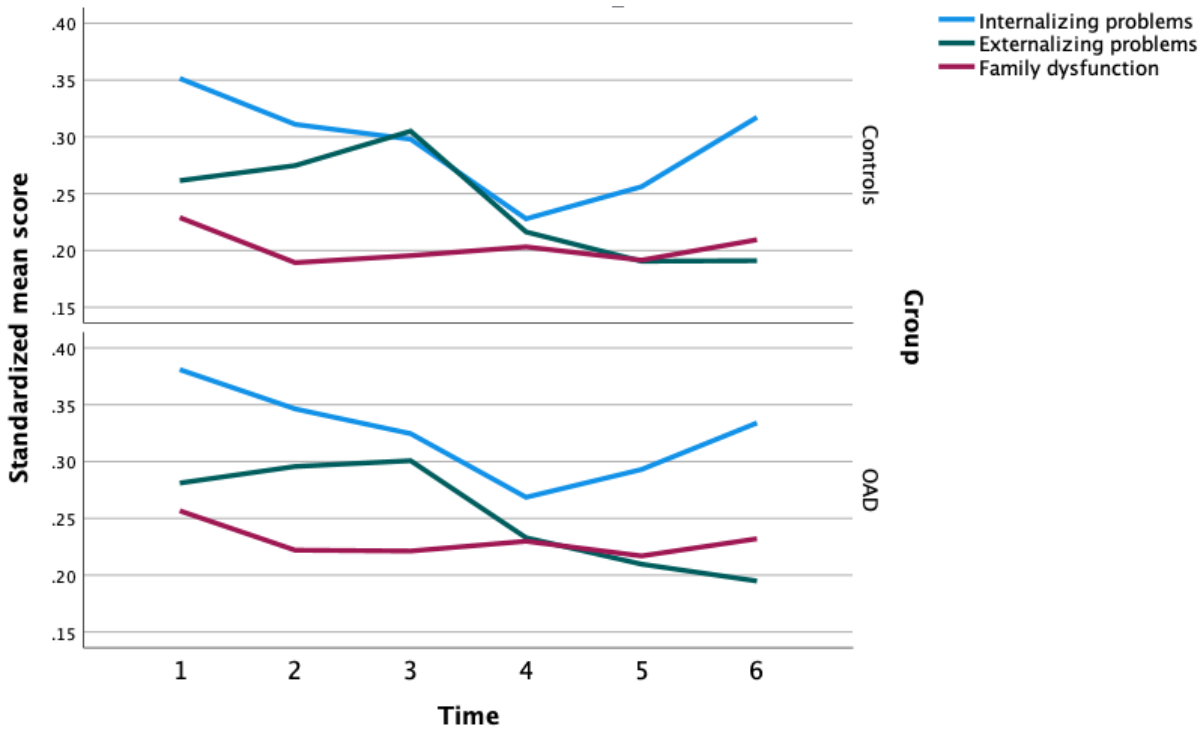
Note. Conceptual diagrams of latent growth curve model presented in Data Analysis section.

Figure 2.



Note. Diagram representing all three separate moderated mediation models

Figure 3.



Note. Diagram representing plotted curves for the three variables of interest across time

Transition Paragraph

Building on prior research exploring associations between environmental risk factors and the development of psychopathology in the OAD, the first study of the thesis used data from a 15 year longitudinal project of youth in the Netherlands to provide evidence of the OAD's sensitivity to a dysfunctional family environment. The results demonstrated that the OAD's emotional and behavioural well-being is associated with the level of family functioning in their home across middle childhood, adolescence, and early adulthood, and that this was not the case for controls. The second study of the thesis aimed to extend these findings while adding new methodology and research questions.

First, we previously assessed stress in the family using a single measure, albeit over time. However, the aggregation of stressors may better predict future mental health struggles than single risk-factors (Mitjans et al., 2019; Shonkoff et al., 2012). We thus set out to create a variable measuring cumulative stress in the family environment, in order to estimate paths between stress in the home and mental health service use in the OAD, as compared to controls. Second, having well established the burden of disease on an individual and familial level, we set out to extend our outcomes of interest from mental health symptoms to service use, which can have implications for health service use in high risk families.

Study 2 assessed cumulative stress in the early environment and investigated its impact on future mental health care use. Our primary aim was to determine whether the OAD would be more sensitive to cumulative family stress, as evidenced by greater subsequent mental health need, and eventual use of more intensive mental health service, as compared to their control counterparts.

Chapter 3: The influence of cumulative environmental risk on mental health care utilization in the offspring of parents with affective disorders

Resendes, T., Oldehinkel, A. J., Ellenbogen, M. A. (2024). The influence of cumulative environmental risk on mental health care utilization in the offspring of parents with affective disorders. [Manuscript submitted for publication]. Department of Psychology, Concordia University.

Abstract

The offspring of parents with affective disorders (OAD) are known to be exposed to more environmental risk factors than offspring of parents with no mental disorders, including ineffective parenting styles and familial dysfunction. The objective of this study was to better understand the relationship between cumulative environmental risk, subsequent mental health need, and mental health help-seeking in adulthood. It was predicted that the OAD would be more sensitive to environmental risk than controls, which in turn would lead to high need and more intensive care in adulthood. As part of the TRacking Adolescents' Individual Lives Survey, 2230 participants (51% female, M_{age}= 11.1 years, SD = 0.6) and their parents were assessed across 6 timepoints, spanning 15 years. Children of parents reporting lifetime occurrence of depressive or manic episodes were categorized as OAD (n = 761). Using principal component analysis, cumulative risk scores were created from measures of socioeconomic status, parenting styles, familial dysfunction, and parenting stress. Mental health and mental health care use in adulthood were measured, respectively, with the Achenbach Self-Report and an in-house questionnaire. From moderated mediation analyses, it was found that the OAD were more likely to seek out more intensive mental health services as adults than controls (B = 0.40, SE = 0.18, p = .025), as a function of cumulative risk and subsequent mental health need. Given that OAD appear to be more sensitive to environmental risk, the OAD could benefit from early interventions to prevent future need of intensive and costly mental health care.

Introduction

The offspring of parents with affective disorders (OAD) are at high risk of developing mental disorders, given the high familial transmission of both depressive and bipolar disorders (Merikangas et al., 2014; Vandeleur et al., 2012). Rates of both mood and anxiety disorders are higher in the OAD as compared to controls (Vandeleur et al., 2012), and as adults, the OAD are at high risk of poor psychosocial outcomes, including poor interpersonal functioning and engagement in risky behaviours (Bella et al., 2011; Duffy et al., 2014; Nijjar et al., 2014; Ostiguy et al., 2009; Shaw et al., 2005; Weissman et al., 2006). Studies have shown that, in addition to genetic risk (Fernandez-Pujals et al., 2015; Kieseppä et al., 2004; McGuffin et al., 2003), familial transmission of affective disorders is strongly influenced by the family environment. The rearing environment of the OAD is characterized as less supportive, that is displaying less warmth and nurturance, than that of families of parents without affective disorders (Cummings et al., 2005; Iacono et al., 2018; Lau et al., 2018). Parents with affective disorders may struggle with emotional sensitivity, whereby they express fewer emotions or display blunted emotional responses, and display a tendency to engage in ineffective parenting practices (Cummings et al., 2005; Iacono et al., 2018; Wilson & Durbin, 2010). Together, these deficits contribute to the family dysfunction which is often characteristic of families of parents with affective disorders (Barron et al., 2014; Romero et al., 2005; Weinstock et al., 2006; Wiegand-Grefe et al., 2019). Indeed, we recently observed a robust association between children's mental health and family dysfunction in the OAD, but not in controls, in a large cohort of families in the Netherlands who were followed from middle childhood to adulthood (Resendes et al., 2024). Similar to other studies of youth at risk for affective disorders (Ostiguy et al., 2012), these findings indicate that

OAD are more sensitive to stress and dysfunction in the family than children of families whose parents have no mental disorder.

Although family functioning remains an important risk factor for OAD, there is growing evidence that exposure to cumulative environmental risk factors might be a better predictor of poor mental health outcomes than exposure to single specific risk factors (Mitjans et al., 2019). It is speculated that repeated exposure to known risk factors may accumulate to alter certain stress-sensitive systems early in development, eventually sensitizing youth to later exposure to stressful life events (Blair et al., 2011; Dich et al., 2015). Studies have found linear and non-linear associations between the number of risks present in early childhood and future maladaptive outcomes. Negative outcomes in youth, in terms of mental health (Appleyard et al., 2005), brain functioning (Burani et al., 2022), and stress physiology (Evans & Cassells, 2014; Ouellet-Morin et al., 2021), are better predicted by cumulative exposure to adversity in childhood than single risk factors (Shonkoff et al., 2012). Thus, a focus on cumulative exposure to different environmental adversities might be most relevant to understanding health outcomes in the OAD.

Much research on the OAD has focused on mental health outcomes and identifying risk factors and mechanisms of transmission in these families (Gotlib et al., 2020). However, less effort has been dedicated to analyzing how these factors may impact mental health service use. It is known that individuals living with mental illness are more likely to use inpatient, emergency, and primary physical and mental health care services, as compared to individuals without mental health problems (Ronaldson et al., 2020). The burden of mental disorders are well represented by the high costs they entail; the annual cost of health care services from this relatively small proportion of the population can be upwards of twice the expenditure of individuals without mental health disorders (de Oliveira et al., 2016; Larrañaga et al., 2023). Certain risk factors have

even been linked to frequency and length of service use, or overall cost associated to care, often dating back to childhood (Ssegonja et al., 2019; van Duin et al., 2019). Children of parents with mental disorders have been documented to use significantly more health and social services, as well as school-based resources, than children of healthy parents (Waldmann et al., 2021). More specifically, children of parents living with major depressive disorder report higher service use rates and expenditures than children of healthy parents (Olfson et al., 2003; Stalujanis et al., 2019). Experiencing high levels of conflict, parental separation, and emotional neglect are the strongest predictors of mental health service use when compared to other adverse early experiences (van Duin et al., 2019). Family dysfunction, parents' internalizing problems, and high levels of stress are also key predictors of which children go on to use services (Ezpeleta et al., 2002; Jansen et al., 2013). Family dysfunction, characterized as ineffectual parenting styles, poor parent-child relationships, and high levels of disorganization in the home, is a known risk-factor for children's mental health service use (Oltean et al., 2020). Despite the fact that families of parents with an affective disorder are characterized by chaotic familial environments, low cohesion, high levels of conflict and stress, and poor parent-child relationships (Beardslee et al., 2013; Iacono et al., 2018; Moulin et al., 2022; Stapp et al., 2020), there is a paucity of research exploring service use type and rates for the OAD.

The primary aim of the current study is to analyze both the indirect, via mental health need (i.e., internalizing and externalizing problems), and direct relationship between cumulative environmental risk and severity of mental health service use, and whether these differ between the OAD and controls. For cumulative risk, the present study will use socioeconomic status, number of parents in participants' family (representing parental separation), family dysfunction, parenting stress, and parenting styles (i.e., low parental warmth and high parental rejection). The

cumulative risk score builds upon prior research conducted using data from the Tracking Adolescents' Individual Lives Survey (TRAILS) project. Across studies, the risk factors listed above were shown to uniquely predict trends in mental health care use (Amone-P'Olak et al., 2010; Jansen et al., 2013; Raven et al., 2018). The first aim of the study is to compare groups (OAD vs. controls) on cumulative risk scores, mental health need, and intensiveness of mental health service use. It is hypothesized that the OAD will have greater cumulative risk scores, which represents their exposure to various environmental risk factors in early life. In addition, it is hypothesized that the OAD will report more mental health need than controls in adolescence, and more intensive use of mental health care services as adults. Second, we aim to assess the extent to which mental health care use in adolescence and adulthood can be explained by early exposure to cumulative risk, and subsequent mental health need. Lastly, we hypothesize that the OAD, relative to controls, would show heightened sensitivity to cumulative risk and its effect on mental health need and mental health care use. We hypothesize that risk-status (i.e., OAD vs. controls) will impact the strength of the indirect relationship between cumulative risk and later mental health care service use, via mental health need. This would support a stress sensitivity hypothesis, that the OAD may be more likely than controls to report worse mental health functioning following cumulative environmental adversity, and, as a result of worsening mental health problems, would utilize more intensive mental health services than controls.

Methods

Participants

Study participants are from the TRAILS project, an ongoing longitudinal study of social, psychological, and physical development of youth growing up in the Netherlands. The data for the current study spans 15 years, and is sourced from 6 time points, occurring once every 2-3

years. Data collection started in 2000/2001 and consisted of 2230 participants (51% female, M_{age}= 11.1 years, SD = 0.6). At the second time point, there were 2149 participants (96% retention rate, 51% female, M_{age}= 13.6, SD = 0 .5). At time point 3, there were 1816 participants (81% retention rate, 52% female, M_{age}= 16.3, SD = 0.7). At time point 4, there were 1881 participants (84% retention rate, 52% female, M_{age}= 19.1, SD = 0.6). At time point 5, there were 1778 participants (80% retention rate, 53% female, M_{age}= 22.3, SD = 0.6). At time point 6, 1618 participants remained (73% retention rate, 54.5% female, M_{age} = 25.6, *SD* = 0.6; for more details see Oldehinkel et al., 2015). The population cohort includes participants born between October 1989 and September 1991, living in the north of the Netherlands at the time of the baseline assessment. School attendance was required for study eligibility, as was Dutch fluency, as data collection occurred in schools and in Dutch. The majority of participants were from middle or high socio-economic classes, as measured by maternal education and parental work status. About one third (32.6%) of the parents did not complete high school at a level that would give access to higher vocational or university education. Exclusion criteria included severe intellectual disabilities, as well as serious physical illness or handicap, in either offspring or parent. The study was approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO) and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from both children and parents.

Measures

Affective disorders in parents

The presence of an affective disorder in parents was assessed at time point 1, using the Family History Interview. The interview assesses five domains of psychopathology: depression, anxiety, substance use, antisocial behaviours, and psychosis (including mania). Parents were

presented with vignettes that described the DSM-IV criteria of each domain (available upon request), with specific questions targeting lifetime occurrence, professional treatment, and medication use. Extensively trained interviewers then coded responses provided by parents on a 4-point Likert scale, consisting of "*0 = no*", "*1 = probably not*", "*2 = probably yes*", and "*3 = yes*" (for a more detailed description, see Ormel et al., 2005). Responses higher than or equal to 2 on questions pertaining to lifetime depressive and manic episodes were used to categorically represent the data as having or not having an affective disorder in a parent (*0=no/probably not, 1=probably yes/yes*). Adolescents were identified as offspring of parents with affective disorders (i.e., OAD; n = 761), or as offspring of parents with no affective disorders (i.e., controls; n = 1468). A high probability of a lifetime affective disorder was reported for 601 mothers and 319 fathers.

Internalizing and externalizing problems

The Youth Self-Report (YSR) questionnaire was designed for 11- to 18-year-olds. Its 112 items assess various strengths and difficulties in youths' functioning (Achenbach, 2001). The Adult Self-Report (ASR) was designed for individuals aged 18-59 years, and includes 126 items assessing psychopathology and aspects of adaptive functioning (Rescorla & Achenbach, 2004). Composite scores are derived from subscales on both the YSR and ASR representing internalizing and externalizing symptoms. The YSR's and ASR's psychometric properties are moderate-to-strong (Achenbach, 2001; Rescorla & Achenbach, 2004). Items are rated on a 3-point scale (*0=absent/not true, 1=occurs sometimes/somewhat true, 2=occurs often/very true*). Higher scores represent more dysfunction. Scores representing mental health need in adolescence were drawn from ASR data collected at time point 4, while scores used in the post-hoc analyses, representing mental health need in early adolescence were drawn from the YSR at time point 3.

Cumulative risk scores

A cumulative risk score was compiled using data gathered at time point 1 from various measures representing known environmental risk factors for offspring maladjustment.

Sociodemographic information. A developmental history interview was created by the TRAILS research team and administered at time 1. Data used from this in-house measure pertained to the number of parents in the participants' household, as well as the family's socioeconomic status. Participants' socioeconomic status (SES) was obtained by analyzing both parental educational attainment, work status, and income. Three SES categories were constructed based the data's distribution: the lowest 25%, the middle 50%, and the highest 25%.

Family dysfunction. The Family Assessment Device (FAD; Epstein et al., 1993) assesses family dysfunction in the areas of communication, roles, behaviour control, affective responsiveness, affective involvement, and problem-solving. It is theoretically anchored in the McMaster Model of Family Functioning. The current study used the 12-item General Functioning short-form of the FAD (Epstein et al., 1983). The 12 items assess functioning in each of the areas mentioned above at time point 1. Each item is scored on a 4-point scale (strongly agree to strongly disagree), with higher scores indicating higher levels of dysfunction. The 12-item short-form presents with adequate reliability and validity (Byles et al., 1988).

Parenting styles. The Egna Minnen Beträffande Uppfostran – Child Version (EMBU-C; Markus et al., 2003) is a measure of perceived parenting styles which assesses participants' memories of their upbringing and relationship with their parents. Children filled out the EMBU-C based on their perceptions of each parents' rearing behaviours on a 4-point scale (never to most of the time) at time point 1. Ratings were then combined across parents (Bouma et al., 2007). In this study, two scales were used: The Rejection Scale and the Emotional Warmth Scale.

Internal consistency for the EMBU-C scales range from .66 to .81, while reliability coefficients range from .79 to .84 (Muris et al., 2003).

Parenting stress. The Dutch version of the Parenting Stress Index (PSI; Abidin, 1983; De Brock et al., 1992) is a 25-item questionnaire aimed at evaluating various domains of stress related to parenting. The questions assess both parent and child characteristics which can exacerbate stress on a 6-point scale (completely disagree to completely agree). For this study, we used the score summing parent domains at time point 1, which include perceived competence in one's role as a parent, attachment style, presence of depressive symptoms, and parental health. The Dutch PSI has shown excellent internal consistency (a = .92-.95).

Mental health service use

An in-house measure was created to assess care utilization. At time points 5 and 6, participants were asked questions regarding their use of mental health services in the last two years. Data was gathered surrounding use of outpatient services, part-time treatments (i.e., day hospitals), crisis centers, and other psychiatric and psychological support (i.e., mental health clinics, private psychologists/psychiatrists, online mental health support). In order to capture the nature of services sought, types of services were assigned ordinal values representing severity (0 = none, 1 = used private psychiatric or psychological support, 2 = used a crisis service, 3 = attended outpatient services, 4 = attended part-time treatment, 5 = admitted to inpatient services). Participants received a score representing only the most intensive type of service sought across time points 5 and 6. Scores on intensiveness were then treated as continuous, where higher scores represented more intensive service use. For post-hoc analyses, the same process was applied to data gathered from time points 3 and 4, at which points parents served as informants for questions surrounding types of services used by their children.

Data analysis

Analyses were run using SPSS version 28.0 (IBM, 2021). A principal component analysis (PCA) was employed in order to create a risk-score. PCAs can be used to summarize multiple variables into common components which represent shared underlying variance between variables (Bro & Smilde, 2014). For this study, a PCA was used to reduce variables representing known environmental risk factors into a single component. A first principal component analysis was initially run using eigenvalue-based extraction of greater than 1 to explore how the data freely loaded onto unspecified components. Inspection of the Kaiser-Meyer-Olkin measure of sampling adequacy (value of 0.58) and Bartlett's Test of Sphericity ($X^2 = 889.09$, $p<.001$) revealed appropriate data use (Dziuban & Shirkey, 1974). Although 3 components were freely extracted, inspection of the scree plot indicated that the first component had the largest eigenvalue (1.77) and accounted for nearly double the variance of the other two components (29.41%). A second PCA was then run extracting one fixed factor, and residual regression coefficients were saved to represent participants' unique cumulative risk score. Group differences on the cumulative risk score, as well as other key variables, were analyzed using a one-way ANOVA. Bivariate correlations were run to identify associations between variables.

Moderated mediations were run on the Process Macro for SPSS version 4 (Hayes, 2022). Model 59 was used for both moderated mediations, to evaluate the presence of a moderation effect of the indirect paths. The analyses aimed to assess whether mental health need mediated the relationship between cumulative risk and mental health service use, and whether OAD, relative to controls, show worse mental health effects in response to cumulative risk (path a) and more service use in response to mental health need (path b; see Figure 1). Given statistical evidence that data were not missing completely at random (Little MCAR test, $p < .001$; Little,

1998), no means of imputation were used, and cases with missing data were excluded. The strength of indirect effects are discussed using 95% bias corrected bootstrapped confidence intervals (MacKinnon et al., 2004; Miočević et al., 2018). The bootstrap sample was set to 5000 iterations.

Results

Cumulative risk scores

From the principal component analysis, factor loadings of each variable onto the risk score component can be seen in Table 1. As expected, parental warmth, socioeconomic status, and number of parents in the family each loaded negatively onto the component, representing an inverse association to offspring's cumulative risk. The means of the cumulative risk score are presented in Table 2.

Moderated mediation analyses of intensiveness of mental health service use in adulthood

A mediation model was established examining the association between cumulative risk in childhood and mental health need in adolescence (path a), and subsequent mental health care use (path b). Risk-status was entered as a potential moderator of the indirect effect (the combination of paths a and b). Scores used in the moderated mediation analyses are presented in Table 2. Mental health need in late adolescence combined both internalizing and externalizing problems across T4. Group mean comparisons were run to compare key variables between the OAD and controls using a one-way ANOVA. All were statistically significant ($p < .001$; see Table 2). Bivariate correlations between all variables used across both mediation analyses are presented in Table 3. All were statistically significant ($p < .001$).

Higher cumulative risk scores predicted more mental health problems (B = 0.08, SE = 0.02, $p < .001$), which in turn, predicted more intensive mental health service use (B = 0.79, SE =

0.11, $p < .001$). Direct and indirect effects between groups are presented in Table 4. The bias-corrected bootstrap 95% confidence interval for the indirect effect, based on 5000 bootstrap samples, was entirely above zero for both groups (0.08 to 0.21 for OAD; 0.03 to 0.10 for controls), indicating significant mediation across groups. Mental health need fully mediated the relationship between cumulative risk and intensiveness of mental health service use across both groups. In addition, the index of moderated mediation (Index = 0.08, SE = 0.04, 95%CI = [0.01, 0.15]) suggested that the indirect effect varied based on risk-status; the indirect effect for the OAD (B = 0.14, SE = 0.03, 95%CI = [0.08, 0.20]) was more than double that of controls (B = 0.06, SE = 0.02, 95%CI = [0.03, 0.10]). A visual representation of the moderated mediation results is depicted in Figure 1. The OAD were thus more likely to receive more intensive mental health services than controls as a function of early cumulative risk and subsequent mental health problems.

Moderated mediation analyses of intensiveness of mental health service use in adolescence

Post-hoc analyses were then run to identify whether this pattern of results could be replicated using mental health care use in adolescence. Mental health need in early adolescence combined internalizing and externalizing problems across T3. The intensiveness of mental health service use in adolescence was determined using parent-reported data from T4. Mean comparisons revealed significant differences between groups on both the mediator variable ($p < .05$) and the outcome ($p < .001$).

Results supported a partial replication in adolescence. Across groups, higher cumulative risk scores predicted more mental health problems (B = 0.11, SE = 0.01, $p < .001$), which in turn, predicted more intensive mental health service use (B = 0.37, SE = 0.12, $p < .001$). Direct and indirect effects between groups are presented in Table 5. Once again, the bias-corrected bootstrap

95% confidence interval for the indirect effect, based on 5000 bootstrap samples, was entirely above zero for both groups (0.01 to 0.10 for OAD; 0.03 to 0.06 for controls), indicating significant mediation across groups. Across groups, mental health need partially mediated the relationship between cumulative risk and severity of mental health service use, given the significant direct effect. However, the index of moderated mediation (Index = 0.01, BootSE = 0.02, 95%BootCI = [-0.03,0.06]) did not find evidence of moderated mediation. That is, the indirect effect was not significantly stronger in the OAD than controls.

Discussion

The results of the present study are in line with our hypotheses. First, the OAD demonstrated significantly higher levels of cumulative risk in their rearing environment than controls. In addition, the OAD reported higher levels of mental health problems across adolescence, and also reported using more intensive mental health care than controls across adolescence and adulthood. As predicted, the data support a model where more intense mental health service use in adolescence and adulthood was elicited by exposure to cumulative risk factors in childhood and subsequent mental health symptoms. However, no moderation effect was found in predicting intensiveness of mental health care in adolescence. Overall, results supported our second hypothesis, yet failed to support a replication of findings in adolescence.

The results of the study corroborate previous research indicating heightened risk for mental health difficulties among OAD compared to controls. The OAD may in fact exhibit high stress sensitivity and react more strongly to environmental risk factors, particularly within the family system, than children of healthy parents (Nijjar et al., 2016; Ostiguy et al., 2011, 2012). Recent findings from the TRAILS study provide evidence of the OAD's sensitivity to stress in their rearing environments. Research suggests a robust association between family dysfunction

and offspring mental health, persisting from middle childhood well into adulthood, for the OAD and not for controls (Resendes et al., 2024). Although the underlying cause of stress sensitivity in high-risk youth is not known, studies thus far propose a combination of genetic risk, pre- and perinatal events, and exposure to early adversity including post-partum depression (Flouri et al., 2020; LeMoult et al., 2020; Vrshek-Schallhorn et al., 2014). The findings thus provide further evidence that the OAD are not only exposed to a higher incidence of cumulative risk factors than offspring of parents without affective disorders, but are also more sensitive to environmental risk as evidenced by a higher number of subsequent reported internalizing and externalizing problems and use of more intensive mental health services.

The present findings support the view that cumulative exposure to multiple adversities might be more useful in predicting negative outcomes, particularly in the OAD, rather than focusing on single risk factors. Studies on cumulative risk have been important in understanding the development of behaviour problems such as aggression (Hagenbeek et al., 2023; Mitjans et al., 2019). With regards to the development of affective disorders, a recent study from the Social and Psychiatric Epidemiology Catchment Area of the Southwest of Montreal (ZEPSOM) explored the relationship between exposure to cumulative stress and depression. Evidence suggested a combined effect of childhood maltreatment, poor parent-child relationships, and stressful life events, in explaining the development of depression in the community (Su et al., 2022). These findings were in line with results from a longitudinal study, which demonstrated that cumulative exposure to low socio-economic status, family size, maternal depression, parental criminality and age of mother at offspring birth positively predicted depression in a community sample from Ontario (Atkinson et al., 2015). However, less efforts have been dedicated to understanding the specific role of cumulative risk within the OAD specifically. The

present study thus supports the importance of accounting for early exposure to adverse environments and events. Future studies should aim to investigate whether certain risk factors hold more weight when aggregating cumulative risk, and whether we could ascertain during which developmental periods the OAD may be most susceptible to the impact of cumulative adversity.

Lastly, our results meaningfully contribute towards research efforts aimed at understanding patterns of, and pathways to, mental health care service use. Whereas previous studies identified specific unique risk factors which predicted the incidence of mental health service use (Jansen et al., 2013; Raven et al., 2018), our findings highlight that as adults, the relationship between intensiveness of mental health care and environmental risk factors is fully explained by mental health problems emerging in adolescence. This is in line with studies highlighting rates of health care use in adults with mental health problems (Ronaldson et al., 2020). Importantly, individuals who reported the emergence of clinical or sub-clinical affective disorders in adolescence, and even more so in individuals suffering from depressive episodes in early adulthood, incurred high health care-related costs into mid-adulthood (Ssegonja et al., 2019). Importantly, the high costs were linked to the care of psychiatric conditions and a range of accompanying dysfunction.

In adolescence, however, the pathways to intensive mental health care use may be less intuitive, as they were only partially explained by mental health need. This may be indicative of other important influences on adolescents' mental health care use. In one study, a large portion of adolescents requiring mental health care did not receive such services, due to a lack of parental awareness of their struggles and of adaptive parental support (Jansen et al., 2013). Indeed, Raven and colleagues (2018) demonstrated that between the ages of 13 and 16 years, parental reports

are the driving factor behind initial specialist care contacts. Therefore, focusing efforts on increasing awareness of mental health difficulties and appropriate interventions for families of young teenagers, regardless of risk-status, may be pertinent. By understanding the pathways through which these factors contribute to mental health outcomes and service utilization, clinicians and policymakers can better allocate resources and implement targeted interventions to support the mental well-being of vulnerable populations.

Strengths and limitations

There are a number of study limitations to consider. The study sample consisted of predominantly ethnically Dutch, caucasian, middle-class adolescents, with two parents. The results may therefore not generalize to other, more diverse, populations. Additionally, evidence-based structured diagnostic interviews were not used to identify affective disorders in parents; diagnoses were probable and based on parents' endorsing of symptoms presented to them with vignette-style descriptions. As pertaining to the cumulative risk score, variables included are gathered from data across one timepoint, in middle childhood. We are therefore unable to ascertain the role of repeated adversity or length of exposure, nor can we account for adversity occurring in early childhood or the possibility of chronic adversity, lasting into adolescence and adulthood. In addition, the cumulative risk score created in this study does not include well-established risk-factors, such as abuse, maltreatment, or violence in the home. Lastly, we measured mental health care use through self-report from participants and parents, instead of government records of documented service use. However, this allowed for the assessment of mental health care use outside of government establishments such as private care or crisis centers.

Despite these limitations, there are notable strengths to the present study. Longitudinal data collection with repeated measures allowed us to study individuals across a 15-year span. In addition, the study highlights the unique vulnerability of the OAD to the effects of cumulative environmental risk, as evidenced by their increased likelihood of seeking more intensive forms of mental health services. This highlights the importance of tailored family-based interventions and support systems targeting this high-risk population (Compas et al., 2015; Miklowitz et al., 2006). Furthermore, we extend this understanding by demonstrating the mediating role of mental health need in the relationship between cumulative environmental risk and intensiveness of mental health service use in adulthood. This underscores the importance of early intervention strategies aimed at addressing mental health problems among at-risk youth to mitigate the escalation of service needs into high health care costs in adulthood. In future research, longitudinal studies of health service use could provide a means to directly assess later cost-benefits of early interventions in high risk youth, by comparing trends in service use in those having received or not received preventative care. Additionally, qualitative research exploring the subjective experiences and perceptions of the OAD and their families regarding mental health services could further inform the development of culturally sensitive and family-centered interventions.

Conclusion

Our findings highlight the OAD's sensitivity to cumulative environmental risk, as evidenced by their heightened likelihood to seek out more intensive mental health care than controls as a function of mental health need. Our study provides evidence of the critical need for comprehensive mental health services that address the complex interplay between genetic predispositions, familial dysfunction, and environmental stressors. By identifying and addressing

these factors early in life, we can promote resilience and well-being among this vulnerable population, ultimately reducing the burden of mental illness on individuals, families, and society as a whole.

Table 1.

Factor loadings of variables included in cumulative risk score

Variable	Factor Loading
Family Functioning	.687
Parenting Stress	.646
Parenting Style: Warmth	-.557
Parenting Style: Rejection	.505
Socioeconomic Status	-.414
Number of Parents in the Family	-.387

Table 2.

Means and standard deviations between groups on variables in the mediation analyses

	OAD	Controls		
	Mean (*SD*)	Mean (*SD*)	F	*p*
Cumulative risk score in childhood	0.25 (1.07)	-0.17 (0.91)	85.965	<.001
Mental health need in early adolescence	0.65 (0.40)	0.61 (0.37)	5.212	.023
Mental health need in late adolescence	0.53 (0.43)	0.44 (0.39)	14.256	<.001
Intensiveness of mental health care in adolescence	0.75 (1.58)	0.42 (1.15)	25.194	<.001
Intensiveness of mental health care in adulthood	0.87 (1.34)	0.61 (1.17)	12.264	<.001

Note. OAD = offspring of parents with affective disorders

Table 3.

Bivariate correlations between variables used in mediation analyses

	1.	2.	3.	4.	5.
1. Cumulative risk score in childhood	-				
2. Mental health need in early adolescence	.220**	-			
3. Mental health need in late adolescence	.216**	.585**	-		
4. Intensiveness of mental health care in late adolescence	.150**	.186**	.224**	-	
5. Intensiveness of mental health care in adulthood	.106**	.240**	.324**	.226**	-

**. Correlation is significant at the .001 level.

Table 4.

Unstandardized model results of mental health need mediating the relationship between cumulative environmental risk and severity of mental health service use in adulthood

	Indirect effect (*ab*)		Direct effect (*c'*)	
Group	B (SE)	95%CI	B (SE)	95%CI
OAD	0.13 (0.03)	[0.08, 0.21]	0.05 (0.06)	[-0.07, 0.17]
Controls	0.06 (0.02)	[0.03, 0.10]	0.01 (0.05)	[-0.08, 0.11]

Note. Outcome variable = intensiveness of mental health service use; 95% bias-corrected bootstrap confidence intervals are presented in square brackets for indirect and direct effects.

Table 5.

Unstandardized model results of mental health need mediating the relationship between cumulative environmental risk and severity of mental health service use in adolescence

	Indirect effect (*ab*)		Direct effect (*c'*)	
Group	B (SE)	95%CI	B (SE)	95%CI
OAD	0.05 (0.02)	[0.01, 0.10]	0.19 (0.06)	[0.07, 0.31]
Controls	0.04 (0.01)	[0.03, 0.06]	0.13 (0.05)	[0.03, 0.22]

Note. Outcome variable = intensiveness of mental health service use; 95% bias-corrected bootstrap confidence intervals are presented in square brackets for indirect and direct effects.

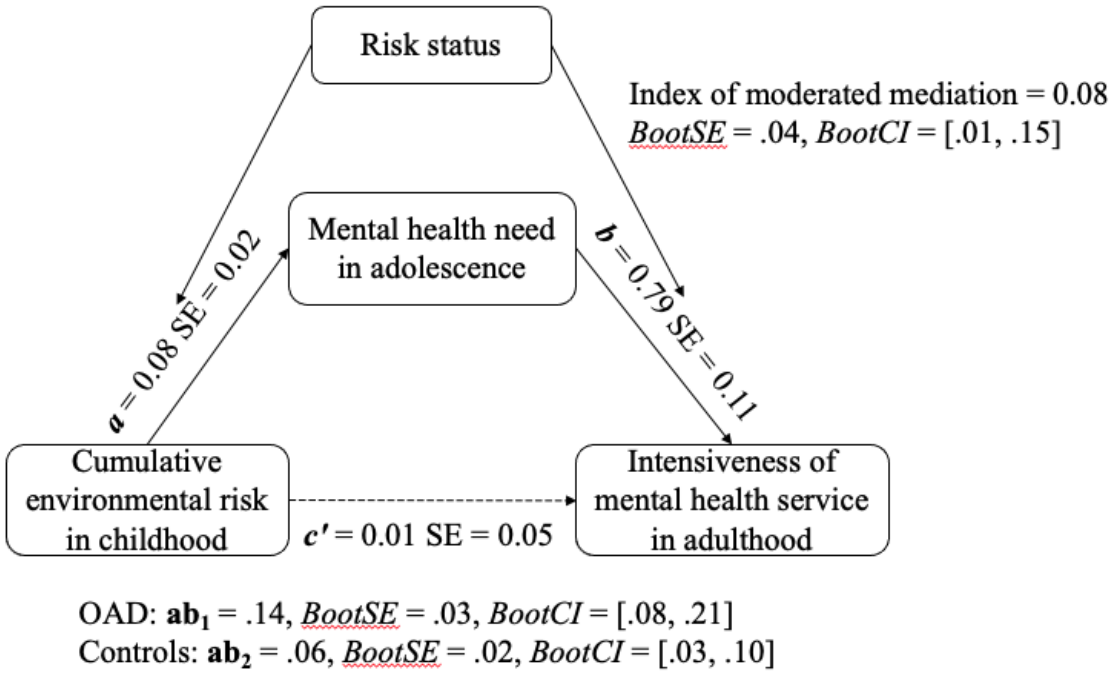


Figure 1. *Diagram of moderated mediation model for cumulative risk and intensiveness of mental health service in adulthood with risk status as moderator.*

a, independent-mediator path; b, mediator-dependent path; c', direct path;

ab, conditional indirect effect of cumulative risk in childhood on intensiveness of mental health service in adulthood through mental health need in adolescence;

index of moderated mediation = difference between conditional indirect effects;

OAD = offspring of parents with affective disorders

Transition Paragraph

Building on prior research examining mental health outcomes in the TRAILS cohort, the second study of the thesis aimed to investigate differences in mental health service use in adulthood between the OAD and controls, as explained by early adversity in the family environment and subsequent emotional and behavioural problems. Results from study 2 demonstrated that the OAD not only experienced higher levels of cumulative risk in their early environment than controls but were more likely to seek out more intensive mental health services in adulthood as a function of their worsening mental health difficulties. Together, study 1 and study 2 highlight behavioural evidence of the OAD's sensitivity to stress in the rearing environment, and their long-term individual, familial, and societal burdens.

While the studies 1 and 2 of the thesis identified robust links between the family environment and youth outcomes, study 3 focuses on improving family functioning via a preventative intervention. To accomplish this aim, study 3 focuses on a small sample of OBD who underwent the RUSH program (Serravalle et al, 2021). The RUSH program is structured intervention that aims to improve the quality of the family environment to prevent the development of emotional or behavioural problems in children who have not yet developed an affective disorder. It was developed for families where one or more parents has bipolar disorder. The third study aimed to determine whether the RUSH program improved parenting stress, and whether improvements in parenting stress mediated the relationship between participation in the RUSH intervention program and offspring internalizing and externalizing problems up to 6-months post-intervention.

Chapter 4: Reduced parenting stress following a prevention program decreases internalizing and externalizing symptoms in the offspring of parents with bipolar disorder

Resendes, T., Serravalle, L., Iacono, V., & Ellenbogen, M. A. (2023). Reduced parenting stress following a prevention program decreases internalizing and externalizing symptoms in the offspring of parents with bipolar disorder. *Int J Bipolar Disord, 11*: 10. doi: 10.1186/s40345-022-00284-2

Abstract

Offspring of parents with bipolar disorder (OBD) are at risk for developing mental disorders, and the literature suggests that parenting stress may represent an important risk factor linking parental psychopathology to offspring psychopathology. We aimed to investigate whether improvements in parenting stress mediated the relationship between participation in a prevention program and offspring internalizing and externalizing symptoms at follow-up. Families having a parent with BD ($N = 25$) underwent a 12-week prevention program. Assessments were conducted at pre-intervention, post-intervention, and at 3- and 6-month follow-ups. Families of parents with no affective disorders (i.e., control families) served as a comparison sample ($N = 28$). The *Reducing Unwanted Stress in the Home* (RUSH) program aimed to teach communication, problem-solving, and organization skills to improve the rearing environment. Measures included the Parenting Stress Index - 4th Edition, the Behaviour Assessment Scales for Children – 2nd Edition, and the UCLA Life Stress Interview. Families having a parent with BD reported more parenting stress at pre-intervention, and more change across time, than control families. Improvements in parenting stress mediated the relationship between participation in the intervention and reduced offspring internalizing and externalizing symptoms. While families having a parent with BD reported more chronic interpersonal stress at pre-intervention, no linear effects were found. The findings demonstrate that a preventative intervention targeting parenting stress in families may serve to prevent the development of mental disorders in at-risk children.

Introduction

The offspring of parents living with bipolar disorder (OBD) are at heightened risk for developing mental disorders (Duffy et al., 2014b; Mesman et al., 2013; Nijjar et al., 2014). Despite evidence of bipolar disorder's (BD) heritability (McGuffin et al., 2003), environmental factors may have a robust influence on the OBD's developmental outcomes (Ferreira et al., 2013; Stapp et al., 2020). Previous research indicates BD in parents might influence their offspring's functioning through parenting practices and by creating a stressful family environment. Specifically, families having a parent with BD, relative to families with parents having no mental disorders, are known to have ineffective parenting practices, poor family cohesion, disorganization, poor marital adjustment, and dysfunctional parent-child interactions (Ellenbogen & Hodgins, 2004; Ferreira et al., 2013; Iacono et al., 2018; Ostiguy et al., 2012; Serravalle et al., 2021). Indeed, the OBD, relative to control offspring, report more chronic interpersonal stress, which appears to be the familial instability created by parents with BD (Ostiguy et al., 2009). For these reasons, there has been increased attention to family-environmental factors in the study of the OBD.

Researchers have thus suggested that families should be the target of interventions for the OBD (Miklowitz et al., 2006). Studies have shown that family-focused therapy (FFT) is helpful for OBD between 9 and 17 years of age presenting with symptoms of BD, but not the full syndrome. That is, FFT was found to improve the course of BD in adulthood and even delay the onset of the disorder altogether (Miklowitz et al., 2006, 2011, 2014). More recently, a multisite randomized controlled trial (RCT) demonstrated that OBD who took part in FFT had longer intervals between recovery and onset of depressive episodes as compared to those who underwent 6 sessions of enhanced usual care (Miklowitz et al., 2020). These findings highlight

the impact of FFT on improving the course of mood disorders post-treatment. However, to our knowledge, no psychosocial prevention efforts have targeted the OBD in middle childhood, prior to the manifestation of clinically significant symptoms of an affective disorder.

To address this gap in the literature, we have developed a family-based preventative intervention program titled *Reducing Unwanted Stress in the Home* (RUSH) to target families having unaffected 6-11 year-old OBD (i.e., who have not yet developed symptoms of an affective disorder). The RUSH program targets the stressful and chaotic family environment of the OBD, with a particular focus on improving organization, consistency, coping, and parenting practices, and aims to prevent the early development of internalizing and externalizing symptoms in OBD. The larger RUSH project was meant to be a proof-of-concept study in comparing OBD to offspring of parents with no affective disorders (i.e., control offspring). The RUSH intervention itself was not associated to direct reductions in symptoms in the OBD (Serravalle et al., in preparation). However, it has been suggested that the success of early interventions is dependent on actual changes in children's environment (Sameroff & Fiese, 2000). For example, positive changes in parent-child interactions in the OBD following the RUSH program were associated with a greater decline in internalizing problems relative to families where no improvement in parent-child interactions was observed (Serravalle et al., 2021). Thus, the current study explores whether RUSH-elicited changes in parenting stress, defined as stress stemming from one's role as a parent, might lead to improved outcomes in the OBD.

Parenting stress is a unique type of stress, as evidenced by its adverse effects on parent-child interactions and on offspring emotional and behavioural functioning (Holly et al., 2019; Louie et al., 2017). In fact, some studies have shown a direct link between parenting stress and offspring behaviour problems (Neece et al., 2012; Verkleij et al., 2015). Some suggest that

parenting stress may increase familial conflict and neglectful parenting practices, which may explain its detrimental effect on at-risk youths (Gerdes et al., 2007; Repetti et al., 2002). More specifically, parenting stress may mediate the relationship between affective disorders in parents and offspring development (Fredriksen et al., 2019). Given that parents with BD are known to experience acute levels of parenting stress (Jones et al., 2017), it may be a viable intervention target for families having a parent with BD.

Our first aim was to determine whether families having a parent with BD would report immediate (i.e., pre-post intervention) improvements in parenting stress and chronic interpersonal stress. Second, we investigated whether these reported improvements would be sustained over time (i.e., at three and six-month follow-up). Third, we aimed to assess whether risk-status (i.e., OBD vs. control offspring) accounted for any variability in levels of stress prior to the start of the intervention, or rates of change in both types of stress across time. Last, we investigated whether improvements across time in parenting stress or chronic interpersonal stress reported by parents living with BD mediated the association between participating in the RUSH program and offspring's internalizing and externalizing symptoms across follow-up. In this proof-of-concept study, OBD were compared to control offspring – who completed all assessments but did not participate in the RUSH intervention. This allowed us to compare OBD with control offspring at baseline, and account for effects attributable to the passage of time or participating in a research project.

We hypothesized that families having a parent with BD would report significant post-intervention and long-term changes in parenting stress. We also hypothesized that there would be significant differences in the level of parenting stress and chronic interpersonal stress reported at baseline (i.e., intercepts) and the rates of change (i.e., slopes) between families having a parent

with BD and control families. Relative to control families, families having a parent with BD were expected to report higher levels of both parenting and chronic interpersonal stress prior to the start of the intervention and follow significantly steeper trajectories of change over time. Lastly, we hypothesized that changes in parenting stress across all timepoints would mediate the relationship between participating in the RUSH program and internalizing and externalizing symptoms in OBD at follow-up.

Methods

Participants

Families were recruited through internet and newspaper services, local clinics, and patient support groups in Montréal, Québec. Families were mostly of white, middle-class, intact, and French-Canadian. Inclusion criteria for all families consisted of having at least one child between the ages of 6 and 11 years, and fluency in either English or French. General demographic information presented by risk status can be found in Table 1. Control families were excluded if either parent presented with a current axis-I disorder or reported a history of affective disorders. Inclusion criteria for families having a parent with BD consisted of have one parent with a BD1 or BD2 diagnosis. Psychopathology in parents was assessed with the Structured Clinical Diagnostic Interview for DSM-IV-R (SCID-I; 24). The sample consisted of 25 families with a parent having BD (72% mothers) and 28 families with parents having no mental disorders (90% mothers).

Within families having a parent with BD, most affected parents presented with BD-I (90%), and all reported a history of depression. At the start of the study, most parents with BD were asymptomatic, while two were in a current manic episode. While the latter two individuals were included in the study on the basis of their diagnosis, it was their partners who completed the

RUSH program and all accompanying assessments. For the other 23 families, the affected parents attended the program and completed all assessments. All parents with BD were receiving pharmacological treatment at the time of the study, which included various combinations of antidepressant (bupropion, citalopram, escitalopram, sertraline, venlafaxine; n = 6), anticonvulsant (divalproex, lamotrigine, topiramate, valproate, n = 12), antipsychotic (chlorpromazine, lurasidone, olanzapine, quetiapine, ziprasidone; n = 12) and mood stabilizing medication (lithium; n = 9).

There were 66 children across the 53 families (34 OBD; 32 control; 48% female), aged between 6 and 11 years (M = 8.20 years, SD = 1.20 years). None of the control offspring met criteria for a psychological disorder, while ten OBD had a current diagnosis at T1, including an anxiety disorder (n = 1), enuresis (n=2), oppositional defiant disorder (n=1), and attention deficit/hyperactivity disorder (n = 6; all of whom were being treated with psychostimulants). None of the OBD were receiving any psychosocial treatments throughout the duration of the study. Psychopathology in offspring was assessed with the parent-version of the Kiddie-Schedule of Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL; 25). Children were excluded on the basis of presenting with pervasive developmental disorder, an intellectual or chronic physical disorder, or any history of an affective or psychotic disorder. Groups of children did not significantly differ on any key demographic variable (e.g., sex, ethnicity, or socioeconomic status) (all $p > .05$).

Of the initial 25 families having a parent with BD who underwent the T1 assessment, 20 completed the RUSH program. Of the 20 families who completed the RUSH program, all returned for T2 and T3 assessments, but only 17 families were retained at T4. Families most commonly reported a lack of time as the reason for dropping out at T4. No differences were

observed between the original sample and those who dropped out prior to participating in the RUSH program or at T4 with regards to various demographic variables (offspring and parent sex and age, socioeconomic status), parental diagnosis (BD-I v. BD-II), offspring psychopathology at T1, as well as parents' baseline scores across all four scores of parenting stress (all $p > 0.05$).

Measures

Parenting Stress Index – 4th Edition Short Form (PSI-4 SF)

The PSI-4-SF (Abidin, 2012) is a 36-item questionnaire aimed at evaluating various domains of stress related to parenting. The questions assess both parent and child characteristics which can exacerbate stress, as well as situational and demographic life stressors. This short form yields four scores. The *parental distress* subscale represents the extent to which parents feel conflicted and depressed in their role as a parent. The *dysfunctional interaction* subscale identifies whether parents feel satisfied of their child and the interactions they share with them. The *difficult child* subscale assesses the parent's perception of their child, and whether they are difficult to take care of. Finally, the *total stress* score combines the latter scores to represent child characteristics (e.g., adaptability, demandingness, mood), parent characteristics (e.g., competence, isolation, attachment), and situational stressors. Higher scores represent more dysfunction. One parent from each family completed the questionnaire at each timepoint (85% mothers). The PSI-4-SF yields good psychometric properties, with moderate-to-excellent internal consistency for the four scales (a = .71-.92) and adequate-to-strong reliability (k = .68-.84; 27).

Behavior Assessment System for Children, Second Edition (BASC-2)

The BASC-2 assesses children's internalizing (anxiety, depression, and somatic complaints) and externalizing (hyperactivity, aggression, and conduct problems) difficulties at home (Reynolds & Kamphaus, 2002). Higher scores on either scale represent more dysfunction.

The BASC shows adequate test–retest reliability (k = 0.64—0.95; Reynolds & Kamphaus, 2002) and high internal consistency (a = 0.80—0.90; Merydith, 2001).

UCLA Life Stress Interview

The UCLA semi-structured interview (Adrian & Hammen, 1993; Hammen, 1991) assesses the levels of both interpersonal and non-interpersonal stress in individuals' lives over the last six months. Questions span nine life domains, and are scored using a 5-point scale, where higher scores represent higher levels of stress and more dysfunction. The interview may yield two subscale scores, differentiating between interpersonal and non-interpersonal stress; interpersonal stress is represented as the sum of scores across the domains of close friends, social life, romantic relationships, and family relationships, whereas non-interpersonal functioning consists of the domains of school, work, finances, health, and health of family members (Eberhart & Hammen, 2006; Hammen et al., 2004). The score used in this study represents reported levels of chronic interpersonal stress, given the aforementioned hypotheses. Importantly, the UCLA provides an objective, observer rated representation of participants' stress-related dysfunction.

Intervention Program: Reducing Unwanted Stress in the Home (RUSH)

The RUSH program aims to improve the quality of the caregiving environment and strengthen stress-coping and resilience among the OBD and their parents. This new prevention program was developed from validated cognitive-behavioural treatments for stress-coping, family relationships, child-rearing, and the management of bipolar disorder (Abramowitz, 2012; Kendall & Hedtke, 2006; Severe, 2000; Shapiro & Sprague, 2009). The program consists of 12 manual-based, closed weekly group sessions; parent and child sessions were run separately but simultaneously.

Parent sessions lasted two hours and were divided into three core modules: problem-solving skills, healthy communication, and organization and discipline in the home. Sessions also provided psycho-education about stress, its negative impact on families, and adaptive stress-coping strategies. Parents were provided with bi-weekly, 15-min booster calls aimed to encourage the use of skills in the home and provide individualized support. Child sessions lasted one hour, followed by an hour of play. Sessions were geared towards enhancing resilience while teaching age-appropriate coping strategies, cognitive restructuring, problem-solving, emotion labelling, relaxation, and assertiveness.

Therapist competence (child group: 5.65 ± 0.40; adult group: 5.44 ± 0.30, on a six point scale) and adherence to intervention protocol (child group: 2.88 ± 0.40; adult group: 2.81 ± 0.30, on a three point scale) were assessed by a trained observer who coded video recorded sessions. A second observer coded a random sample of videos (30%), and established good inter-rater reliability (ICC = 0.89-0.98). The coding scheme used by observers was a modified version of a previously validated scheme developed for cognitive-behavioural group treatments of adults (Hepner et al., 2011).

Procedure

Parents first underwent a brief telephone interview to assess for eligibility. Next, parents were invited to the University to undergo a diagnostic interview (SCID-I). If eligible for the study, parents underwent the pre-intervention T1 assessment where they filled out questionnaires assessing parenting stress and child emotional and behavioural adjustment. Parents also underwent the UCLA Life Stress Interview, as well as a structured parent-child interaction task (Serravalle et al., 2021). The offspring underwent neuropsychological testing and provided saliva samples at home to assess cortisol levels (not reported here). The assessments were repeated at

post-intervention (T2), as well as three (T3) and six (T4) months following the end of the RUSH program.

Following the T1 assessment, parents with BD were enrolled into the RUSH program, in groups of 3 to 10 participants. The number of sessions attended by families having a parent with BD varied between 8–12 (M = 11.15, SD = 1.18). Participants were remunerated for the assessments with CDN$100 at T1 and T4, and CDN$80 at T2 and T3. Children received small toys for their participation. Voluntary and informed consent and assent were obtained from the parents and their offspring, respectively, to participate in the study and have their data published. All procedures were approved by the Human Research Ethics Committee at Concordia University, Montréal, Canada (certification number: 30002475).

Data Analysis

The main analyses were conducted on SPSS version 28 (IBM Corp., 2021), with mixed effects modelling using maximum likelihood estimation (Heck et al., 2013). We first assessed the immediate improvements (pre-post intervention) reported by families having a parent with BD, followed by long-term changes reported across the four assessments. We then modeled changes in parenting stress and chronic interpersonal stress for the entire sample to investigate whether risk-group (OBD vs. controls) accounted for any variability in intercepts and slopes. Scores on parenting and chronic interpersonal stress were nested within time, and an auto-regressive heterogeneity covariance structure was specified. Offspring age was entered as a covariate for the analyses as to account for variability attributable to the five-year age-range. Offspring sex was also entered as a covariate. All variables were standardized prior to running any statistical analyses. All analyses were run a second time following a random deletion of data obtained from siblings of both OBD and control families (results not shown here). As the previously established

effects were maintained following the random deletion of siblings, independence of events was ascertained and additional statistical approaches (i.e., nesting of data within families) were not deemed necessary.

Parallel mediations were run using Mplus version 8.0 (Muthén & Muthén, 2017). These analyses aimed to determine whether intervention-related improvements in parenting stress or chronic interpersonal stress across time predicted offspring internalizing and externalizing symptoms at follow-up. A conceptual representation of this model can be seen in Figure 1. Change scores were calculated by subtracting scores at T4 from scores obtained at T1. Greater positive change scores were indicative of greater reductions in parenting stress across time. There was no evidence that the data were not missing completely at random (MCAR), given Little's MCAR test (Little, 1988) (p = 1.00). For the three families having a parent with BD who completed T3 assessments but discontinued participation at T4, missing data were handled using full information maximum likelihood estimation. The strength of indirect effects are discussed using 95% bias corrected bootstrapped confidence intervals (MacKinnon et al., 2004; Miočević et al., 2018). The bootstrap sample was set to 5000 iterations. Means and standard deviations of reported parenting stress by families having a parent with BD and control families at each assessment phase can be seen in Table 2.

Results

Changes in parenting and chronic interpersonal stress in families having a parent with BD

Families having a parent with BD reported significant pre-post improvements on the difficult child subscale (b = -0.40, SE = 0.16, p = .016), but not on the parental distress subscale (b = -0.25, SE = 0.20, p = .232), the dysfunctional interaction subscale (b = -0.24, SE = 0.15, p = .132), or on the total stress score (b = -0.32, SE = 0.18, p = .079). Reported pre-post changes in

chronic interpersonal stress were not significant for families having a parent with BD (b = 0.10, SE = 0.22, p = .661).

Across the four assessment points, reported changes on the difficult child subscale followed a quadratic curve (b = .12, SE = 0.04, p = .008). While improvements were noted until T3, scores on the difficult child subscale significantly increased at T4. Similarly, changes on the total stress score also followed a quadratic curve (b = .26, SE = 0.05, p < .001); scores improved until T3, but worsened at T4 . Finally, changes on the parental distress subscale across time followed a linear curve (b = -0.12, SE = 0.07, p < .001), with continued improvements reported until T4. Linear change on the dysfunctional interaction subscale also improved over the four timepoints, although the effect fell short of conventional levels of statistical significance (b = -0.28, SE = 0.15, p = .063). In sum, despite a small post-intervention effect, improvements in parenting stress continued long after the termination of the intervention (see Fig. 2, panels a through d). In terms of chronic interpersonal stress, no significant changes were reported by families having a parent with BD across the four timepoints (b = 0.07, SE = 0.07, p = .319).

Between-group differences between families having a parent with BD and control families

Differences in reported levels of parenting and life stress at baseline

There was statistically significant variation in the intercepts of the total stress score (*Wald* Z = 4.07, p < .001), the parental distress subscale (*Wald* Z = 2.88, p = .004), the dysfunctional interaction subscale (*Wald* Z = 4.47, p < .001), and the difficult child subscale (*Wald* Z = 4.37, p < .001). In addition, there was significant variation in the intercept of the chronic interpersonal stress score (*Wald* Z = 4.11, p < .001). These findings indicate that between-subject effects influence scores at T1.

Risk-status significantly predicted intercepts for the total stress score (b = -1.19, SE = 0.19, $p < .001$), as well as the parental distress (b = -1.04, SE = 0.16, $p < .001$), dysfunctional interaction (b = -0.91, SE = 0.22, $p < .001$), and difficult child subscales (b = -0.99, SE = 0.20, $p < .001$). Significant intercept effects indicated that families having a parent with BD, as expected, reported higher levels of parenting stress than control families at T1. Additionally, risk status predicted initial levels of chronic interpersonal stress (b = -0.54, SE = 0.27, p = .044). Neither offspring sex or age at T1 accounted for any variability in intercepts.

Differences in reported changes in parenting and chronic interpersonal stress over time

There was statistically significant variability in the linear effects of time for the difficult child subscale (*Wald Z* = 2.27, p = .023), which indicates that between-subject effects influence its rate of change. For the total stress score (*Wald Z* = 1.77, p = .076) and the dysfunctional interaction subscale (*Wald Z* = 1.86, p = .063), the amount of inter-individual variability was trend-level. Finally, for the parental distress subscale, the observed between-subject differences in changes over time were not statistically significant (*Wald Z* = 1.34, p = .180). In terms of chronic interpersonal stress, the level of variability in the linear effects of time was non-significant (*Wald Z* = -.723, p = .470).

Change across time varied by risk-status for the total stress score (b = 0.95, SE = 0.18, $p < .001$), the dysfunctional interaction subscale (b = 0.64, SE = 0.21, p = .003), and for the difficult child subscale (b = 0.94, SE = 0.23, $p < .001$) (see Fig. 1, panels a, c, and d, respectively). Families having a parent with BD reported changes which followed a steeper curve than control families. Upon further investigation, families having a parent with BD also reported greater pre-post improvement on both the total stress score (b = 0.54, SE = 0.24, p = .027) and on the difficult child subscale (b = 0.56, SE = 0.22, p = .012). Finally, the rate of change for chronic

interpersonal stress scores did not vary between groups (b = -0.01, SE = 0.09, p = .925); this means that improvements in observer-rated levels of stress were not associated to risk-status. Offspring sex and age were not significantly associated to variability in growth trajectories.

Parallel mediations models

Standardized model results predicting both internalizing and externalizing symptoms are summarized in Table 3 and Table 4, respectively. Internalizing and externalizing scores were each averaged across T3 and T4. The mean internalizing score (± *SD*) for OBD was 12.64 (11.71), while it was 9.11 (8.10) for control offspring. The mean externalizing score for OBD was 17.08 (15.36), and 6.72 (8.72) for control families. Mediations were run using change scores on parenting stress, however changes in chronic interpersonal stress were omitted from these analyses given the non-significant slope terms for families having a parent with BD reported above.

Improvements on the total stress subscale mediated the relationship between participation in the RUSH intervention program and internalizing symptoms across follow-up (β = -.31, SE = 0.10, Cl = -0.55, -0.13; Table 2). Additionally, reported improvements on the total stress subscale also mediated the relationship between participation in the RUSH program and externalizing symptoms across follow-up (β = -.35, SE = 0.10, Cl = -0.57, -0.16; Table 3). None of the other indirect effects were significant.

Discussion

Three key findings emerged from the present study. First, families having a parent with BD reported more parenting stress than control families pre-intervention. Families having a parent with BD reported less perceived difficulty in caring for their child (i.e., difficult child subscale), as well as less overall interpersonal and situational stress (i.e., total stress score)

immediately following the end of the RUSH intervention than control families, and continued to do so until 6-months post-intervention. Second, the relationship between participating in the RUSH program and OBD's internalizing and externalizing problems at follow-up was mediated by decreased parenting stress, as assessed via the total stress score. Third, families having a parent with BD also reported more chronic interpersonal stress than control families pre-intervention. However, these families did not report significant changes across time on chronic interpersonal stress. Interestingly, the RUSH program had robust effects in reducing aspects of parenting stress over time but had no impact on chronic interpersonal stress. Thus, the intervention was particularly helpful in reducing perceptions of stress around one's role as a parent, but did not influence interpersonal stress more generally.

Parents living with affective disorders experience detrimental levels of parenting stress (Gelfand et al., 1992; Jones et al., 2017), and studies have shown that parenting stress may mediate the relationship between parents' depressive symptoms and offspring developmental outcomes (Fredriksen et al., 2019). Thus, the relationship between parenting stress and offspring development is especially relevant in the study of offspring of parents with affective disorders. In line with the current findings, Jones and colleagues (Jones et al., 2017) reported that an online parenting intervention for families having a parent with BD led to significant improvements in both parenting stress and offspring emotional and behavioural problems. However, the present study is the first to demonstrate that the relationship between participating in a preventative intervention and OBD internalizing and externalizing symptoms is mediated by improvements in parenting stress. In addition, the finding that families with a parent having BD have higher parenting stress than control families is an important addition to the literature; only one study thus far had demonstrated differences on the Parenting Stress Index between depressed and non-

depressed mothers (Gelfand et al., 1992). This finding complements the previously documented dysfunction present in the family environment of parents with BD (Iacono et al., 2018; Ostiguy et al., 2012; Serravalle et al., 2021).

Support for our hypotheses was mixed. Pre-post intervention changes in parenting stress were found only on the difficult child subscale. However, there were marked long-term improvements for three of the four parenting stress subscales (i.e., the total stress, parental distress, and difficult child subscales). This trend is similar to the findings from Jones and colleagues (Jones et al., 2017), where larger improvements in parenting stress were reported throughout follow-ups, but not immediately post-intervention. Additionally, changes across time for both the total stress and difficult child subscales were not stable. Following steady improvements, levels of reported parenting stress had increased significantly by the final timepoint. However, nonlinear trajectories of change are common following clinical interventions; many individuals reporting initial improvements will eventually stabilize, or sometimes even worsen before improving again (Owen et al., 2015). Importantly, levels of parenting stress reported by families having a parent with BD were comparable to those of control families at the final timepoint.

The present results highlight the value of targeting parenting stress when working with at-risk families. The results present early evidence in favour of preventative approaches for at-risk youths. Intervening in middle childhood, prior to the onset of affective disorders in adolescence (Warner et al., 1992), may be central to effective prevention efforts. Without the urgent need to manage offspring symptoms, such as interventions catered to an older population (Compas et al., 2009; Garber et al., 2009), the RUSH program can target well-established family-related risk factors for OBD (Serravalle et al., 2021). Despite the positive implications of

our findings, this study was not without limitations. The sample size was small, limiting statistical power. However, mixed effects modelling with maximum likelihood estimation was used to minimize this limitation. The sample consisted of mostly white French-Canadians which may limit the generalizability of our findings. Finally, the present study did not utilize a RCT design – the gold standard in intervention research. In this proof-of-concept project, the control families served only as a comparison group. While our results provide evidence that families having a parent with BD benefitted from the RUSH intervention, we are unable to conclude if the RUSH intervention would fare better than a waitlist or active control intervention in families having a parent with BD. However, the effects reported here support the need for future RCTs to explore the efficacy of the RUSH program, as well as putative mechanisms of change.

Conclusion

To conclude, the present findings contribute to the literature on the role of the caregiving environment in the development of OBD (Iacono et al., 2018). This study presents findings that highlight the link between reported improvements on parenting stress following the RUSH program and OBD functioning. Our findings build on recent developments in family-based approaches to the treatment of BD (Miklowitz & Chung, 2016). Broader implications may lie in adopting a preventative approach for at-risk youths such as OBD. Future studies should submit the RUSH intervention to a more rigorous RCT design to better understand its benefits as compared to other types of interventions, and for other at-risk populations.

Table 1. Demographic characteristics presented by risk-status.

Variable	OBD	Control Offspring
Offspring age at first timepoint	7.77 years (*SD* = 1.74)	8.67 years (*SD* = 1.68)
Offspring sex		
Girls	17	18
Boys	17	14
Family ethnicity		
Aboriginal (e.g., First Nations, Inuit, Metis, Native American, Native Australian)	1	0
Black (e.g., African-American, Nigerian, Haitian, Jamaican, Somali)	0	4
East Asian, South-East Asian, Pacific Islander (e.g., Chinese, Japanese, Korean, Vietnamese, Thai, Filipino, Indonesian)	1	2
Hispanic/Latino/Latin-American (e.g., Brazilian, Chilean, Mexican, Cuban)	1	3
Middle Eastern, North African, Central Asian (e.g., Jordanian, Saudi, Egyptian, Moroccan, Iranian, Afghan, Tajikistani)	2	3
White (Caucasian)	20	16
Parental marital status		
Single	5	2
Married	18	18
Separated	2	5
Divorced	0	3
Parental educational attainment		
Highschool Diploma	1	0
CÉGEP Diploma	4	4
Some university achievement	1	3
University Degree	19	21
Family annual income		
Less than $25,000	4	4
$25,001 to $50,000	8	8
$50,001 to $75,00	5	5
$75,001 to $100,000	1	7
more than $100,000	7	3
Family SES Composite*	9.44 (*SD* = 2.10)	9.48 (*SD* = 1.67)

Note. SES Composite = socioeconomic composite score, which combines both parental educational attainment and family annual income.

Table 2. Means and standard deviations for parenting stress across time and groups

	T1	T2	T3	T4
Variable	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Total stress				
OBD	50.35(18.71)	42.04(24.61)	29.68(13.75)	37.65(23.54)
Control offspring	26.28(10.94)	32.33(18.79)	29.10(16.23)	34.52(23.01)
Parental distress				
OBD	18.71(7.18)	16.08(9.89)	14.16(8.89)	4.65(6.77)
Control offspring	8.41(5.12)	11.07(8.69)	12.73(10.80)	4.72(9.33)
Interaction				
OBD	12.09(8.88)	9.60(8.83)	9.20(8.33)	8.40(8.92)
Control offspring	4.78(4.76)	7.03(7.04)	8.57(7.88)	7.72(8.39)
Difficult child				
OBD	19.56(6.25)	16.36(7.81)	15.52(6.46)	16.40(7.82)
Control offspring	13.09(3.84)	14.23(5.37)	16.37(6.42)	15.59(6.21)

Note. OBD = offspring of parents with bipolar disorder

T1 = pre-intervention; T2 = post-intervention, T3 = 3-month follow-up; T4 = 6-month follow-up

Table 3. Standardized model results of parallel mediations predicting parent-reported internalizing problems across follow-up

Mediator	Effect of *IV* on mediator (*a*) β (SE)	Unique effect of mediator (*b*) β (SE)	Indirect effect (*ab*) β (SE)	BC 95% CI
Total stress	0.41 (0.10)**	-0.75 (0.19)**	-0.31 (0.10)**	[-0.55, -0.13]
Parental distress	0.38 (0.12)*	0.16 (0.16)	0.07 (0.07)	[-0.05, 0.22]
Interaction	0.28 (0.12)*	0.30 (0.19)	0.07 (0.08)	[-0.07, 0.22]
Difficult child	0.32 (0.13)*	0.11 (0.15)	0.01 (0.05)	[-0.07, 0.14]
Total indirect	-	-	-0.15 (0.06)*	[-0.31, -0.03]

Note. IV = independent variable; *BC* = bias-corrected bootstrap; *CI* = confidence interval.

*$p < .05$, **$p < .001$

[a]The (*a*) paths are identical across both mediation models.

Table 4. Standardized model results of parallel mediations predicting parent-reported externalizing problems across follow-up

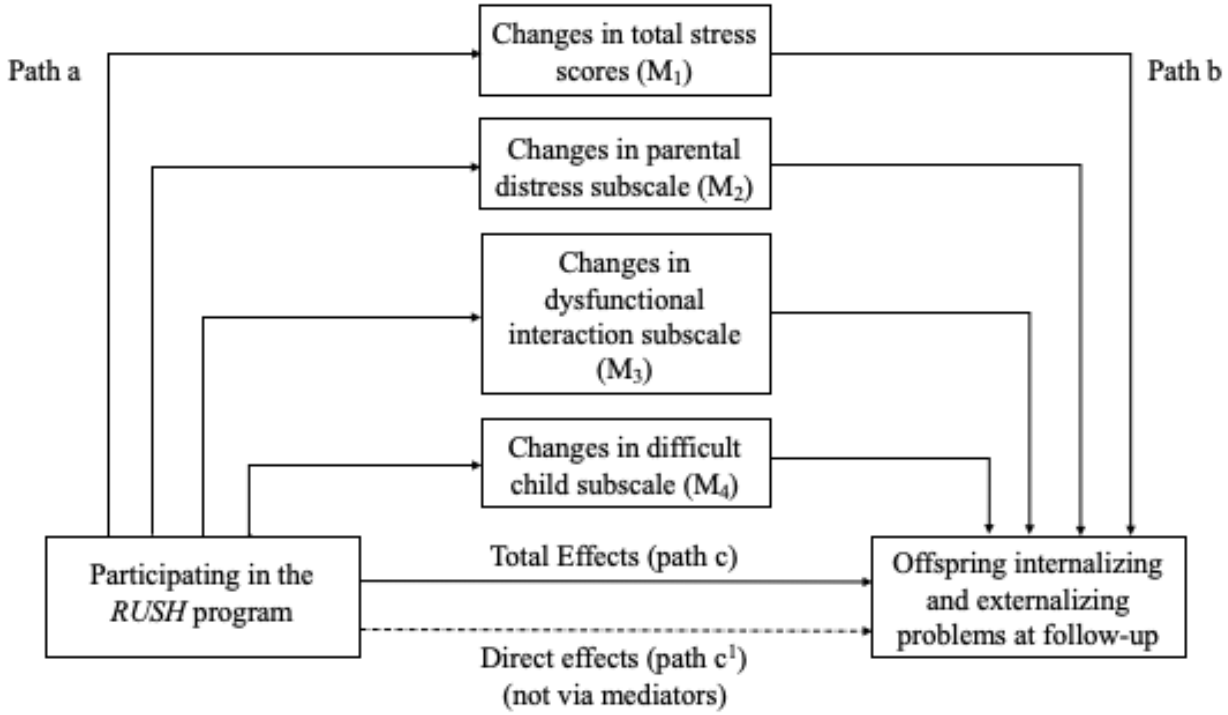
Mediator	Effect of *IV* on mediator (*a*) β (SE)	Unique effect of mediator (*b*) β (SE)	Indirect effect (*ab*) β (SE)	BC 95% CI
Total stress	0.41 (0.10)**	-0.84 (0.09)**	-0.35 (0.10)**	[-0.57, -0.16]
Parental distress	0.38 (0.12)*	0.14 (0.15)	0.07 (0.07)	[-0.05, 0.23]
Interaction	0.28 (0.12)*	0.42 (0.14)*	0.12 (0.06)	[0.01, 0.26]
Difficult child	0.32 (0.13)*	0.18 (0.11)	0.06 (0.05)	[0.00, 0.21]
Total indirect	-	-	-0.10 (0.06)	[-0.22, 0.02]

Note. IV = independent variable; *BC* = bias-corrected bootstrap; *CI* = confidence interval.

*$p < .05$, **$p < .001$

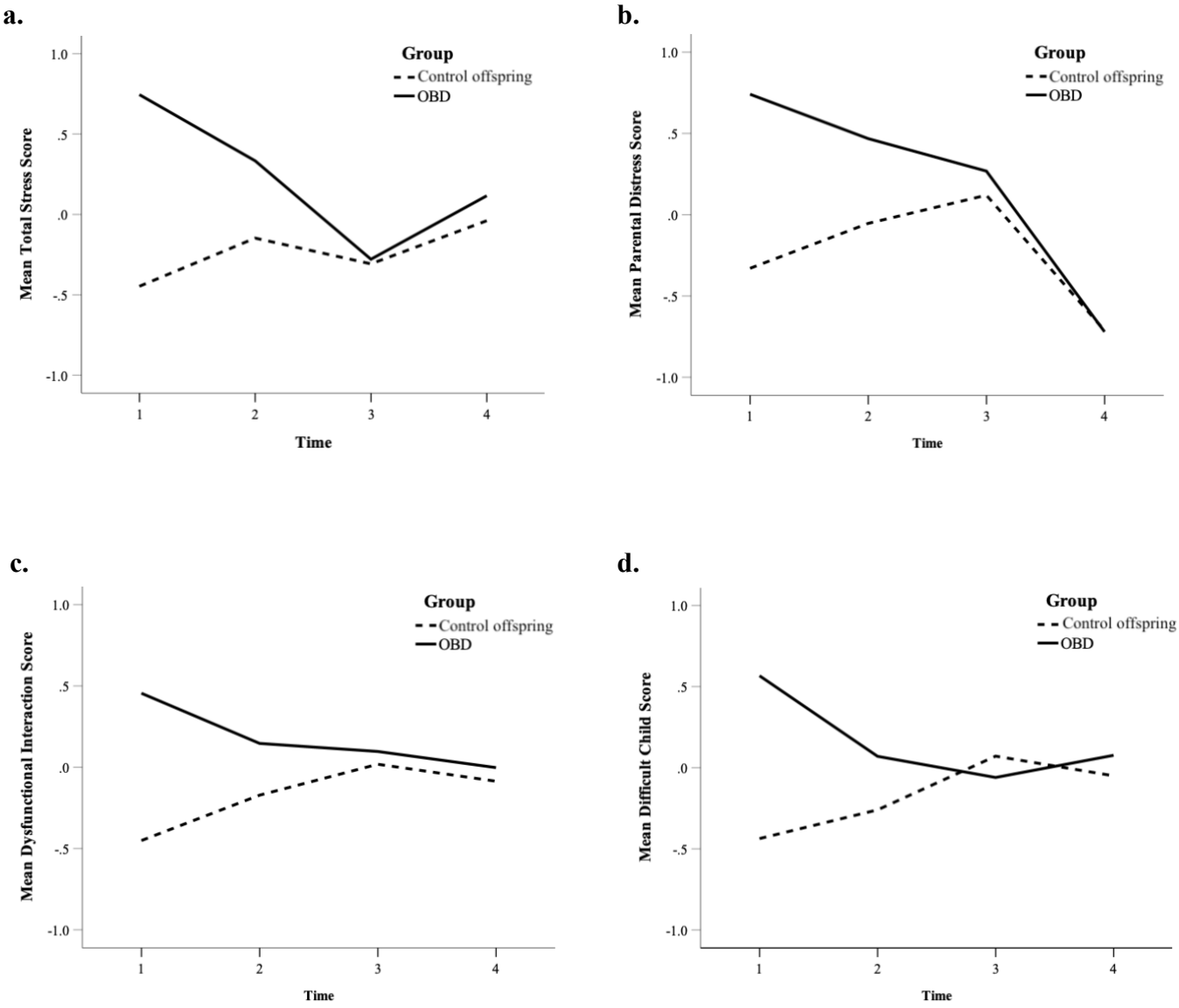
[a]The (*a*) paths are identical across both mediation models.

Figure 1.



Note. Included mediators represent scores yielded from the Parenting Stress Index. Participating in the RUSH program is considered equivalent to having a parent with BD or not (OBD vs. control offspring).

Figure 2.



Note. The linear effect of time on all four subscales by intervention group

OBD = offspring of parents with bipolar disorder

General Discussion

The literature has established the OAD as an at-risk population given the high prevalence of mental disorders and accompanying psychosocial dysfunction that is documented throughout their lifespan (Henin et al., 2005; Vandeleur et al., 2012). The evidence suggests that inherited vulnerabilities and exposure to adverse events in the early environment may interact to explain the OAD's unique risk to emotional and behavioural difficulties, and the high levels of familial transmission of psychopathology. Several important findings emerged from the studies presented in the thesis.

Study 1 used data collected across a 15-year period to provide evidence of an association between levels of family dysfunction and both emotional and behavioural problems in the OAD, but not in controls, which was comparable throughout middle childhood, adolescence, and early adulthood. By building on the findings from study 1, and using data from the same project, study 2 assessed both mental health symptoms and mental health care service use in the OAD and controls. In addition, it attempts to represent the aggregation of risk within the rearing environment, as opposed to using a singular measure of family functioning. Study 2 provided evidence that the OAD are more likely than controls to use more intensive mental health services in adulthood as a result of cumulative risk in the rearing environment and the subsequent development of mental health difficulties. Finally, study 3 provides preliminary evidence of the effectiveness of a preventative intervention which aims to offset the individual and familial burdens associated to the OAD, which is highlighted across studies 1 and 2. Study 3 demonstrated that participating in the 12-week RUSH program led to significant improvements in parenting stress (i.e., parents' own beliefs of their competence and attachment to their children), which were maintained up to 6-months post-intervention. Thus, consistent with studies

1 and 2 showing prospective links between stress in the family environment and child outcomes, study 3 demonstrated that positively changing aspects of the family environment can have positive effects on high risk children.

This thesis aimed to further elucidate the OAD's psychological and behavioural sensitivity to stress in the rearing environment, which converge on certain themes. First, and at the core of this thesis, all three studies provide evidence which suggests that the rearing environment, consisting of parenting styles, parent-child relationships, and effective stress-coping in the family, may be an important mechanism of intergenerational transmission of psychopathology for the OAD. More specifically, the three facets of the rearing environment appear to each play a role in the early environment, and may aggregate to increase the OAD's level of risk for maladaptive outcomes. However, targeting even one of the underlying risk factors, as seen in study 3, may be beneficial in mitigating pathways to emotional and behavioural problems in the OAD. Other commonalities which emerged across the studies pertain to the importance of capturing perceptions of stress closely related to the rearing environment, as opposed to measurable objective life stressors. In addition, results from this thesis document the quantifiable multi-level burden of care associated to the OAD, consisting of the development of psychopathology in offspring, high levels of dysfunction in the family, and the need for more intensive and expensive mental health services.

Are the OAD more sensitive to stress in their early rearing environment than controls?

The present studies add to the growing literature investigating the role of the rearing environment as a potential mechanism of familial transmission of psychopathology in the OAD. As discussed throughout the introduction, studies have well documented that families of one of more parents living with an affective disorder report overall higher levels of family dysfunction

than control families (Barron et al., 2014; Jones et al., 2017; Romero et al., 2005; Weinstock et al., 2006; Wiegand-Grefe et al., 2019). More specifically, stressors within the family environment, such as parental separation and financial difficulties, are also more present in families of the OAD (Loechner et al., 2020). The evidence suggests that specific facets of the family environment may be especially important in understanding environmental risk in the OAD. For example, the parent-child relationship tends to be a particularly impactful dynamic for the OAD. Studies have shown that parents with affective disorders are often less warm and nurturing than parents without affective disorders, and display lower levels of expressed emotion and emotional responsiveness than their counterparts as well (Cummings et al., 2005; Iacono et al., 2018; Lau et al., 2018; Wilson & Durbin, 2010). Together, the lack of emotional connection may lead to sub-optimal attachment between parent and child, which has long-lasting impact on offspring's psychosocial development. In addition, parenting strategies may also interact with inherited vulnerabilities in the OAD; parents with affective disorders may rely on ineffectual strategies such as exerting control over their children, or engaging with high levels of criticism and negativity, which create stressful situations for offspring and lead to adverse outcomes.

Recently, evidence has suggested that ineffectual parenting styles and poor parent-child relationships in middle childhood interact with existing vulnerabilities in OAD and mediate the relationship between psychopathology in parents and offspring mental health later in life (Iacono et al., 2018). However, conflictual findings have been reported, in which similar mediation effects were not found when using measures of family functioning or of cohesion and bonding (Lau et al., 2018; Moulin et al., 2022). However, these latter studies examined whether family functioning would mediate the relationship between parent and offspring psychopathology, making them only partially comparable with the first two studies of this thesis. The aim of study

1 was to document a moderator effect of risk-status (i.e., OAD vs. controls) on the relationship between stressful life events and offspring mental health in adulthood as mediated by family functioning. However, the results are partly consistent with the literature, as family dysfunction mediated the relationship between stressful life events and offspring mental health in adulthood for both the OAD and controls. In addition, recent efforts to parse out within- and between-family effects of family dysfunction on offspring mental health have failed to provide evidence of a within-family association between the family environment and offspring well-being in the general population (Kim et al., 2022; Mastrotheodoros et al., 2020), but this same methodology had not yet been used to investigate differences between the OAD and controls. Study 1 is thus the first study to document a concurrent within-family effect of the family environment on internalizing and externalizing problems in the OAD specifically, which was shown to be consistent from middle childhood to early adulthood.

As previously mentioned, various factors within the early environment, such as parental mental health, levels of organization and conflicts in the home, parental separation, parenting styles, emotional support, and exposure to adverse events, predict offspring use of mental health care service use (Ezpeleta et al., 2002; Jansen et al., 2013; Oltean et al., 2020; Stalujanis et al., 2019; van Duin et al., 2019; Waldmann et al., 2021). Despite the evidence highlighting risk factors characteristic of OAD family environments to mental health service use, there is paucity of research documenting pathways from early adversity in the rearing environment to types of mental health service use in adult OAD. Study 2 is thus the first to document the indirect pathway from cumulative stress specific to the rearing environment and intensiveness of mental health service use in adulthood via internalizing and externalizing problems, which appears to be especially salient for the OAD.

Together, the first two studies of the thesis provide further evidence of the OAD's sensitivity to stress in their rearing environment, and proposes that family-related stress exposure is a mechanism of the transmission of risk for the development of psychopathology. In addition to stressful life events, the nature of the rearing environment which consist of parent-relationships and parenting styles may be relevant to both understanding and mitigating the risk faced by these at-risk youth. Indeed, while future studies of longitudinal designs may directly compare various facets of the rearing environment on specific types of offspring outcomes, as well as their compounding effects, the literature thus far presents a sound foundation for the shift to family-based preventative interventions for the OAD.

The rearing environment as an intervention target for the OAD

As mentioned earlier, while the rearing environment poses an important risk factor for the OAD, it also provides a viable intervention target. Research efforts aiming to identify malleable environmental targets common in at-risk youth stem from a growing interest to prevent the slew of difficulties to individuals, families, and societies. As documented across studies 1 and 2, the development of internalizing and externalizing problems and accompanying dysfunction have long-lasting effects into adulthood. It is thus imperative to investigate the potential costs and benefits associated with early preventative efforts, and weigh the latter against rising costs associated with the burdens of mental health disorders.

Study 3 therefore presents preliminary findings surrounding the effectiveness of a preventative intervention in OBD. The development of the RUSH program was based research aiming to identify key risk factors in families having a parent with bipolar disorder and their offspring, such as the stressful family environment, parenting practices, personality traits in parents, and stress-related neuroendocrine function in offspring, prior to the development of

symptoms of mental disorders (Ellenbogen & Hodgins, 2004; Ellenbogen et al., 2006; Ellenbogen et al., 2011; Ellenbogen et al., 2009; Halligan et al., 2004; Ostiguy et al., 2012). In creating a preventative program for at-risk offspring, the RUSH program aimed to determine whether eliciting change in the family environment might ameliorate outcomes of youth at risk for affective disorders. The results of study 3 compliment recent findings on preventative efforts in the OAD (Beardslee et al., 2013; Loechner et al., 2018), while providing further evidence of the key role of perceptions of parenting stress in parents with affective disorders (Jones et al., 2017). Future studies aiming to investigate the effectiveness of preventative programs should aim to utilize rigorous designs such as randomized-controlled trials, which allow researchers to infer causality from their results. Of interest, future research may examine the possible interactions between improved parent-child relationships, the use of effectual parenting strategies, and the development of adaptive stress-coping strategies, in creating long-lasting improvements in offspring outcomes.

Strengths and limitations

The presented manuscripts build on past research and highlight the unique role of the rearing environment in the OAD. To our knowledge, studies 1 and 2 are among a small number of studies to compare associations between familial factors and emotional and behavioural outcomes between the OAD and controls across time. Using data from an ongoing population cohort study spanning 15 years and counting, longitudinal designs and accompanying statistical methods allowed for the rigorous testing of associations, and subsequent comparisons between the OAD and controls. Across studies 1 and 2, different types of assessment tools were used, including administered interviews and questionnaires, and included data from different informants (parents and offspring). The RUSH program presented in study 3 was firmly based in

evidence-based principles of prevention (Abramowitz, 2012; Kendall & Hedtke, 2006; Severe, 2000; Shapiro & Sprague, 2009), as well as various established theories of familial transmission of psychopathology (Cicchetti & Toth, 1997; Rosenthal, 1963; Zuckerman, 1999).

The studies included in this thesis are also accompanied by several limitations. Across all three studies, characteristics of the parents' affective disorders which may fluctuate across time, such as intensity or severity of current symptoms or episodes, were not assessed. The evidence suggests that offspring mental health may parallel that of their parents (Mars et al., 2012), and as such future studies should aim to statistically account for changes in parental mental health across time. In addition and based of previously discussed studies documenting the likelihood of adults with affective disorders choosing partners with similar presenting difficulties (Serravalle et al., 2020), the studies in this thesis did not account for the effect of having more than one parents with an affective disorder. Although supplementary analyses in study 1 were run in OAD of mothers with affective disorders, and then including OAD of fathers with affective disorders, the relative samples were too small to confidently compare and contrast effects within these sub-samples across both studies 1 and 2. Similarly, statistically accounting for parent sex in study 3 was deemed impossible due to the small sample size. Finally, across studies, we did not account for the presence of comorbidities in parents, which has been shown to impact the transmission of disorders (McLaughlin et al., 2012; Merikangas et al., 1988). Future studies should aim to formally assess both the trajectory of psychopathology in parents as well as the cumulative effects tied to having more than one parent with an affective disorder.

An important limitation which spans across all three studies pertains to the transactional model of developmental psychopathology (Cicchetti & Toth, 1997), which posits that offspring vulnerabilities and environmental stressors share a bi-directional relationship. However, the

presented studies did not assess the transactional nature of the rearing environment and offspring mental health. Recent studies have employed random-intercept cross-lagged models (Kim et al., 2022; Mastrotheodoros et al., 2020; Peng et al., 2023) to estimate continuous reciprocal effects of key variables; while the results of study 1 provide an estimation of a unidirectional effects, future studies should prioritize the statistical estimation of transactional effects. In terms of study 3, statistical limitations were tied to the small sample size, as this was a pilot proof-of-concept study. In the next steps, the RUSH program's efficacy will be evaluated using a randomized-controlled design spanning a longer post-intervention timeframe, and more rigorous statistical approaches.

Conclusions

Overall, the findings presented within this thesis meaningfully contribute to the growing body of evidence highlighting specific factors within the rearing environment as potential causal mechanisms for the intergenerational transmission of psychopathology. More specifically, we documented individual, familial, and societal burdens associated uniquely to the OAD, and provided a foundation for future research. Finally, we highlight the importance of developmentally-sensitive preventative efforts targeting key family-related risk factors to promote adaptive emotional and behavioural outcomes in youth at risk for affective disorders.

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Appendix 1. Supplemental materials for Chapter 2

Supplemental Materials

Results

Internalizing problems

Modeling changes in internalizing problems across time. Prior to incorporating time-variant and time-invariant predictors, the first step was to identify the baseline model. To select the appropriate baseline model, four models were considered: the intercept-only model (Model 1), the linear-growth model (Model 2), the linear-growth model with constrained residuals (Model 3), and the quadratic-growth model with constrained residuals (Model 4). Goodness-of-fit indexes are found in Table S1. The Chi-square goodness of fit test shows that only Model 4 fit the data well ($p > .05$). In addition, the AIC (Akaike information criterion), BIC (Bayesian information criterion), RMSEA (root mean square error of approximation), and SRMR (standardized root mean squared residual) were smaller, while both the CFI (comparative fit index) and TLI (Tucker-Lewis index) are larger in Model 4, as compared to Models 1, 2, and 3. This suggests that the quadratic curve fit the data better than an intercept-only or linear model, as well as the parsimony gained from constricting residuals to equality across time. Model 4 was retained as the baseline model.

Table S1. Goodness-of-fit results in establishing the baseline model of internalizing problems

Model	χ^2	df	*p*	AIC	BIC	CFI	TLI	RMSEA	SRMR
Model 1	32.006	9	.000	-2830.069	-2727.334	0.990	0.984	0.034	0.025
Model 2	190.844	11	.000	-2652.792	-2561.472	0.925	0.898	0.086	0.081
Model 3	184.939	15	.000	-2646.814	-2578.324	0.929	0.929	0.071	0.074
Model 4	17.357	11	.098	-2855.520	-2764.200	0.997	0.996	0.016	0.021

The estimated growth parameters for the baseline model are found in Table S2. The average starting point across the sample was 0.363 (SE = 0.099). Among individual intercepts, there was a statistically significant amount of variation, $p = .000$. The average linear rate of change was of -0.089 (SE=0.061), while the quadratic slope was 0.015 (SE = 0.010), both statistically significant at $p = .000$. This indicates that participants significantly improved on internalizing scores across time, and experienced some fluctuations, as evidenced by a worsening of symptoms in early adulthood.

Table S2. Estimated parameters of model 4 and 5, with sex and SES as time-invariant predictors

	Model 4			Model 5		
	I	S	Q	I	S	Q
Sex (0=female, 1=male)				-0.068 (0.010)**	-0.044 (0.009)**	0.009 (0.002)**
SES				-0.010 (0.007)	-0.004 (0.005)	0.001 (0.001)
Estimated means	0.363 (0.005)**	-0.092 (0.010)**	0.015 0.002)**	0.363 (0.099)**	-0.089 (0.061)**	0.015 (0.010)**
R-squared				0.047*	0.091*	0.145*

Note: n_{OAD} = 761. $n_{controls}$ = 1426. I = Intercept, S = Slope, Q = Quadratic.

Estimated means are derived from the model, and estimated standard errors are in parentheses.

Unstandardized coefficients are presented with their standard errors in parentheses.

$* = p < .05$, $** = p < .001$.

Sex and SES as time-invariant predictors of slope and intercept. Sex and socioeconomic status were added to the baseline model to investigate their effect on both intercept and rates of change (Model 5; see Table S2). Offspring sex significantly predicted individual intercepts of internalizing problems, such that girls reported higher initial levels of internalizing problems. Sex also significantly predicted individual rates of change, such that girls followed a more gradual slope than boys, meaning they reported less change on internalizing symptoms through time. In line with this, the rate of change of internalizing problems across time was more volatile for boys, given the statistically significant effect of sex on quadratic estimates. Socioeconomic status did not predict intercept or slopes.

Family functioning as a time-varying predictor of internalizing problems. Having established the role of sex and SES within the quadratic model of internalizing problems, the next step was the investigate family functioning as a concurrent time-varying predictor. To establish the best representation of changes in family functioning across time, four models were considered: an intercept-only model (Model 6), a linear model (Model 7), a linear model where residuals were constrained to equality across time (Models 8), and a quadratic model with constrained residuals (Model 9). Table S3 shows the goodness-of-fit results for Models 6 to 12, from which it was established that Model 9 was retained as the best representation of the data.

Table S3. Goodness-of-fit results in establishing growth curve for family functioning and the invariance of its relationship to internalizing problems across time

Model	χ^2	df	*p*	AIC	BIC	CFI	TLI	RMSEA	SRMR
Model 6	126.285	63	.000	3398.234	3688.439	0.989	0.985	0.021	0.022
Model 7	158.688	60	.000	3439.801	3747.077	0.983	0.975	0.027	0.040
Model 8	162.446	64	.000	3439.821	3724.336	0.983	0.977	0.027	0.044
Model 9	97.301	55	.000	3383.474	3719.201	0.993	0.988	0.019	0.028
Model 10	105.492	60	.000	3381.876	3689.152	0.992	0.989	0.019	0.029
Model 11	199.626	120	.000	3297.476	3912.027	0.987	0.980	0.025	0.039
Model 12	244.521	123	.000	3340.858	3938.338	0.980	0.970	0.030	0.040

In addition, the relationship between family functioning and internalizing problems was constrained to equality across time (Model 10). Results showed that constraining the effect of family functioning to equality across time did not worsen model fit; in fact, most goodness-of-fit indexes were comparable, while the AIC and BIC were lower in Model 10 than in Model 9. Model 10 was thus used as the baseline model for the multi-group comparison. Model 11 includes the addition of the grouping variable, and allows residuals and effects to vary between both groups, whereas model 12 constrains effects to equality between groups; the interpretation of model fit is found in the results section. The estimated parameters for Model 10 can be found in Table S4. Results show that high scores on the Family Assessment Device significantly predict internalizing problems comparably across all 6 timepoints.

Table S4. The estimated parameters of growth curve model 10, modelling both internalizing problems and family functioning as a time-varying predictor.

Model 10	Internalizing Problems			Family Dysfunction		
	I	S	Q	I	S	Q
Sex (0=female, 1=male)	-0.069 (0.010)**	-0.043 (0.009)**	0.009 (0.002)**	0.018 (0.015)	-0.024 (0.012)*	0.005 (0.002)*
SES	-0.008 (0.007)	-0.004 (0.005)	0.001 (0.001)	-0.084 (0.011)**	0.022 (0.009)*	-0.004 (0.002)*
Estimated means	0.326 (0.098)**	-0.088 (0.058)**	0.015 (0.010)**	1.775 (0.154)**	-0.182 (0.092)*	0.021 (0.014)
R-squared	0.048**	0.094*	0.152*	0.045*	0.034	0.049

Note: $n_{OAD} = 761$. $n_{controls} = 1426$. I = Intercept, S = Slope, Q = Quadratic.

Estimated means are derived from the model, and estimated standard errors are in parentheses.

Unstandardized coefficients are presented with their standard errors in parentheses.

$* = p < .05$, $** = p < .001$.

Externalizing problems

Modeling changes in externalizing problems across time. Four models were considered to identify the baseline model of changes in externalizing problems across time: the intercept-only model (Model 13), the linear-growth model (Model 14), the linear-growth model with constrained residuals (Model 15), and the quadratic-growth model (Model 16). Goodness-of-fit indexes are found in Table S5. As seen by the worsening goodness-of-fit criteria going from Model 14 to Model 15, the residuals for externalizing problems were made free to vary across time prior to adding the quadratic-growth term. Results from the goodness-of-fit tests revealed that the quadratic curve best explained the data. Model 16 was retained as the baseline model for externalizing problems.

Table S5. Goodness-of-fit results in establishing the baseline model of externalizing problems

Model	χ^2	df	*p*	AIC	BIC	CFI	TLI	RMSEA	SRMR
Model 13	72.022	9	.000	-7381.860	-7279.117	0.968	0.946	0.056	0.037
Model 14	88.707	11	.000	-7379.901	-7288.573	0.960	0.945	0.056	0.050
Model 15	297.589	15	.000	-7248.665	-7180.170	0.854	0.854	0.092	0.079
Model 16	29.288	7	.000	-7446.395	-7332.236	0.989	0.975	0.038	0.032

The estimated growth parameters for Model 16 are found in Table S6. The average starting point across the sample was 0.273 (SE = 0.004). Among individual intercepts, there was a statistically significant amount of variation, $p = .000$. The average linear rate of change was of -0.069 (SE=0.016), while the quadratic slope was 0.014 (SE = 0.004), both statistically significant at $p = .000$ and $p = .001$, respectively. This indicates that participants significantly improved on externalizing scores across time, and yet exhibited some variability, as evidenced by a sharp increase in symptoms in adolescence. This trend was opposite to that observed for internalizing problems.

Table S6. The estimated parameters from model 16 and 17, with sex and SES as time-invariant predictors

	Model 16			Model 17		
Predictors	I	S	Q	I	S	Q
Sex (0=female, 1=male)				0.058 (0.008)**	-0.034 (0.006)**	0.006 (0.001)**
SES				-0.011 (0.005)*	-0.004 (0.005)	0.001 (0.001)
Estimated means	0.273 (0.004)**	-0.069 (0.016)**	0.014 (0.004)**	0.273 (0.004)**	-0.061 (0.015)**	0.012 (0.004)*
R-squared				0.084*	0.160	0.224

Note: n_{OAD} = 761. $n_{controls}$ = 1426. I = Intercept, S = Slope, Q = Quadratic.

Estimated means are derived from the model, and estimated standard errors are in parentheses.

Unstandardized coefficients are presented with their standard errors in parentheses.

$* = p < .05$, $** = p < .001$.

Sex and SES as time-invariant predictors of slope and intercept. Sex and socioeconomic status were then added as time-invariant predictors of intercept and slope (Model 17; see Table S6). Offspring sex significantly predicted individual intercepts of externalizing problems, such that boys reported higher initial levels of externalizing problems. Sex also significantly predicted individual rates of change, such that girls followed a more gradual slope than boys, meaning they reported less change in externalizing symptoms across time. In line with this, the statistically significant effect of sex on quadratic estimates suggest that slopes were more likely to change over time for boys than for girls. Interestingly, socioeconomic status was linked to initial levels of externalizing problems, such that individuals from higher income households reported less externalizing problems at time 1. There were no statistically significant associations between socioeconomic status and either linear or quadratic estimates.

Family functioning as a time-varying predictor of externalizing problems. Having established the role of sex and SES within the quadratic model of externalizing problems, the next step was the investigate family functioning as a concurrent time-varying predictor. To establish the best representation of changes in family functioning across time, four models were considered: an intercept-only model (Model 18), a linear model (Model 19), a linear model where residuals were constrained to equality across time (Models 20), and a quadratic model with constrained residuals (Model 21). Table S7 shows the goodness-of-fit results for Models 18 to 23.

Table S7. Goodness-of-fit results in establishing growth curve for family functioning and the invariance of its relationship to externalizing problems across time

Model	χ^2	df	*p*	AIC	BIC	CFI	TLI	RMSEA	SRMR
Model 18	105.889	59	.000	-1008.219	-695.254	0.991	0.987	0.019	0.020
Model 19	137.150	56	.000	-969.041	-639.004	0.985	0.976	0.026	0.038
Model 20	140.615	60	.000	-969.282	-662.007	0.985	0.977	0.025	0.042
Model 21	68.461	51	.052	-1031.351	-672.863	0.997	0.994	0.013	0.025
Model 22	99.871	56	.000	-1007.381	-677.345	0.992	0.987	0.019	0.030
Model 23	165.820	112	.001	-1018.173	-358.100	0.990	0.984	0.021	0.038
Model 24	239.155	123	.000	-949.174	-351.694	0.978	0.968	0.029	0.041

Model fit results support that a quadratic curve, with added parsimony of constrained residuals, best explained the changes in family functioning across time. In addition, the relationship between family functioning and externalizing problems was constrained to equality across time (Model 22). Results showed that constraining the effect of family functioning to equality across time maintained model fit. Model 22 was thus used as the baseline model for multigroup comparisons. Model 23 includes the addition of the grouping variable, and allows residuals and effects to vary between both groups, whereas model 24 constrains effects to equality between groups; the interpretation of model fit is found in the results section. The estimated parameters for Model 21 can be found in Table S8.

Table S8. The estimated parameters of growth curve model 22, modelling both externalizing problems and family functioning as a time-varying predictor.

Model 22	Externalizing Problems			Family Functioning		
	I	S	Q	I	S	Q
Sex (0=female,	0.057	-0.034	0.006	0.018	-0.024	0.005
1=male)	(0.008)**	(0.006)**	(0.001)**	(0.015)	(0.012)*	(0.002)*
SES	-0.009	-0.004	0.001	-0.084	0.022	-0.004
	(0.006)	(0.005)	(0.001)	(0.011)**	(0.009)*	(0.002)*
Estimated	0.265	-0.090	0.020	1.776	-0.183	0.022
means	(0.040)**	(0.034)**	(0.007)*	(0.008)**	(0.059)*	(0.014)
R-squared	0.058**	0.102*	0.103	0.045***	0.034	0.050

Note: $n_{OAD} = 761$. $n_{controls} = 1426$. I = Intercept, S = Slope, Q = Quadratic.

Estimated means are derived from the model, and estimated standard errors are in parentheses.

Unstandardized coefficients are presented with their standard errors in parentheses.

$* = p < .05$, $** = p < .001$.

Table S9. Simple slope comparisons between groups on paths a, b, and c across mediation models

	Slope difference (*SE)*	*CI* (95%)
Internalizing Problems		
Independent mediator (path a)	0.026 (0.021)	[-0.010, 0.068]
Mediator dependent (path b)	-0.03 (0.054)	[-0.135, 0.075]
Direct effect (path c)	0.011 (0.018)	[-0.026, 0.045]
Externalizing problems		
Independent mediator (path a)	0.026 (0.021)	[-0.014, 0.068]
Mediator dependent (path b)	0.001 (0.036)	[-0.070, 0.072]
Direct effect (path c)	0.009 (0.010)	[-0.011, 0.030]
Sexual risk behaviours		
Independent mediator (path a)	0.072 (0.044)	[-0.016, 0.154]
Mediator dependent (path b)	0.083 (0.063)	[-0.042, 0.209]
Direct effect (path c)	0.025 (0.039)	[-0.047, 0.104]

Note. *SE* = Standard Error, *CI* = Confidence Interval.