Risk factors and prevention in the offspring of parents with an affective disorder: associations between neuroendocrine function, the caregiving environment, and child emotional and behavioural problems

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ABSTRACT

Risk factors and prevention in the offspring of parents with an affective disorder: associations between neuroendocrine function, the caregiving environment, and child emotional and behavioural problems

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The offspring of parents with an affective disorder (OAD) are at high risk of developing mental disorders. This thesis examines the influence of hypothalamic-pituitary-adrenal (HPA) axis functioning and the caregiving environment on the transmission and prevention of psychopathology in the OAD. First, meta-analytic procedures were used to quantitatively summarize studies comparing diurnal cortisol levels in the natural environment in the OAD to control offspring. Relative to controls, the OAD had higher mean levels of cortisol at different timepoints throughout the day (Hedges' g = .21). These findings suggest that changes in HPA function may predate the onset of a full-blown affective disorder (AD). In the second study, data from a longitudinal study of offspring of parents with bipolar disorder (OBD) was used to study the relations between HPA axis functioning, the caregiving environment, and offspring psychopathology. As expected, the OBD who developed an AD had a higher cortisol awakening response (CAR) than OBD who did not have an AD (Cohen's d = 0.423) and controls (Cohen's d = 0.468). Serial mediation analyses revealed that family structure in childhood and the CAR in offspring mediated the relationship between risk status (having a parent with bipolar disorder) and offspring internalizing symptoms 12 years later (CI [.01, .66]). The last study aimed to evaluate the efficacy of the *Reducing Unwanted Stress in the Home* program using a quasi-experimental design with an assessment-only control group. Assessments were conducted at pre-

and post-intervention, and at a three- and six-month follow-up. Multilevel modelling revealed reduced externalizing symptoms in the OBD and enhanced family organization immediately post-intervention. The gains in organization remained at the six-month follow-up, while reductions in family conflict became apparent. Mediation analyses indicated treatment induced changes in organization, but not other aspects of the family environment, were associated with reduced externalizing problems in the OBD at the six-month follow-up. Taken together, HPA abnormalities may represent a biomarker of risk among the OAD which may be shaped, at least in part, by specific, early experiences in the caregiving environment. These findings highlight the need for targeted, developmentally-informed treatments to offset adverse outcomes in the OAD.

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Dedication

This piece of work is dedicated in loving memory of my mother, Luciana Ottoni, a woman who taught me to always believe in myself, to dream big, to pursue my goals with perseverance and to approach challenges fearlessly.

Contribution of Authors

This thesis consists of three manuscripts. The relative contributions of my colleagues to each manuscript is outlined below:

Study 1: Serravalle, L., Trespalacios, F., & Ellenbogen, M.A. (2023). Hypothalamic-pituitary-adrenal axis functioning in offspring of parents with an affective disorder: A meta-analytic review. [Manuscript submitted for publication]. Department of Psychology, Concordia University.

Lisa Serravalle conducted the systematic review, screened the articles, and coded the included studies. Florencia Trespalacios was the secondary coder. Lisa Serravalle conducted the statistical analyses and wrote the first draft of the manuscript. Lisa Serravalle and Mark Ellenbogen edited subsequent versions of the manuscript. All authors contributed to and approved the final manuscript.

Study 2: Serravalle., L., Walker, D-L., Walker, E., Hodgins, S., & Ellenbogen, M.A. (2023). Structure provided by parents in middle childhood predicts cortisol levels and internalizing symptoms 12 years later among the offspring of parents with bipolar disorder. [Manuscript submitted for publication]. Department of Psychology, Concordia University.

Elaine Walker, Sheilagh Hodgins, and Mark Ellenbogen contributed to the design of the study. Dominique Walker conducted the cortisol immunoessays and contributed to interpretations of the cortisol data. Lisa Serravalle conducted the statistical analyses and wrote the first draft of the manuscript. Lisa Serravalle and Mark Ellenbogen edited subsequent versions of the manuscript. All authors approved the final manuscript.

Study 3: Serravalle. L, Iacono, V., & Ellenbogen, M.A. (2023). Reductions in offspring externalizing problems and improvements in the home following a prevention program for families with a parent with bipolar disorder: A pilot study. [Manuscript submitted for publication]. Department of Psychology, Concordia University.

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

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Chapter 1: General Introduction

Affective disorders (AD), including major depressive disorder (MDD) and bipolar disorder (BD), impact populations worldwide and are associated with significant societal cost (Bessonova et al., 2020; Greenberg et al., 2021; Zhdanava et al., 2021). Having a parent with a severe mental illness, such as MDD and BD, put offspring at risk for psychopathology throughout their lifespan (Thorup et al., 2018). The risk for mental disorders in these high-risk youth is not specific to affective disorders. In fact, the offspring of parents with an affective disorder (OAD) have greater lifetime prevalence rates of a host of mental health disorders compared to offspring of parents with no history of an affective disorder (e.g., Lau et al., 2018; Mesman et al., 2013; Vandeleur et al., 2012). The OAD also often face various socio-emotional, behavioural, academic and occupational difficulties throughout development (e.g., Nijjar et al., 2014). The familial transmission of mental disorders among families having a parent with an AD is complex and multifactorial (Maciejewski et al., 2018; Remes et al., 2021; Sawyer et al., 2019). Thus, the OAD represent a vulnerable group of youth that require ongoing research efforts to better understand how risk is conferred. This knowledge can then be translated into preventive intervention programs targeting malleable risk factors to ultimately offset adverse outcomes in offspring (Maciejewski et al., 2018).

The present thesis focuses on risk factors and preventive intervention in the OAD. The diathesis-stress (or vulnerability-stress; Rosenthal, 1963; Zuckerman, 1999), adaptation calibration (Del Giudice et al., 2011), and social buffering (Hostinar et al., 2014) models serve as the theoretical frameworks of this research, as well as transactional models of psychopathology (Cicchetti & Toth, 1997). In the context of the OAD, these models posit that offspring possess a vulnerability to stress and highlight the bi-directional transactions between youth and their

environment as a significant contributor and buffer to risk. First, we will quantitatively summarize the literature on dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis, one of the most robust and consistent findings in the etiology of ADs (Bao & Swaab, 2019; Ellenbogen et al., 2019), in the OAD. Using a 10-year longitudinal cohort project on families with a parent having BD, we will then examine the associations between alterations in HPA axis functioning in youth, the early caregiving environment, and the development of offspring psychopathology. In the final study, we focus on knowledge translation and the application of past research to prevention. We examine the efficacy of the Reducing Unwanted Stress in the Home (RUSH) program, a treatment designed to reduce adverse outcomes in offspring by targeting stress in the early caregiving environment of families with a parent having BD.

Affective disorders and their impact on individuals, families, and society

MDD is amongst the most common mental health disorders affecting populations worldwide. In North America, MDD affects approximately 16.2% of adults in the United States (Kessler et al., 2003) and 12.2% of individuals aged 15 and above in Canada (Patten et al., 2006). Based on a review and meta-analysis of epidemiological studies in adult bipolar disorder, the lifetime prevalence rate of any bipolar spectrum disorder was 1.02% (Moreira et al., 2017). In a separate large-scale meta-analysis of epidemiological studies examining the age of onset of mental disorders worldwide, a significant rise in the prevalence of ADs begins in adolescence with the peak age being in young adulthood (Solmi et al., 2021).

The burden of disease of ADs comes with significant costs to society at large (Bessonova et al., 2020). In recent years, the total annual economic cost of MDD and BD in the United States was approximately $326 billion and $195 billion, respectively (Bessonova et al., 2020; Greenberg et al., 2021). While 25-35% of these figures stem from direct medical costs (e.g.,

emergency room visits, outpatient/inpatient services, pharmaceutical expenditures), the majority of the national economic burden of ADs is a result of indirect costs related to unemployment and losses in work productivity for both patients and caregivers. Some of the factors that have been found to drive total costs are the presence of co-morbid medical or psychiatric conditions, being in an active mood episode, and non-adherence to treatment (Bessonova et al., 2020; Ekman et al., 2013).

MDD is primarily characterized by low mood and/or anhedonia, with varying combinations of other symptoms, including fatigue, lethargy, psychomotor agitation, lack of concentration, sleep disturbances, significant changes in appetite/body weight, and suicidality. These symptoms occur for a minimum of two consecutive weeks and cause functional impairment (Diagnostic and statistical manual of mental disorder, 5th ed. (DSM-5); American Psychiatric Association, 2013). As described in the DSM-5 (American Psychiatric Association, 2013), BD is characterized by episodes of (hypo)mania and major depression. Manic episodes are described as a persistently elevated or irritable mood accompanied by abnormally high levels of energy and goal-directed behaviour that occur for a minimum of one consecutive week. During this period, the person may experience feelings of grandiosity, a reduced need for sleep, flight of ideas, distractibility, and/or risk-taking behaviour. Hypomanic episodes consist of the same symptoms but for a shorter period of time (four consecutive days). The two main types of BD include BD-1 (requires a minimum of one manic episode in the individual's lifetime) and BD-2 (requires a minimum of one hypomanic and one depressive episode in the individual's lifetime). While both MDD and BD are episodic in nature, symptoms often persist in between mood episodes (Grover et al., 2021; Zajecka et al., 2013).

In addition to the debilitating symptoms, individuals with an AD have greater functional impairment across various life domains compared to comparison groups, including occupational functioning, cognitive ability, interpersonal relationships, leisure and finances (e.g., Evans et al., 2013; Léda-Rêgo et al., 2020; Whisman, 2017). In fact, data has shown that individuals with MDD experience greater functional impairment than individuals with chronic illness in terms of psychosocial disability, decreased workplace productivity, and increased work absenteeism (Lépine & Briley, 2011). The burden of disease in ADs is on the rise; the number of disability-adjusted life years (the sum of years of life lost due to premature mortality and years lived with disability) in individuals with MDD increased by 38% from 1990 to 2010 (Murray et al., 2012) and MDD was ranked amongst the top ten most common causes of burden in Canada (Murray et al., 2015). One of the most commonly cited contributing factors of functional impairment are the residual depressive symptoms between mood episodes (Léda-Rêgo et al., 2020; Xiao et al., 2018). The strong link between ADs and suicide is yet another example of the significant impact ADs have on individuals and their close ones (Baldessarini, 2020). With rates greater than 20-30 times that of the general population, individuals with BD are at the largest risk for suicide across all psychiatric conditions (Plans et al., 2019). Taken together, the impact of ADs on the affected and surrounding individuals as well as society as a whole is profound and far-reaching. The following section will narrow in on the impact of ADs in parents on their offspring.

The effects of affective disorders in parents on offspring mental health and other areas of functioning

Lifetime prevalence rates of ADs are substantially greater in the OAD compared to controls. Several studies have shown lifetime prevalence estimates of any AD to be above 20% in the OAD (Sandstrom et al., 2020; Vandeleur et al., 2012). Based on a 30-year longitudinal

study, the OAD are at a three- to four-fold risk of developing MDD compared to offspring of parents with no history of MDD (Weismann et al., 2016). The OBD specifically are between 10-15 more likely to develop a bipolar spectrum disorder and typically experience their first mood episode at a younger age compared to offspring of parents with a non-BD psychiatric diagnosis and offspring of healthy parents (Mesman et al., 2013; Nijjar et al., 2014; Birhamer et al., 2021; Vandeleur et al., 2012). In line with the phenomenon of assortative mating (Merikangas & Spiker, 1982), individuals with an affective disorder are more likely to select partners who also suffer with mental health challenges (Matthews et al., 2001; Serravalle et al., 2020). Having both biological parents with an AD increases the risk of psychopathology in offspring by two-fold (Vandeleur et al., 2012).

The increased risk of mental health disorders in the OAD is not specific to ADs. Research has shown that the OAD are at increased risk of developing various other mental health and neurodevelopmental disorders across the lifespan, as well as increased co-morbidity between conditions (e.g., Birmaher et al., 2021; De la Serna et al., 2021; Propper et al., 2023). There is data to suggest that neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, communication disorders, motor disorders as well as intellectual and learning disabilities, are more prevalent in offspring of parents with MDD (Odds ratio = 1.87) and BD (Odds ratio = 2.34) compared to controls. Differences in the number of neurodevelopmental disorders can be observed as early as the preschool years, especially in the rates of ADHD in the OBD (Birhamer et al., 2021). After the age of five years old, the OAD begin to experience other mental disorders, including anxiety, substance abuse, and disruptive disorders (e.g., Birhamer et al., 2021; Lau et al., 2018; Vandeleur et al., 2012). Moreover, the OAD are more likely to have co-morbidity between axis-I and axis-II (personality) mental

disorders (Fan & Hassel, 2008; Merikangas et al., 2011). There is evidence to suggest a bi-directional transaction between the clinical course of parent AD and offspring psychopathology. Specifically, recent exposure and greater severity of parental depression has been shown to exacerbate mood symptoms in their children (Mars et al. 2012), while depressive symptoms and behaviour problems in offspring can predict episode recurrence in mothers (Baker et al., 2020; Sellers et al., 2016). Studies using cross-lagged statistical procedures have further elucidated the transactional nature of the relation between ADs and offspring psychopathology (Hails et al., 2018).

Compiled with these mental health challenges, the OAD are at risk of various non-psychiatric difficulties throughout development. While the findings on intellectual functioning in the OAD are mixed (Klimes-Dougan et al., 2017), a number of studies have identified neurocognitive and executive dysfunctions in this high-risk population. Relative to healthy controls, the OAD have been shown to have impairments in mental flexibility, inhibitory control, working memory, and processing speed (e.g., de la Serna et al., 2016; Meyer et al., 2004; Park et al., 2018). Difficulties in executive functions related to emotion control and affective lability have also been documented in the OAD (Spang et al., 2017; Zwicker et al., 2020). Partly driven by shortcomings in executive functioning (Pearson et al., 2016), exposure to parental AD across different points of development has been associated with poorer academic performance in offspring, as indexed by low grades, difficulty achieving educational milestones, and diminished likelihood of graduation (Brophy et al., 2021; Ranning et al., 2018; Shen et al., 2016). A tendency towards sensation seeking (Chang et al., 2003; Jones et al., 2006), along with the accompanying risky behaviours (Nijjar et al., 2014), have also been observed in the OAD. Socially, the OAD tend to have greater difficulty than their healthy peers in developing and

maintaining positive relationships with their family, friends, and intimate partners (Hammen et al., 2008; Linnen et al., 2009). They are also more likely to experience interpersonal stressors, such as conflict with others and relationship dissolution, that are dependent on their own behaviour (Gershon et al., 2011; Ostiguy et al., 2009).

Given the many mental health, neurocognitive, academic, and social challenges that the OAD face, it is not surprising that these youth tend to experience significant reductions in their quality of life compared to their low-risk counterparts (Goetz et al., 2017). Taken together, the OAD represent a vulnerable population that are at-risk of a host of adverse outcomes. For this reason, researchers have investigated different pathways of the intergenerational transmission of ADs to identify the salient factors that confer risk in the OAD. In the next section, the various genetic, biological, and environmental factors that have been associated with having a parent with an AD will be outlined.

Genetic, biological and environmental factors associated with the intergenerational transmission of risk in the offspring of parents with an affective disorder

Genetic and brain basis of affective disorders

Over four decades of research on the genetics of MDD and BD have highlighted the contribution of shared genes in the intergenerational transmission of ADs. Earlier family-based studies provided preliminary evidence for familial aggregation of ADs, with increased risk in first-degree relatives of individuals with an AD (Fiedorowicz et al., 2012; Sullivan et al., 2000). Using sophisticated methodologies involving twin and adopted offspring, researchers have accumulated further support for the influence of shared genes, with the proportion of variance in BD due to genetic contributions, or heritability estimates, being between 70-90% (see Gordovez et al., 2020 for a review). Moderate heritability estimates (between 29-49%) have also been

found in MDD (see Kendall et al., 2021 for a review). Based on a growing number of genome-wide association studies, the risk for ADs is considered to be polygenetic in nature, with each genetic loci contributing small effects (see Sandstrom et al., 2019 for a review) and involves genetic variants that have considerable overlap with other mental health disorders, namely schizophrenia (e.g., Taylor et al., 2019; Wu et al., 2020).

Gottesman and Gould (2003) were one of the first to introduce the possibility of endophenotypes bridging the gap between genetics and psychiatric diagnoses, which has been explored in the context of ADs (e.g., Hasler et al., 2004, 2006). An endophenotype is described as a latent, but measurable trait that is heritable and presents in persons with, or at risk of developing, a disorder. Numerous candidate endophenotypes have been identified in the OAD. Researchers have outlined functional and anatomical differences in brain regions and networks involved in various psychological functions, such as socio-emotional processing (Foland-Ross et al., 2015; Hirshfeld-Becker et al., 2019), goal-directed behaviour (e.g., working memory, problem-solving; Minami et al. 2022), and reward sensitivity (Alloy et al., 2016). The corresponding behavioural manifestations of these brain abnormalities as endophenotypes of ADs have also been well-documented. For example, compared to controls, the OAD have been found to display an oversensitivity to emotion cues in facial expressions (Lopez-Duran et al., 2013), a negative bias when interpreting and attending to emotional stimuli (Joorman et al., 2007; Kujawa et al., 2011), and greater difficulty identifying emotional faces accurately (Hanford et al., 2016; Székely et al., 2014), unless provided with salient emotional information (Brotman et al., 2008; Joorman et al., 2010).

Several biological processes following a circadian rhythm are also being debated as potential endophenotypes of ADs (Dallaspezia et al., 2021), including immune, sleep, and stress

regulatory systems (Duffy et al., 2012; Feng, 2020; Sebela et al., 2019). One of the key biological factors that has been long studied in relation to ADs (Bao & Swaab, 2019; Ellenbogen et al., 2019), and one of the main focuses of this thesis, is dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis plays an important role in mediating the effects of stress in the central nervous system and is particularly important in shaping various outcomes across development, as alterations in the HPA axis may reflect upward or downward adaptations in response to the experience of adversity, including parental mental illness (Del Giudice et al., 2011).

Biological sensitivity to stress: hypothalamic-pituitary-adrenal axis

The HPA axis is an important neuroendocrine system responsible for orchestrating the mammalian stress response by regulating various bodily functions. This biological process can be described as a cascade of hormonal releases, starting with the hypothalamic release of corticotropin-releasing hormone, which activates the release of adrenocorticotropic hormone from the anterior pituitary gland, finally stimulating the release of cortisol from the adrenal cortex (Spencer & Deak, 2017). Basal patterns of cortisol, or the natural fluctuations in cortisol levels that occur throughout the day, follow a circadian rhythm. Specifically, cortisol levels will sharply increase within the first 30 minutes of awakening, followed by a short period of steep decline which eventually decreases at a more steady rate until bedtime (Nicolaides et al., 2014; Nicolson, 2007). The cortisol rise in response to awakening (CAR) has been of particular interest as alterations in this measure of HPA functioning has been shown to predict later AD in pediatric (Adam et al., 2010) and adult populations (Harris et al., 2000). In moments of acute stress, cortisol is quickly released to mobilize energy resources and prepare the individual to act, and

then will remain elevated until the threat dissipates and the body can return to its resting state via a negative feedback loop (Nicolaides et al., 2014).

Alterations in the HPA axis across development in individuals with a diagnosis of AD have been well-documented in the literature. Based on multiple meta-analytic reviews, the overall pattern of cortisol secretion in youth, adults, and elderly persons with an AD suggest elevations in mean levels of cortisol throughout the day and in response to an acute stressor compared to controls (Knorr et al., 2010; Lopez-Duran et al., 2009; Murri et al., 2014, 2016; Stetler & Miller, 2011). There is also evidence to suggest that high levels of basal cortisol tend to persist during periods of remission (Beluche et al., 2009). As in pertains to the OAD, Klimes-Dougan and colleagues (2022) recently provided a qualitative summary of the literature on HPA axis functioning in the OAD. Similar to the HPA axis hyperactivity seen in symptomatic individuals (Knorr et al., 2010; Lopez-Duran et al., 2009; Murri et al., 2014, 2016; Stetler & Miller, 2011), the OAD display higher levels of cortisol levels throughout the day and a pattern of hyperarousal in their stress reactivity, especially for social challenges.

While these findings suggest that HPA axis dysregulation in ADs can be characterized by a hyperactivation of this system, opposite patterns in cortisol levels have been observed. For example, Maripuu and colleagues (2017) found lower or blunted HPA axis activity in older individuals with BD. Evidence of hypocortisolism has also been found in individuals remitted from recurrent MDD (Ahrens et al., 2008). Another study demonstrated mixed findings. Specifically, females with MDD demonstrated decreased levels of plasma cortisol, while males and older individuals with MDD had increased levels, compared to controls (Bremmer et al., 2007). These inconsistencies have led some researchers to believe that HPA axis dysregulation is less likely to be a risk factor of ADs, but rather a pathophysiological mechanism that impacts the

clinical course of ADs (Murri et al., 2016). Other researchers have suggested that dysregulation of the HPA axis may represent both a trait and state biomarker of disease in ADs (Duffy et al., 2012). Changes in the HPA axis functioning have also been speculated to be a result of disruptions in their environment (Klimes-Dougan et al., 2022). Indeed, longitudinal data have shown that the OBD who were exposed to adverse childhood environments demonstrated a stronger stress response than healthy controls (Ellenbogen & Hodgins, 2009; Mackrell et al., 2014). Thus, the childrearing environment represents yet another potential risk factor relevant to the intergenerational transmission of ADs.

Exposure to suboptimal childrearing environments

The nature of the clinical features of ADs can introduce elevated levels of disruption and instability into the lives of the affected individuals and their families. In addition to the typically recurrent mood episodes that can last months and the chronic residual symptoms that tend to persist between episodes (Grover et al., 2021; McIntyre & Calabrese, 2019; Zajecka et al., 2013), individuals with ADs experience elevated levels of substance abuse (Crowe et al., 2022), job instability (Lépine & Briley, 2011), hospitalization (Desai et al., 2020), and risk of suicide (Baldessarini, 2020). It is thus not surprising that families with a parent having an AD are often faced with high levels of parental absenteeism (Pini et al., 2005) as well as marital conflict and divorce (Lam et al., 2005; Madigan et al., 2017; Serravalle et al., 2020). There is also evidence to suggest that parents with an AD and their intimate partners possess various maladaptive personality traits and experience difficulties in their psychosocial functioning (Dudley et al., 2001; Serravalle et al., 2020). Specifically, both parents with BD and their intimate partners display high levels of neuroticism, more emotion-focused coping, and poor perceived social support compared to their healthy counterparts. Compared to controls, low levels of

agreeableness and conscientiousness as well as frequent exposure to negative life events appeared specific to parents with BD, while their intimate partners uniquely displayed low levels of extraversion (Serravalle et al., 2020). Similar findings have been outlined in individuals with MDD and their partners (Dudley et al., 2001).

Individuals with an AD and their intimate partners are not the only dyadic relationship to suffer challenges within the caregiving environments of the OADs. With regards to parent-child relationships, parents suffering from an AD tend to display and perceive more negativity in their interactions with their offspring (Doucette et al., 2016; Lovejoy et al., 2000), and lack sensitivity and flexibly in responding to their child's needs (Lunkenheimer et al., 2013; Stein et al., 2012) as well as mutual responsiveness/reciprocity (Anke et al., 2019; Serravalle et al., 2020). Partners of mothers with MDD display similar patterns in parent-child interactions (Vakrat et al., 2018). The OAD appear to be conscious of these disruptions in family functioning, as they tend to perceive their relationship with their parents and their home life as more problematic relative to controls (Goetz et al., 2017). Impairments within the overall family dynamics are also present. Stapp and colleagues (2020) recently provided a qualitative summary of the extant literature on the caregiving environment of families with a parent having BD. The most consistent finding across studies was a lack of cohesion (i.e., displays of commitment and support) in these high-risk families. The remainder of the findings were mixed. When compared to families with parents having no history of psychiatric illness or US normative samples, some studies demonstrated evidence of both lower and higher levels of expressiveness (i.e., the degree to which emotional expression is encouraged) as well as poor structure/organization (i.e., the amount of planning that goes into family activities/responsibilities) in families with a parent having BD. Other studies found no difference in these aspects of family functioning. Difficulties with the family

dynamics have also been described in the context of parental MDD (Riley et al., 2008; Sharma & Sharma, 2022).

Summary of contributing factors in the intergenerational transmission of risk in the offspring of parents with an affective disorder

While the OAD are at elevated risk of mental health challenges and other adverse outcomes, there are many offspring who display resilience (Collishaw et al., 2016; Lewandowski et al., 2014). This suggests that the intergenerational transmission of ADs is complex and likely involves the interplay between genetics and the environment. A gene-environment interaction describes the differential influence the environment can have on individuals that vary in genotype (Ottman, 1996). Gene-environment interactions can be understood through a diathesis-stress framework, such that individuals of a certain genotype may be more susceptible to environmental stress (Rosenthal, 1963; Zuckerman, 1999). Thus, part of the intergenerational transmission of ADSs in families occurs through genetic mechanisms, which may involve the inheritance of risk factors, such as structural and functional brain abnormalities related to various important psychological processes. Dysregulation in the HPA axis has been emphasized as a potential biomarker of risk and/or biological correlate of ADs. Based on theories that have emphasized the importance of the interactions between a parent and child (Ainsworth, 1985; Bowlby, 1982) and within the family (Sameroff & Fiese, 2000) on child development, the role of the caregiving environment has also been identified as a key factor in the intergenerational transmission of ADs. To be considered a risk factor, the variable must not only be correlated with negative consequences, but also *precede* the onset of these adverse outcomes (Kraemer et al., 1997). Research implementing prospective study designs across the lifespan have allowed us to further elucidate the role of various contributing factors in this field of research. As previously

mentioned, we will focus on HPA axis functioning and the caregiving environment as important risk factors for psychopathology in the OAD.

Predicting psychopathology in the offspring of parents with an affective disorder from alterations in hypothalamic-pituitary-adrenal axis functioning and the caregiving environment

Dysregulation in hypothalamic-pituitary-adrenal axis and psychopathology in the offspring of parents with an affective disorder

The study of HPA axis functioning predicting later psychopathology in the OAD remains limited. Evidence from large community-based longitudinal studies have provided some insight into this topic. For example, the Tracking Adolescents' Individual Lives Survey (TRAILS) tracks the development of a large cohort of youth from adolescence to young adulthood. In terms of their longitudinal findings, there was no association found between abnormalities in the CAR in early adolescence and the development of MDD three years later (Nederhof et al., 2015). In a separate longitudinal study that included a large sample of high-risk youth (oversampled for high neuroticism), an amplified CAR predicted a significant increase in risk of developing MDD one year later, even when adolescents with MDD at baseline were excluded from the analyses (Adam et al., 2010).

As in pertains to the OAD, six-month old infants of mothers with MDD who exhibited a blunted response immediately after exposure to a social stressor exhibited greater behaviour problems during toddlerhood compared to controls (Lawler et al., 2019). Hypocortisolism in offspring of parents with a history of MDD during middle childhood has also been associated with elevated levels of internalizing symptoms over a one-year period (Badanes et al., 2011). In older offspring, it was elevated levels of morning cortisol in early adolescence that mediated the

relation between exposure to postnatal maternal MDD and offspring depressive symptomatology at 16 years of age (Halligan et al., 2007). Based on a subsample of high-risk and control offspring from the Flourish Canadian Offspring Cohort Study, total cortisol output throughout the day and evening levels of cortisol increased the risk of a new onset AD or recurrence by 2.7 and 3.5 times, respectively, in the OBD compared to offspring with low genetic risk of BD (Goodday et al., 2016). Ellenbogen and colleagues (2011) found that elevated daytime cortisol levels predicted a two-fold increase in the risk of an AD up to six years later in youth, regardless of a history of BD in parents. There is evidence to suggest that pubertal stage may moderate the relation between HPA axis functioning in the OAD and subsequent psychopathology. Specifically, hypoactivity in early pubertal development and hyperactivity in later pubertal development have been associated with later risk of MDD in daughters with no history of ADs, but these youth were majorly at high-risk due to a maternal history of MDD (Colich et al., 2015). Taken together, alterations in the HPA axis may be one way in which risk for psychopathology is transmitted to the OAD.

Suboptimal caregiving environments and psychopathology in the offspring of parents with an affective disorder

Longitudinal associations between having a parent with an AD, suboptimal caregiving environments, and offspring psychopathology is another developing area of research among the OAD. The impact of parent-child relationships on offspring psychopathology within the context of MDD in mothers has been a main area of focus in this field of literature. In a large sample of mothers and their children, maternal warmth and hostility during early adolescence were found to mediate the relation between maternal MDD and offspring psychopathology measured approximately 2.5 years later (Sellers et al., 2014). Specifically, maternal hostility increased the

risk for offspring psychopathology while maternal warmth acting as a protective factor. Exposure to maternal MDD in early development has also been associated with offspring psychopathology at age 3 as a function of greater parenting stress and lower maternal sensitivity and parenting self-efficacy (Russotti et al., 2022). In both these studies, co-morbid antisocial behaviours in mothers with MDD was found to exacerbate the impact of parent-child relationship on offspring mental health. A lack of maternal sensitivity and low parenting self-efficacy in mothers mediating the relation between maternal MDD and offspring psychopathology has been replicated in other samples (Ahun et al., 2018; Bödeker et al., 2019), and poor dyadic affective flexibility has also been shown to play a role (Lunkenheimer et al., 2013). Negative consequences, including child internalizing/externalizing problems and frontal lobe dysfunction, of difficulties in the parent-child relationship have been documented within the context of paternal MDD (Kane & Garber, 2009) and parental BD (Meyer et al., 2006).

At the level of the family unit, expressed emotion (i.e., the intensity and range of negative and positive emotions that are openly expressed) between family members is has been long viewed as an important risk factor for ADs. Specifically, high levels of expressed emotion in the family have been considered an important pathway from history of ADs in parents to offspring internalizing and externalizing problems (Nelson et al., 2003; Schwartz et al., 1990; Silk et al., 2009; Tompson et al., 2010; Yeh et al., 2016). A subset of studies have examined other aspects of family functioning in predicting prospective offspring psychopathology in the OAD and have found mixed findings. In an adolescent sample, elevated family conflict was found to mediate the association between maternal and offspring depressive symptoms, while positive family problem-solving promoted positive emotions in high-risk youth (Yeh et al., 2016). In the OBD, parental control (i.e., disciplinary control, monitoring of activities) in middle childhood

presented as the strongest predictor of offspring substance abuse and depressive symptoms up to 12 years later (Iacono et al., 2018). Similarly, exposure to higher levels of family conflict was associated with future affective disorder in the OBD (Du Rocher Schudlich et al., 2008). Conversely, a longitudinal study conducted by Koenders and colleagues (2020) found that childhood trauma, but not family functioning, was associated with future affective disorder onset in the OBD. Overall, there is evidence to suggest that suboptimal caregiving environments may represent another mechanism of risk for psychopathology in the OAD.

Incorporating a prevention-science framework in the study of the intergenerational transmission of risk for affective disorders

As recently outlined by one of the leading researchers in the field (Gotlib et al., 2020), incorporating a prevention-science framework into the study of the intergenerational transmission of risk in ADs serves two important purposes. First, preventive interventions that target malleable environmental factors predictive of psychopathology in the OAD provides us with further insights into mechanisms of risk. That is, if a specific environmental risk factor is targeted in treatment and the population of interest shows improvement, then that environmental factor may represent an important mechanism of risk. Second, it allows for the development of innovative treatment approaches tailored to the needs of target populations, such as the OAD. In contrast to universal prevention measures that target the general population, selective prevention is intended to serve unaffected individuals or subgroups of the population whose risk of developing negative outcomes is significantly higher than the general public by virtue of biological, psychological or social risk factors (Hage et al., 2007). Selective prevention in the OAD represents the final focus of this thesis, starting by outlining the existing treatment program aimed at reducing offspring psychopathology in this high-risk population.

Selective preventive intervention programs for the offspring of parents with an affective disorder

Prevention of psychopathology in offspring of parents with major depressive disorder

In a recent systematic review and meta-analysis, Loechner and colleagues (2018) identified fourteen articles that evaluated the effectiveness of five different preventive interventions designed to reduce depressive symptoms in never-depressed OAD using a randomized controlled design. Psychoeducation about MDD and building stress resilience in parents and/or children were common components across preventive interventions. The family members involved (parents, offspring, or both), the age range of offspring, and the number of sessions varied across treatment programs. For example, Family Talk Intervention is a preventive intervention program that was designed for youth aged 8-15 years old (Beardslee et al., 1997). Sessions focus on psychoeducation and family communication that include the whole family as well as individual sessions for parents and offspring. In contrast, Coping with Depression is a preventive intervention program that mainly focuses on teaching cognitive behavioural therapy (CBT) techniques, such as cognitive restructuring and problem-solving, to help adolescents (13-18 years old) cope with having a parent with MDD (Clarke et al., 2001). The Raising Healthy Children program combines elements from both Family Talk Intervention and Coping with Depression programs by offering psychoeducation and CBT strategies throughout individual parent and child sessions, as well as combined family sessions.

Across these preventive intervention programs, there was evidence of immediate effects on pre- to post-treatment depressive (or internalizing) symptoms (up to 4 months follow-up; Hedges g' = -.20), but little evidence for treatment effectiveness at short-term (5-12 month follow-up; Hedges g' = -.11) and long-term (15-72 month follow-up; Hedges g' = -.05) follow-

up (Loechner et al., 2018). The magnitude of the immediate treatment effects is comparable to interventions designed for children and adolescents with MDD (Hedges g' = -.32; Hetrick et al., 2016). These data provide support that preventive intervention programs aimed at reducing psychopathology in the OAD prior to the development of mood symptoms is a worthwhile research and clinical endeavour, with the caveat that treatment effects seem to dissipate over time.

Prevention of psychopathology in the offspring of parents with bipolar disorder

To date, the efficacy of preventive intervention programs for OBD is majorly based on Adapted Family-Focused Therapy, a psychosocial intervention designed for OBD who already evidence symptoms of an AD, such as a lifetime diagnosis of major depressive disorder (MDD) or subthreshold BD (Miklowitz & Chung, 2016). The efficacy of Adapted Family-Focused Therapy in improving various clinical outcomes, such as reducing recovery periods, increasing intervals between mood episodes, and lengthening time in remission, has been demonstrated across multiple randomized controlled trials (RCTs; e.g., Miklowitz et al., 2015; Miklowitz et al., 2020). Interpersonal and Social Rhythm Therapy is another psychosocial treatment that has been shown to optimize clinical course in a similar sample (Goldstein et al., 2018). While there has been significant efforts and promising findings in treatments for symptomatic high-risk youth, prevention efforts aimed at improving clinical outcomes among the OBD *prior* to the onset of clinical mood symptoms have mostly emerged in recent years.

In an earlier study, a web-based parenting program based on the Triple-P Positive Parenting programme was compared to a waitlist control condition in a sample of parents with BD (diagnosed via self-report questionnaires; Jones et al., 2014). Parents in the intervention group reported decreases in child behaviour problems from pre- to post-intervention compared to

controls. Based on data from a recent pilot study (Cotton et al., 2020), the long-term effects of Mindfulness-Based Cognitive Therapy for Children on anxiety and emotion regulation in OBD aged 9-18 years old was examined in comparison to a waitlist control group. The OBD included in this study did not have a history of clinical mood disturbances, but had a diagnosis of an anxiety disorder. The results indicated that overall clinical severity in the OBD seemed to improve following treatment compared to the waitlist control group. Significant changes in clinician- and child-rated anxiety and emotion regulation were only observed in children who demonstrated increases in mindfulness following treatment. Using a quasi-experimental design, Wirehag Nordh and colleagues (2022) compared two manual-based preventive interventions, Family Talk Intervention and Let's Talk about Children, to interventions as usual. The studies included offspring aged 8-17 years old of individuals diagnosed with an anxiety disorder, MDD or BD. Both preventive intervention programs focus on teaching parenting strategies and skills to enhance family communication. The results revealed reductions in parent-rated mental health problems in offspring who participated in either treatment program, while those in the control group demonstrated increases in psychopathology from baseline to 12 months follow-up. Developed by our research team, the Reducing Unwanted Stress in the Home (RUSH) program is another example of a preventive intervention program designed to offset adverse outcomes in the OBD prior to the onset of serious mood symptoms.

The RUSH program is a 12-weeks, cognitive-behavioural preventative intervention program that teaches parents and their children how to cope with stress, problem-solve, and communicate more effectively, with an additional focus for parents to better manage child behavior and improve organization and consistency in the home. Similar to the Raising Healthy Children program for offspring of parents with MDD and Family-Focused Therapy for

symptomatic OBD, the RUSH program includes both parents and their offspring to *simultaneously* target challenges in the family system. In addition, the RUSH program is designed as an *early* preventive intervention as it exclusively targets children in middle childhood (6-11 years old). A more detailed description of the RUSH program as well as efficacy findings will be discussed in Chapter 4.

Rationale and goals of the current thesis

The three primary goals of this dissertation are to: 1) quantitively summarize HPA axis functioning in the OAD, 2) examine the associations between HPA axis functioning, suboptimal caregiving environments and the development of psychopathology in the OAD, and 3) establish preliminary efficacy for the RUSH program, a selective preventive intervention aimed at reducing offspring internalizing and externalizing problems in the OAD via improvements in the early caregiving environment.

Specifically, in **Chapter 2** (Study 1), we will use meta-analytic statistical procedures to quantitatively summarize studies comparing HPA axis functioning in the OAD to control offspring. We will focus on diurnal cortisol levels in the natural environment as indexed by mean levels of cortisol at discrete timepoints throughout the day, the CAR, and total daily cortisol output. Efforts to summarize studies examining HPA axis functioning in individuals with ADs have been conducted in pediatric, adult, and elderly populations (Knorr et al., 2010; Lopez-Duran et al., 2009; Murri et al., 2014, 2016; Stetler & Miller, 2011). While Klimes-Dougan and colleagues (2022) have recently provided a comprehensive qualitative summary of HPA axis functioning in the OAD, we aim to examine the topic quantitatively and obtain effect sizes of various indices of diurnal cortisol in the unaffected OAD. These estimates can then be compared to previous meta-analyses on affected populations. Consistent with previous speculations (Duffy

et al., 2012; Gotlib et al., 2020; Hammen, 2017), an aggregation of the existing literature will allow us to explore whether alterations in HPA predate the onset of a full-blown AD. We will also conduct several exploratory analyses on various characteristics of the sample and methodological features of cortisol measurement that may moderate the relation between an AD in parents and diurnal cortisol in their offspring.

In **Chapter 3** (Study 2), we used a prospective cohort study that followed a sample of OBD from middle childhood until adolescence/young adulthood to gain further insight into HPA axis functioning and its relation to the caregiving environment and offspring psychopathology in this high-risk population. We first examined whether the CAR is heightened in the OBD with an AD relative to the OBD with no history of an AD and a control sample. Next, we tested whether parenting structure/organization in middle childhood and the CAR in offspring mediated the relation between having a parent with BD and offspring depressive symptoms up to 12 years later. Implementing a longitudinal design with a control group will allow us to identify the direction of effect and whether these mechanisms are specific or more pronounced in the OBD relative to control offspring. The study of parenting practices and its relation to HPA functioning in OBD allows us to examine whether the data support the social buffering hypothesis, which posits the environment acts as a modulator of stress-mediating neurobiological systems.

Lastly, **Chapter 4** (Study 3) aimed to integrate knowledge on potential risk factors in the OBD and prevention science by evaluating the efficacy of the RUSH program. As previously described, the RUSH program is a novel treatment approach designed as a function of research on the individual and environmental risk factors associated with poor mental health functioning in the OBD. We will focus on evaluating the primary outcomes: offspring internalizing and externalizing problems and aspects of the caregiving environment. The study was designed as a

proof-of-concept clinical trial of the RUSH program, in which offspring internalizing and externalizing problems, and aspects of the caregiving environment, in the OBD were compared to a sample of age-matched controls who completed all assessments, but did not participate in the RUSH program. Future evaluations of the RUSH program would then include RCT designs, the 'gold standard' of program evaluation. First, we sought to evaluate offspring internalizing and externalizing problems, and family functioning, prior to and following participation in the RUSH program, in comparison to the control group. Second, we aimed to investigate changes in the caregiving environment as possible mediators of the relations between participating in the RUSH program and offspring's internalizing and externalizing symptoms six months later. This latter goal would provide further support of the caregiving environment as a salient factor to consider in the intergenerational transmission of ADs and as an important treatment target in preventive intervention of high-risk youth.

Chapter 2: Hypothalamic-pituitary-adrenal axis functioning in offspring of parents with an affective disorder: A meta-analytic review

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Abstract

Because the offspring of parents with an affective disorder (OAD) are at high risk for developing mental disorders, and persons with an affective disorder (AD) show dysfunctional hypothalamic-pituitary-adrenal axis activity, changes in HPA functioning in OAD might be an etiological risk factor that precedes the development of ADs. The primary aim of the meta-analysis was to quantitatively summarize the existing data on different indices of diurnal cortisol in the OAD. The secondary aim was to explore potential moderators of this relation. Following PRISMA guidelines, we included 26 studies (3,052 offspring) on diurnal cortisol in our meta-analysis after an initial screening of 3,408 articles. Intercept-only and meta-regression models were computed using the robust variance estimation method. Analyses examining mean cortisol levels at discrete timepoints, total cortisol output, and the cortisol rise in response to awakening (CAR) were conducted separately. The results demonstrated that the OAD had higher mean levels of cortisol at different timepoints throughout the day compared to controls (Hedge's g = .21). There was evidence of publication bias in studies examining CAR, such that effect sizes were positively bias. The present findings are consistent with a meta-analysis showing elevated cortisol in youth having an AD. Notable limitations across studies include the method of cortisol measurement and assessment of ADs. Altogether, these results highlight the fact that increased cortisol levels may act as a potential neuroendocrine antecedent and/or risk factor for the development of ADs among high risk youth.

Introduction

Affective disorders (AD), including major depressive disorder (MDD) and bipolar disorder (BD), negatively impact millions of individuals worldwide (Ferrari et al., 2016; Lim et al., 2018). In addition to the acute symptoms of these conditions, individuals with an AD often experience poor response to treatment, frequent relapses and elevated risk of suicide (Angst et al., 2003; Monroe & Harkness, 2011). Offspring of parents with an affective disorder (OAD) are also at high risk of mental health disorders and other problems across development (Mesman et al., 2013; Nijjar et al., 2014). Although the etiology and intergenerational transmission of ADs is complex and multifactorial (Sawyer et al., 2019), dysregulated hypothalamic-pituitary-adrenal (HPA) function has long been considered as a key potential biomarker of the disorder and one of the most robust and reliable findings in the literature (Bao & Swaab, 2019; Ellenbogen et al., 2019). The HPA axis is a principal actor in orchestrating the mammalian stress response to prolonged challenges. The HPA axis is regulated via a complex interplay of serotonergic, noradrenergic, and suprachiasmatic nucleus circadian input, as well as cortical and limbic brain regions that detect and appraise threat and contextual factors (Chrousos, 1998; McEwen et al., 2016). The HPA axis is particularly important in shaping adaptive and maladaptive outcomes across development, as alterations in the HPA axis may reflect upward or downward adaptations in response to the experience of adversity, including parental mental illness (Del Giudice et al., 2011).

There is inconsistency in the direction of dysregulation of the HPA axis among persons with an AD. Studies found higher mean levels of both morning and evening cortisol in adult patients with an AD compared to controls (Knorr et al., 2010; Murri et al., 2016; Stetler & Miller, 2011), even during periods of remission (Beluche et al., 2009). Similar findings were

found in pediatric populations (Lopez-Duran et al., 2009). However, researchers have found lower or blunted HPA axis activity in individuals with a history of an AD (Ahrens et al., 2008; Maripuu et al., 2017; Stetler et al., 2005). In sum, there is evidence suggesting a strong association between HPA axis dysregulation and ADs, but the exact nature of the dysregulation (i.e., hyper- vs. hypo-activation) and the variables that may moderate this relation warrants further investigation.

While researchers have conducted several meta-analyses aimed at clarifying the link between ADs and abnormalities in HPA axis functioning in pediatric (Lopez-Duran et al., 2009), adult (Knorr et al., 2010; Murri et al., 2016; Stetler & Miller, 2011) and elderly (Murri et al., 2014) populations, less is known about high-risk populations, such as the OAD. The study of high risk populations can allow us to determine whether changes in the HPA axis might precede the development of an AD, and thus represent an etiological factor or biomarker, rather than a correlate of the disordered state. Recently, Klimes-Dougan and colleagues (2022) conducted a systematic review of the literature on cortisol levels in the OAD and found that high risk youth have elevated basal cortisol compared to controls. We aim to extend these qualitative findings by conducting a meta-analysis that will summarize the data quantitively and allow us to explore potential moderators of HPA axis functioning in the OAD.

In the current study, we will conduct a meta-analytic review of cortisol levels in the natural environment among the OAD compared to their healthy counterparts. We will focus on both mean levels of cortisol at discrete timepoints throughout the day, the cortisol rise in response to awakening (CAR), and total daily cortisol output. Based on the results of previous meta-analyses and systematic reviews (e.g., Klimes-Dougan et al., 2022; Stetler & Miller, 2011), we hypothesize that the offspring of parents with an affective disorder, compared to controls,

will show increased cortisol levels across all indices of HPA axis functioning. We will also conduct several exploratory analyses on various characteristics of the sample and methodological features of cortisol measurement that may moderate the relation between an AD in parents and HPA axis functioning in their offspring.

Method

The current meta-analytic review has been submitted for registration in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021224351) and was conducted using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Search Strategy

The following search strategy was developed in consultation with the library staff at Concordia University (Montréal, QC). A systematic search was first conducted in specific electronic databases across the disciplines of psychology (PsycINFO, Psychology and Behavioural Sciences Collection) and medicine (PubMed), as well as broad-based electronic databases (Academic Search Complete, Web of Science). The search terms used to identify relevant literature are outlined in Table 1. Search terms were applied across all fields with no date restrictions. Articles written in English, French or Spanish were retained. The search included peer-reviewed articles, dissertations, and conference abstracts published on or before July 28th, 2020. A follow-up search was conducted on July 25th, 2022 to capture articles released after the original search. Backward and forward searchers were also conducted on the included articles.

Inclusion Criteria

Study design

Studies were included when the design either: 1) compared cortisol levels in the natural environment (i.e., home or school) of the OAD to a control group or 2) examined the association between an AD in parents and offspring cortisol levels in the natural environment. The control group consisted of offspring of parents with no history of an AD.

Participants

Human studies examining the role of MDD or BD in parents on their offspring's cortisol levels were included. Both mothers and fathers with a history of an AD were included. ADs in parents could either be measured categorically (i.e., based on a structured diagnostic interview or on a clinical cut-off from questionnaire data) or continuously (i.e., mood symptom questionnaires). There is evidence to suggest that children of asymptomatic parents who were depressed prior to their birth are at increased risk of developing MDD themselves compared to offspring of parents with no such mental health history (Mars et al., 2015). Therefore, studies of parents who experienced an AD prior to or during the child's lifetime (including during pregnancy) were included. There are also findings suggesting that cortisol levels only stabilize by 6 months of age (Lewis & Ramsay, 1995), thus studies with a mean age was below 6 months were excluded from the study. Since the focus of the meta-analysis is on non-affected high risk children, the majority (i.e., $\geq$ 75% of the sample) of the sample must consist of offspring with no history of an AD to be considered for inclusion. Lastly, laboratory-based studies examining stress reactivity or hair cortisol were excluded.

Cortisol measurement

Studies examining the diurnal rhythm of cortisol in OAD were included. We were interested in three indices of HPA axis functioning: 1) the mean cortisol levels at discrete timepoints during the day, 2) the total cortisol output throughout the day as measured by the total

area under the curve with respect to ground of all samples (AUC_g; Pruessner et al., 2003), and 3) the CAR measured as the difference in cortisol levels between awakening and 30 minutes post-awakening (i.e., +30 mins awakening – awakening) following recommendations by Stalder and colleagues (2016). To warrant inclusion, the AUC_g must be calculated based on at least three samples throughout the day, with at least one sample measured in the morning and one in the evening. While total daily cortisol output can also be measured as a slope, there was an insufficient number of studies that used this HPA axis index to conduct meta-analytic analyses. Given the evidence suggesting strong correlations between measurements of cortisol levels via saliva, serum, or urine collection (e.g., Neary et al., 2002), studies using these sampling methods were included. Cortisol levels could either be measured at the same time as or following exposure to an AD in parents.

Data Extraction and Management

Data extraction was completed using DistillerSR (Evidence Partners, Ottawa, Canada) and was conducted by the author of the current paper. The following data were extracted from the included studies: the year of publication, the type of document (e.g., peer-reviewed journal article, dissertation), study location (country), sample size (divided by group and total), sex of parent with an AD (% of mothers), offspring age and sex (% females), ethnicity, socioeconomic status (either family income or parent education level), type of AD in parents (MDD or BD), method of determining risk status (self-report or diagnostic interview) and name of measure, timing of diagnosis/symptom assessment (current vs lifetime), percentage of children exposed to an AD in parents during their lifetime, percentage of offspring with a history of an affective disorder, offspring internalizing symptoms, the HPA axis index measured (means, AUC_g or CAR), type of fluid collected during sampling (saliva, serum or urine), number of samples

throughout a day, number of sampling days, and timing of cortisol measurement [morning (waking until 11h59), afternoon (12h00 – 18h59), or evening (after 19h00)]. The data was coded a second time by the second author of the current paper and any discrepancies were resolved by discussion.

Study quality and risk of bias were derived using an adaption of two assessment tools specifically designed to evaluate the methodology employed in studies investigating the HPA axis (Powell et al., 2013; Tak et al., 2011). The assessment comprised of nine criteria designed to evaluate three broad areas of methodological quality including: 1) the appropriate selection of participants, 2) the correct quantification and reporting of HPA axis function, and 3) sufficient control of confounding factors. Each criteria is given a score between 0 and 3 points, and its total score can range from 0 to 18. See Table 2 for the specific items of the adapted assessment tool used in the current meta-analysis.

Effect size calculation

We selected Hedges' g as the common effect size metric, given the majority of studies (n = 22) examined group comparisons of cortisol levels in the OAD and controls. Hedges' g is an effect size estimate representing an adjusted mean group differences corrected for small sample size (Hedges & Olkin, 1985). OAD were used as the index group, therefore a positive effect size would indicate greater HPA axis activation in high-risk offspring, where as a negative effect size would indicate lower activation. Effect size calculations were based on the reported means and standard deviations or alternative summary statistics (e.g., F-values, sample sizes). For studies investigating the association between an AD in parents and offspring cortisol levels (n = 4), Pearson correlations (r) were extracted directly from text and converted into Hedges' g (Borenstein et al., 2009). All effect size calculations and conversions were conducted using the

'esc' package in *R* statistical software. When studies did not provide sufficient information to calculate effect sizes (n = 15), authors were contacted. For studies that represented their findings graphically (n = 3), an online program (WebPlotDigitizer) was used to convert information from graphs into numerical values that were then converted into effect sizes.

Analytic Strategy

We first conducted a priori power analyses for both our intercept-only and moderation models. We then estimated the level of heterogeneity between the studies included in the current meta-analysis using the I^2 index, which indicated the percentage of variance explained by heterogeneity (Higgins & Thompson, 2002). An I^2 index of 50% or higher suggests that there is a sufficient amount of heterogeneity among the effect sizes to detect moderation effects.

Before conducting the main analyses, the effect size estimates were screened for outliers. Outliers were defined as values exceeding 3 standard deviations below or above the mean and were removed from the analyses when identified. The main analyses were stratified by HPA axis index: mean levels of diurnal cortisol, AUC_g and CAR. Overall effect sizes comparing HPA axis functioning in the presence and absence of an AD in parents were estimated. Given the correlated nature of the cortisol data (i.e., multiple effect sizes were provided from the same cohort), the robust variance estimation (RVE) method was used. This particular method accounts for dependency among effect sizes by specifying within-study correlations among the effects. The default within-study correlation (rho = .80) was used. The built-in correction for small sample size was used to correct for bias in p-values when analyses are based on fewer than 40 unique samples (Tanner-Smith et al., 2016). Next, the trim-and-fill method was implemented to assess for publication bias (Duval, 2005). Specifically, the number of missing studies required to

offset publication bias was determined by creating funnel plots of the weighted mean effect sizes for each study.

After obtaining the intercept-only (i.e., no predictors) models, separate analyses were conducted to examine the influence of a priori specified moderator variables. The first set of moderators were based on sample characteristics, including: 1) type of affective disorder in parents (MDD vs. BD), 2) offspring age, 3) offspring sex (% female), 4) parent sex (% mothers), and 5) offspring history of affective disorder (% affected). The second set of moderators focused on methodological variables, including: 1) for mean levels, time of day cortisol was measured (morning, afternoon/evening), 2) number of samples included in estimate (both within and across days), 3) method of determining mental health status (diagnostic interview vs. self-report questionnaires), 4) timing of diagnosis/symptom assessment in parents (current vs. lifetime) and 5) study quality. For moderation analyses, a single predictor was added at a time into the meta-regression model. For categorial moderators, dummy codes were used and therefore the regression coefficient can be interpreted as the mean effect size difference between groups. For continuous moderators, the regression coefficient represents the expected change in effect size strength given one unit increase in the moderator variable. All analyses were conducted in *R* (version 4.0.2) using the 'robumeta' package (Fisher & Tipton, 2015).

Results

After duplicate articles were removed, the initial search yielded 3,408 unique articles. Titles and abstracts were then reviewed by the first author. Studies were excluded if there was no mention of an AD in parents or cortisol, or other potentially relevant terms. The title and abstract review yielded 108 articles which then underwent full text review. The inclusion/exclusion criteria were then applied and potential sample overlap was examined. When not specified by the

author, sample overlap was determined based on the list of authors and similarities in the sample characteristics. Studies which consisted of the same sample, but contributed unique effect sizes (e.g., studies conducted at different timepoints, included different indices of HPA axis functioning) were retained. Altogether, our search strategy yielded 26 studies for inclusion in the meta-analysis. See Figure 1 for the PRISMA flow diagram describing the identification and selection of studies for inclusion. Key characteristics of individual studies and an overview of sample characteristics and methodological variables for the total sample are summarized in Table 3 and Table 4, respectively.

Main analyses

Mean cortisol levels

There were two outliers removed from the analyses. The proportion of total variance in overall effect sizes was estimated to be 53%, indicating moderate levels of heterogeneity. An a priori power analysis (effect size Hedges' g = .30, sample size = 40, number of studies = 24) revealed that the power for the intercept-only model was sufficient (99%). The cumulative effect size was small (Hedges' g = .21) and revealed greater mean cortisol levels in the OAD than control offspring (see Figure 2). Review of the funnel plot indicated no evidence of publication bias in the literature on mean cortisol levels in offspring of parents with an AD (i.e., 0 missing studies; see Figure 3). Based on results from our meta-regression analyses, none of the proposed sample characteristics or methodological variables had moderating effects on overall effect size of mean cortisol levels (see Table 5).

AUC_g of diurnal cortisol

The proportion of total variance in overall effect sizes was estimated to be 45%, indicating low heterogeneity. An a priori power analysis (effect size Hedges' g = .25, sample size

= 40, number of studies = 12) revealed sufficient power (92%) to detect a significant group difference when estimating an overall effect size based on total diurnal cortisol output. The cumulative effect size (Hedges' g = .07) was not statistically significant, suggesting there was no significant difference in diurnal cortisol measured using AUC_g between OAD and controls (see Figure 4). Review of the funnel plot indicated no evidence of publication bias in the literature on total daily cortisol output as measured by AUC_g in the OAD (i.e., 0 missing studies; see Figure 5). Meta-regression analyses also revealed no moderating effects (see Table 5). These results should be interpreted with caution as the low level of heterogeneity across the few studies that included a measure of AUC_g may have made it difficult to detect moderating effects.

Cortisol Awakening Response

The proportion of total variance in overall effect sizes was estimated to be 31%, indicating low heterogeneity. An a priori power analysis (effect size Hedges' g = .25, sample size = 40, number of studies = 10) revealed sufficient power (86%) to detect a significant group difference when estimating an overall effect size based on total diurnal cortisol output. The cumulative effect size (Hedges' g = -.03) was not statistically significant, suggesting there was no significant difference in CAR between the OAD and controls (see Figure 6). Review of the funnel plot indicated some evidence of publication bias in the literature on the CAR in the OAD (i.e., 2 missing studies on the left side; see Figure 7). Thus, the overall effect size for CAR may be slightly positively biased. The meta-regression results revealed a statistically significant moderating effect of diagnosis method (diagnostic interview vs self-report questionnaire) and timing of AD diagnosis (see Table 5). Specifically, studies that used a structured diagnostic interview to diagnosis AD had a lower CAR (Hedge's g = -.07) compared to the one study that used self-report questionnaires of depressive symptoms (Hedge's g = .28). With regards to the

timing of AD, the findings suggest that offspring with a parent having a current diagnosis of AD had a supressed CAR (Hedge's g = -.55) compared to the one study that examined offspring of parents with a lifetime AD diagnosis (Hedge's g = .01). However, these results should also be interpreted with caution given the imbalance of studies in each category and the low level of heterogeneity across studies that included a measure of CAR measured as +30 mins awakening minus awakening.

Discussion

The current meta-analysis sought to determine whether there are consistent abnormalities in HPA axis functioning in the OAD and to clarify the nature of the dysregulation (i.e., hyper- vs. hypo-activation). Consistent with our main hypothesis and the previous meta-analytic findings in populations having an AD (e.g., Lopez-Duran et al., 2009; Murri et al., 2016, Stetler & Murri, 2011), the results indicated the OAD, relative to controls, had higher mean levels of cortisol at different timepoints throughout the day. Interestingly, the overall effect size of the current study (Hedges' g = .21) was comparable to the overall effect size of a meta-analysis examining HPA axis functioning in youth with a history of MDD (Hedges' g = .20; Lopez-Duran et al., 2009) and approached levels seen in euthymic adult patients with BD (Hedge's g = .28; Murri et al., 2016). These findings lend support to speculations that changes in HPA axis functioning may predate the onset of a full-blown affective disorder (Duffy et al., 2012; Gotlib et al., 2020; Hammen, 2017). Indeed, a number of studies, but not all (Keenan et al., 2013), have shown that elevated cortisol levels predicts the prospective development of MDD (Adam et al., 2010; Colich et al., 2015; Ellenbogen et al., 2011; Goodyer et al., 2010; Goodyer et al., 2000; Harris et al., 2000) and depressive symptoms (Halligan et al., 2007; Susman et al., 1997). Odds ratios from these studies indicate that having elevated cortisol levels in the natural environment

increase rates of depression by a factor of 1.6 to 7.1. Taken together, these studies and present meta-analysis provide growing support that subtle changes in HPA axis functioning may represent an important etiological factor in the development of an AD.

Despite having sufficient statistical power, no differences in overall effect size between OAD and controls were found for daily cortisol output (AUC_g) and CAR. As it pertains to the studies on the CAR, there was evidence of publication bias such that the overall effect size may be positively biased. It is therefore possible that the overall effect size is even more negative than the non-significant result that was summarized, contrasting the HPA hyperactivity observed in the OAD at discrete timepoints throughout the day. Together, these findings further highlight how the CAR differs from other measures of cortisol in the natural environment, with stronger estimates of heritability and regulated by different brain circuits than daytime cortisol levels (Clow et al., 2010; Ouellet-Morin et al., 2016). The absence of an effect for total daily cortisol output was surprising, as it was expected to parallel the finding for mean cortisol levels assessed at discrete time points. There are at least two possible explanations for the discrepancy. First, it was not possible to estimate daily cortisol output for all studies (i.e., if less than 3 samples were collected; study authors refused to provide raw data), so fewer studies were included in computing the effect size for daily output. Second, the discrepancy may be related to potential limitations in cortisol sampling and measurement. Only about half of the included studies used objective measures (i.e., samples stored in vials with time-stamping caps, actigraphy) to monitor cortisol sampling times. Studies have shown that these methods typically provide more accurate estimates of the individual's compliance to the sampling protocol, including their waking time (Broderick et al., 2004). Various studies noted that non-compliance to protocol can result in altered HPA axis activity compared to individuals with high compliance, especially in the

morning when cortisol levels fluctuate the most (Broderick et al., 2004; Kudielka et al., 2003). The impact of non-compliance to cortisol sampling times may be amplified when measuring AUC_g and CAR, as multiple samples are considered in these estimates. Moreover, the number of samples and sampling days varied between studies (see Table 4), which can have a significant impact on the estimates of AUC_g (Hoyt et al., 2016).

As a secondary study aim, we explored whether sample characteristics would moderate the relation between having a parent with an AD and HPA axis functioning. We found that group differences in diurnal cortisol levels across all indices did not vary as a function of type of an AD in parents, offspring age, offspring sex, parent sex or offspring history of AD. It is important to note that the heterogeneity across studies for each of the HPA axis indices in our study was moderate at best, limiting our ability to detect statistically significant moderating effects. These findings are similar to a meta-analytic review on pediatric depression (Lopez-Duran et al., 2009), where the proposed moderator variables (including youth sex and age) did not influence group differences in HPA axis activity due to limited between-study variability.

Limitations and Future Directions

Although the current meta-analysis contributes to the field by conducting a quantitative examination of differences in HPA functioning between OAD and control offspring, the study is not without limitations. Most of the studies included in the meta-analysis were based on the assessment of saliva samples. While this is well-validated and unintrusive methodology, saliva sampling is typically limited to daytime collection, and thus does not typically assess nighttime functioning of the HPA axis, which can be done via blood sampling (Feder et al., 2004). Moreover, saliva sampling only reflect cortisol levels measured during the specific days and times in which the samples were collected (Sauvé et al., 2007). Twenty-four hour blood

sampling and assessing cortisol in hair samples allow for the measurement of cortisol concentrations over days and months, respectively. Hair cortisol has one advantage by being able to provide an index of chronic stress over extended periods of time (Gow et al., 2010). Associations between maternal depression and youth hormone levels measured via hair sampling have been recently documented in the literature (Hagaman et al., 2020; Liu et al., 2020). Further, one study highlighted the potential mediating effects chronic stress, measured by concentrations of cortisol in hair samples, on the relation between parent and child psychopathology (Ferro & Gonzalez, 2020). Future studies should consider incorporating hair cortisol sampling to better assess the relation between long term HPA axis functioning and risk of developing ADs in high-risk offspring.

Although the study quality appeared to be sufficient across all studies, there were two indices of study quality that were notably lacking. In addition to the inconsistent use of objective measures of adherence for the cortisol sampling protocols, the severity and duration of the AD in parents was rarely reported across studies. Various clinical features of ADs, including the severity (e.g., number of hospitalizations), the chronicity, and the timing within child's lifetime can have a significant impact on the outcomes in their offspring (Hammen & Brennan, 2003; Mars et al., 2012). In fact, one study found that maternal depression accompanied by co-morbid anxiety disorders and medication use, as well as the timing of the episodes were all significantly associated with infant cortisol levels (Brennan et al., 2008). Therefore, future studies should document this information and consider the influence of these clinical variables on the HPA axis activity of high-risk youth.

There are some limitations with regards to the generalizability of the findings of the current study. The majority of offspring were middle-class Caucasians from Western countries

and may not translate to ethnic minorities or populations living in poverty who often experience elevated levels of stress and mental disorders (de Wit et al., 2008; Gilman et al., 2002). Moreover, additional risk factors (e.g., low socioeconomic status, single parenthood) can have a cumulative effect on HPA axis functioning (Zalewski et al., 2012). Therefore, abnormalities in HPA system may be even more pronounced in populations most at risk. Consistent with the historical tendency to focus on maternal mental illness (Edward et al., 2015), few studies included paternal AD in their research design. There is evidence to suggest mental illness in a mother compared to a father may have varying consequences on child outcomes (Connell & Goodman, 2002). For example, MDD in mothers has been found to have a greater impact during earlier developmental periods (Bagner et al., 2010), while MDD in fathers seems to have the largest impact during adolescence (Reeb et al., 2015). Moreover, consistent with a phenomenon known as assortative mating, individuals with an AD often choose romantic partners who also suffer from a mental disorder (Nordsletten et al., 2016). In addition to heightening the risk of genetic transmission (Rietschel et al., 2017), partners of parents with an AD also exhibit various psychosocial deficits that might impact child outcomes (Serravalle et al., 2020). Therefore, future studies should attempt at including both parents in their research design and investigate how different patterns of parental AD (i.e., the presence of an affective disorder in the mother, father or both) may influence offspring HPA axis functioning.

Developmental researchers have outlined the importance of investigating the biological processes underlying mental illness and incorporating this knowledge into prevention and intervention research (Cicchetti & Gunnar, 2008). Other researchers have begun to explore interventions that target the stress hormones, including potential psychopharmacological treatments (Holsboer & Ising, 2010; Menke, 2019). In addition to being highly heritable

(Rietschel et al., 2017), there is evidence to suggest that the environment in which the OAD grow up may also play an important role. In fact, one study found that exposure to depressive symptoms in adoptive mothers at the age of 9 months predicted youth cortisol levels at 54 months, even after controlling for the birth mother's prenatal depressive symptoms and cortisol activity (Laurent et al., 2013). Researchers have begun identifying specific aspects of the childrearing environment that may influence HPA axis activity. For example, maternal negativity (Apter-Levi et al., 2016), low structure in the home (Ellenbogen et al., 2009), and cognitive growth fostering in early years (Letourneau et al., 2011), have all been associated with alterations in the HPA system in the OAD. Furthering this knowledge can inform preventative intervention development by identifying malleable aspects of the environment that can act as treatment targets to help re-calibrate the HPA axis functioning in high-risk youth and offset potential adverse effects on their mental health. Indeed, we have recently found that positive changes in family organization following a 12-week preventative intervention to improve the family environment in families with a parent having BD were associated with a normalization of offspring's cortisol response following awakening and daily cortisol output (Yong Ping et al., 2023).

Summary and conclusion

This meta-analysis supports previous findings that abnormalities in HPA axis functioning play a significant role in the pathogenesis of ADs. Results showed that the OAD displayed an overactive HPA axis activity at discrete timepoints throughout the day as compared to offspring of parents with no history of affective disorders. The moderating effects of various study characteristics were not statistically significant, but there was evidence to suggest that the method of assessing for ADs in parents and episode timing may alter the strength of the study

effect size. Together, these results highlight the fact that small changes in the HPA system may act as both a potential neurobiological antecedent to ADs and as an important risk factor for the OAD. Future research should investigate other indices of HPA axis functioning, attempt to address methodological limitations, as well as focus on identifying mechanisms underlying changes in offspring HPA axis functioning in order to inform preventative research efforts for these high-risk youth.

Table 1

Key terms used in search strategy

	("cortisol" *OR* "hypothalamic pituitary adrenal axis" *OR* "HPA" *OR* "hormone*" *OR* "neuroendocrine" *OR* "hormon* stress response" *OR* "hypercortisol*" *OR* "hypocortisol*" *OR* "chronic stress")
AND	(child* *OR* adolesc* *OR* preschool* *OR* toddler* *OR* kid* *OR* teen* *OR* young *OR* youth *OR* offspring *OR* girl* *OR* boy*)
AND	((parent* *OR* mother* *OR* father* *OR* maternal *OR* paternal) AND (depress* *OR* bipolar *OR* dysphori* *OR* "low mood" *OR* manic *OR* mania *OR* "manic-depressive" *OR* "affective disorder" *OR* "mood disorder"))

Note. All search terms were applied across the title, abstract and keyword fields in PsycINFO (1952-2022), Psychology and Behavioural Sciences Collection (1983-2022), PubMed (1966-2022), Academic Search Complete (1983-2022), and Web of Science (1991-2022).

Table 2

Adapted assessment tool to evaluate methodological quality of studies on hypothalamic-pituitary-adrenal (HPA) axis activity in offspring of parents with a affective disorder

Appropriate selection of participants
1. Has parental affective disorder been reliably assessed and validated? According to internationally established criteria by an experienced professional (2) Not according to internationally established criteria or assessor not specified (1) According to self-report measure or not clearly states (0)
2. Were controls recruited from the same populations as the risk group? Controls recruited from the same population as risk group (2) Risk group is from a selected population, such inpatients (1) Not clearly stated (0)
3. Are sample inclusion/exclusion criteria clearly defined? Psychiatric morbidity (in parents), child pathology and medication use, 3 stated (2) Psychiatric morbidity (in parents), child pathology and medication use, 1-2 stated (1) None stated or not clear (0)
4. Is the severity and duration of the parental affective disorder described? Duration of disease and severity (e.g., # of hospitalizations) of disorder stated (2) Only duration or only severity stated (1) None stated (0)
Correct quantification and reporting of HPA axis activity
5. Are methods of cortisol assessment clearly described and appropriate? Two or more assessment days, repeated measurements throughout day with specified times, procedure for specimen collection described, storage conditions, type of assay, all 5 stated (2) Repeated measurements throughout day with specified times, procedure for specimen collection described, storage conditions, type of assay, 3-4 stated (1) Less than 3 states or not appropriate (0)
6. Is adherence to the protocol controlled? Electronic monitoring, actigraphy, with deviations from protocol observed and controlled, including observed time of awakening (3) As above, but without objective measurement of awakening time (2) Electronic monitoring or actigraphy, but deviations from protocol not observed or controlled; *OR* self-reported sampling times, with deviations observed and controlled (1)

No appropriate controls, or not stated (0)

7. **Were missing cortisol samples dealt with appropriately in the analyses?**
   No missing data; OR principled missing data technique[a] used when estimating parameters (3)
   Parameters based on non-complete but adequate data to provide reliable estimates[b] (2)
   Ad hoc missing data technique[c] used (1)
   Missing data not dealt with, or inappropriate (0)

8. **Is the cortisol outcome presented clearly (including graphically) with appropriate units?**
   Central tendencies and measures of variance presented for each sample and for each measured cortisol index (e.g., AUC_g) (2)
   Central tendencies or measures of variance presented only for cortisol index (1)
   Outcome not clearly presented (0)

Sufficient control of confounding factors

9. **Does the study provide appropriate control/adjustment for confounding variables?**
   Age, sex, body mass index, smoking, hours of sleep, depressive symptoms, medication, physical exercise, eating shortly before sampling, breastfeeding, birthweight, 6-9 stated for adults/adolescents, 5-8 stated for school-aged children and 5-6 stated for infants (2)
   Age, sex, body mass index, smoking, hours of sleep, depressive symptoms, medication, physical exercise, eating shortly before sampling, breastfeeding, birthweight, 3-5 stated for adults/adolescents, 3-4 stated for school-aged children and 3-4 states for infants (1)
   Across all ages, 0-2 variables stated (0)

Note. This assessment tool is an adapted version of two previously established tools on HPA axis functioning (Powell et al., 2013; Tak et al., 2011). [a] Refers to likelihood-based and Bayesian estimation methods, and multiple imputation; [b] Amount of data is considered adequate when each participant had >2 completed samples in a day, for each sampling day; [c] Refers to case deletion or single imputation methods.

Table 3

Overview of the key sample characteristics of the included studies

First author	Year	Country	*N*	Child age in years *M* (SD)[a]	Child sex (%female)	Sex of parent (% mothers)[b]	Parental Diagnosis	HPA axis Index
Azak	2013	Norway	26	.56 (.05)	48.3	100.0	MDD	Mean
Beijers	2020	Netherlands	134	6.03 (.11)	47.2	100 .0	MDD	Mean, AUC_g
Belsky	2015	USA	73	4.64 (.05)	100.0	100 .0	MDD	Mean
Black	2019	USA	303	9.27 (.44)	47	78.6	MDD	Mean, AUC_g, CAR
Dougherty	2009	USA	94	3.62 (.21)	43.6	100 .0	MDD	Mean
Dougherty	2013	USA	228	6.23 (.45)	46.5	100.0	MDD	Mean
Ellenbogen	2006	Canada	58	16.6 (2.1)	51.7	50.0	BD	Mean, AUC_g, CAR
Ellenbogen	2010	Canada	46	18.3 (2.6)	50.0	50.0	BD	Mean, AUC_g, CAR
Foland-Ross	2014	USA	128	12.4 (1.6)	100.0	100.0	MDD	Mean, AUC_g
Goldstein	2017	USA	352	14.4 (.62)	100.0	100.0	MDD	Mean, AUC_g, CAR

First author	Year	Country	*N*	Child age in years *M* (SD)[a]	Child sex (%female)	Sex of parent (% mothers)[b]	Parental Diagnosis	HPA axis Index
Gonul	2017	Turkey	37	21.8 (2.1)	100.0	100.0	MDD	Mean, AUC_g
Goodday	2016	Canada	49	20.0 (7.2)	64.0	49.0	BD	Mean, AUC_g, CAR
Halligan	2004	UK	87	13.3 (.13)	46.5	100.0	MDD	Mean
Leppert	2018	USA	146	4.14 (.81)	51.4	100.0	MDD	CAR
Lupien	2000	Canada	217	8.70 (.50)	52.5	100.0	MDD	Mean
Mannie	2007	UK	102	19.1 (.90)	73.3	71.7	MDD	Mean
Merwin	2017	USA	136	3.74 (.77)	52.2	94.1	MDD	Mean
Osborne	2018	UK	106	1.13 (1.33)	44.4	100.0	MDD	Mean, AUC_g
Pratt	2017	Israel	97	6.33 (1.3)	49.0	100.0	MDD	AUC_g
Rao	2009	USA	96	15.0 (1.50)	58.3	79.0	MDD	Mean
Ruttle	2014	USA	218	13.43 (.33)	54.0	100.0	MDD	Mean
Stonawski	2019	Germany	167	7.6 (4.78)	50.9	100.0	MDD	Mean, AUC_g, CAR
Tarullo	2017	USA	85	0.55 (.04)	48.7	100.0	MDD	Mean

First author	Year	Country	*N*	Child age in years *M* (SD)[a]	Child sex (%female)	Sex of parent (% mothers)[b]	Parental Diagnosis	HPA axis Index
Yong Ping	2022	Canada	63	8.20 (1.60)	48.0	73.0	BD	Mean, AUC_g, CAR
Young	2006	USA	58	10.3 (4.7)	53.4	86.7	MDD	Mean
Zhang	2018	China	189	13.4 (3.0)	51.8	78.6	MDD	Mean, CAR

Note. MDD = major depressive disorder; BD = bipolar disorder; Mean = mean cortisol levels at discrete timepoints, AUC_g = total daily cortisol output, CAR = cortisol awakening response. [a] If age of overall sample was not available, the mean (SD) age of the offspring of a parent with an AD was used; [b] Sex of parent with diagnosis of an affective disorder; *age in weeks

Table 4

Overview of the key sample characteristics and study quality of the total sample

	Mean Cortisol Levels			AUCg			CAR		
Sample Characteristics									
	N	***k***	**M (SD) or [%]**	***N***	***k***	**M (SD) or [%]**	***N***	***k***	**M (SD) or [%]**
Offspring age (years)	3,052	24	10.35 (6.33)	1,598	12	11.86 (6.43)	1,431	9	12.55 (5.45)
Offspring sex (% females)	3,052	24	[59.7%]	1,598	12	[62.3%]	1,431	9	[57.4%]
Parent age (years)	1,785	13	33.80 (3.96)	935	6	35.81 (4.64)	616	3	34.95 (2.15)
Parent sex (% mothers)	3,052	24	[87.9%]	1,598	12	[85.2%]	1,431	9	[77.8%]
Ethnicity (% Caucasian)	2,556	19	[74.9%]	1,324	9	[74.1%]	1,382	8	[68.8%]
Offspring history of affective disorder (% affected)	2,617	22	[5.43%]	1,598	12	[4.94%]	1,431	9	[6.59%]
Methodological Variables									
Type of AD diagnosis									
MDD	2,836	20		1,324	8		1,157	5	
BD	216	4		274	4		274	4	
Assessment of AD									
Structured Interview	1,969	16		1,191	9		1,264	8	
Informal Interview	102	1		-	-		-	-	
Self-report questionnaire	981	7		407	3		167	1	
Timing of AD									
Current	806	7		106	1		1,242	1	
Lifetime	2,246	17		1,492	11		189	8	
Cortisol sampling method									

Saliva	3,015	23	1,561	11	1,431	9
Blood	37	1	37	1	-	-
Number of samples per day						
1-2 samples	994	9		-	-	-
3 samples	1,166	7	895	5	801	3
4 samples	311	3	311	3	49	1
5-7 samples	581	5	392	4	581	5
Number of sampling days						
1 day	1,129	9	310	3	502	3
2 days	658	6	480	5	121	2
3+ days	1,268	9	808	4	808	4
Sampling verification						
Diary logs	2,136	18	899	7	623	4
MEMS® caps	662	4	662	4	808	5
Done in-lab	254	2	37	1	-	-

Note. k = number of studies; AD = affective disorder; MDD = major depressive disorder; BD = bipolar disorder

Table 5

Effect sizes comparing mean cortisol levels between offspring of parents with and without an affective disorder and HPA axis functioning

	Mean Cortisol Levels *k* = 24; # effect sizes = 82		**AUCg** *k* = 12; # effect sizes = 12		**CAR** *k* = 9; # effect sizes = 10	
	Hedges' g (*SE*)	**CI (95%)**	**Hedges' g (*SE*)**	**CI (95%)**	**Hedges' g (*SE*)**	**CI (95%)**
Overall	**.209 (.058)****	**(.087, .331)**	.073 (.076)	(-.098, .244)	-.034 (.048)	(-.158, .090)
Moderators	***B* (*SE*)**	**CI (95%)**	***B* (*SE*)**	**CI (95%)**	***B* (*SE*)**	**CI (95%)**
Sample Characteristics						
Type of parent AD[b]	-.090 (.166)	(-.664, .484)	.223 (.216)	(-.343, .787)	.016 (.107)	(-.328, .296)
Offspring age	-.012 (.025)	(-.069, .048)	.006 (.017)	(-.035, .048)	-.006 (.011)	(-.037, .026)
Offspring sex (% females)	.359 (.326)	(-.453, 1.17)	.000 (.002)	(-.005, .005)	.000 (.003)	(-.013, .014)
Parent sex (% mothers)	.000 (.004)	(-.010, .010)	-.005 (.005)	(-.020, .009)	.000 (.002)	(-.007, .008)
Offspring history of affective disorder (% affected)	.000 (.005)	(-.013, .013)	.011 (.009)	(-.034, .055)	-.002 (.004)	(-.020, .016)
Methodological Variables						
Time of day[c]	-.026 (.106)	(-.250, .198)	-	-	-	-
Number of samples	.010 (.020)	(-.130, .149)	.016 (.022)	(-.037, .069)	-.016 (.015)	(-.054, .022)

Diagnosis method[d]	-.186 (.120)	(-.446, .074)	.142 (.186)	(-.406, .690)	**-.354 (.034)****	**(-.448, -.260)**
Timing of AD diagnosis[e]	-.091 (.107)	(-.351, .170)	.114 (.082)	(-.073, .300)	**-.549 (.039)****	**(-.663, -.436)**
Study quality	-.050 (.031)	(-.121, .020)	.082 (.036)[†]	(-.011, .174)	-.054 (.044)	(-.233, .125)

Note. AD = affective disorder; [a]number of independent studies; [b]MDD = 0, BD = 1; [c]Morning = 1, Afternoon/Evening = 0;

[d]Diagnostic Interview = 1, Self-report questionnaire = 0; [e]Current = 1, Lifetime = 0.

*p = <.05, **p = <.01

Figure 1

PRISMA flowchart

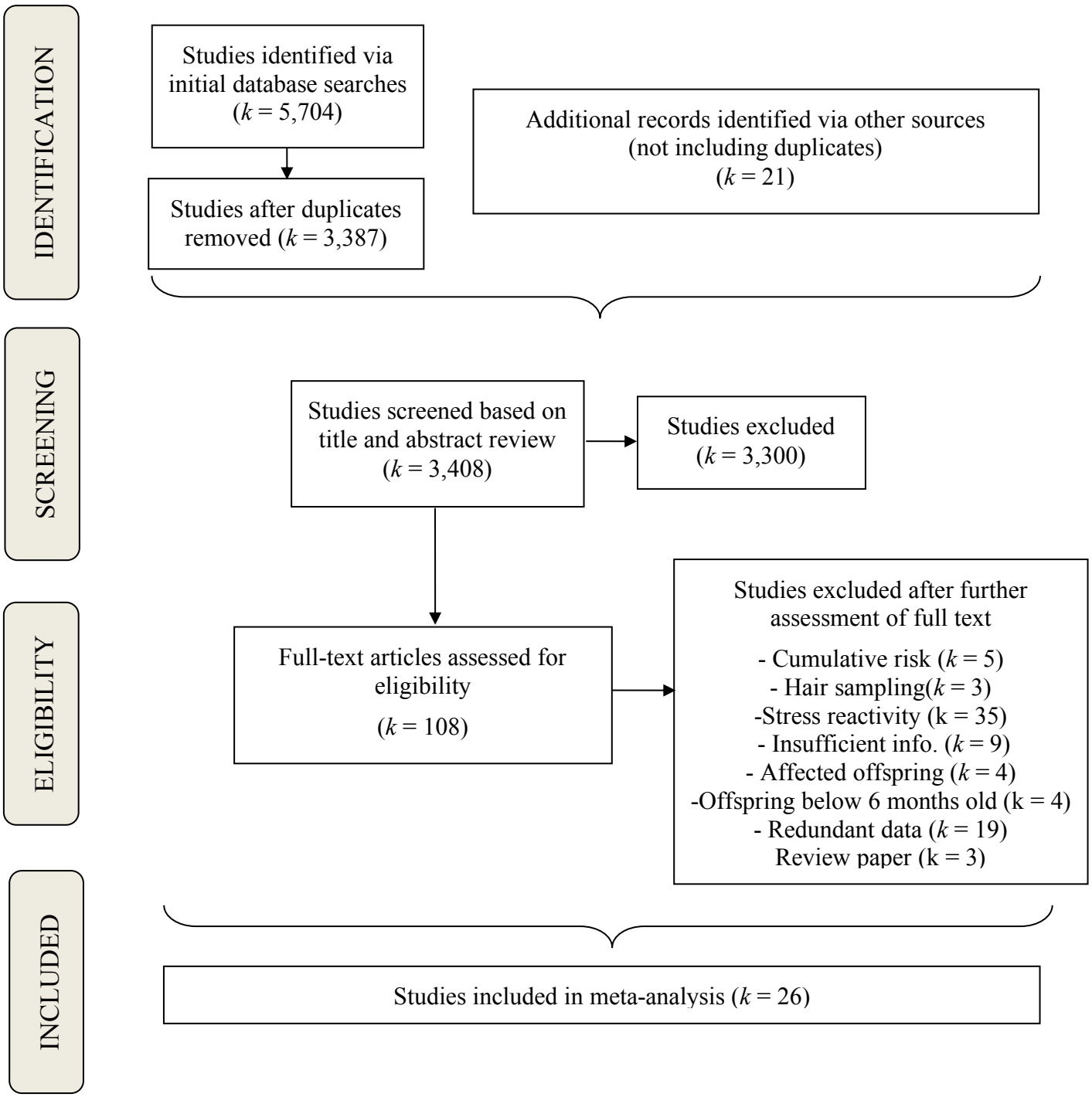
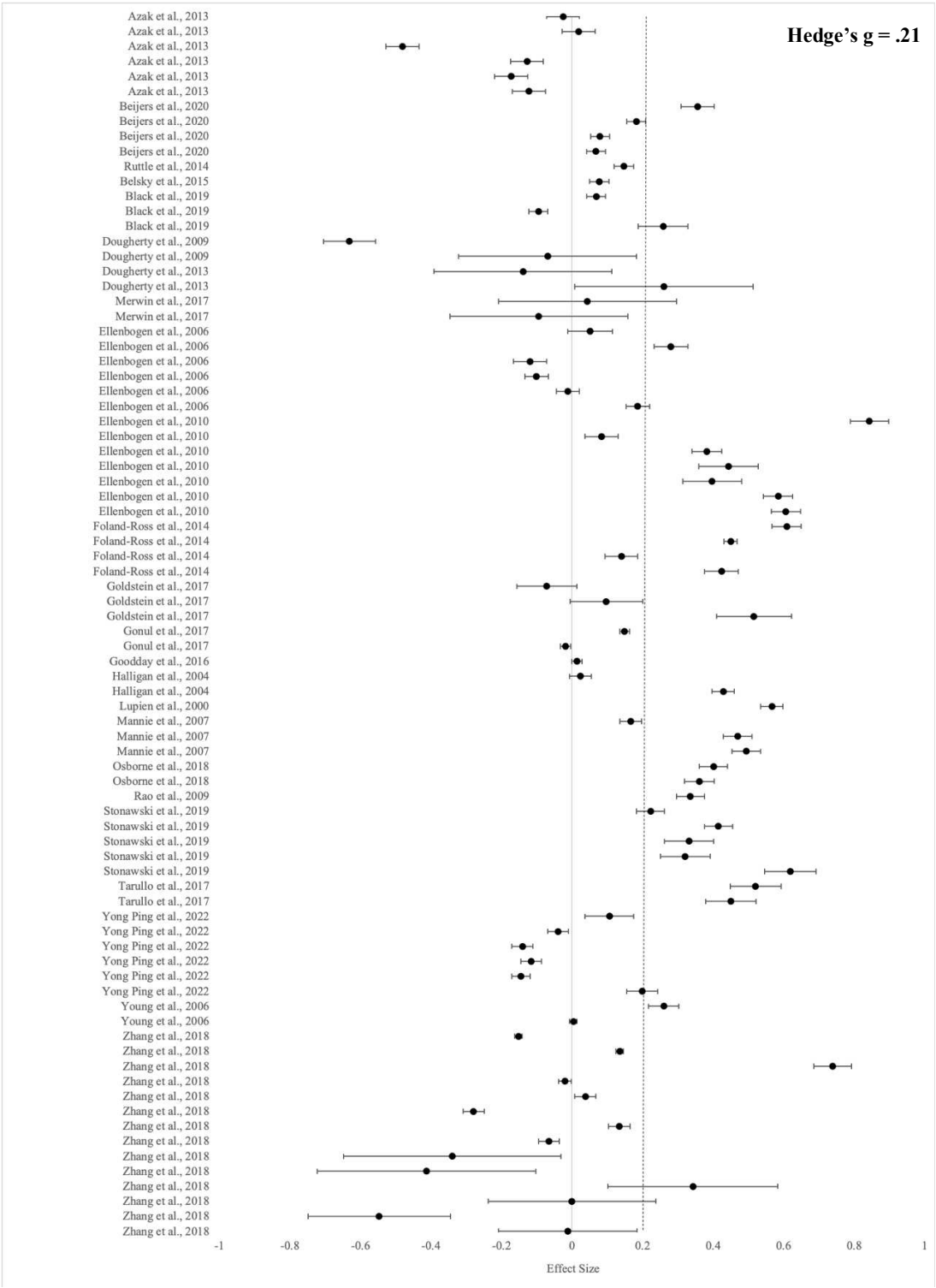


Figure 2

Forest plot of effect size (Hedge's g) for mean cortisol levels at discrete timepoints throughout the day



Note. Offspring of parents with a mood disorder were used as the index group, therefore a positive effect size would indicate greater HPA axis activation in high-risk offspring, where as a negative effect size would indicate lower activation.

Figure 3

Funnel plot of each sample's mean weighted effect size by average variance to assess for publication bias for cortisol measured at discrete timepoints of the day

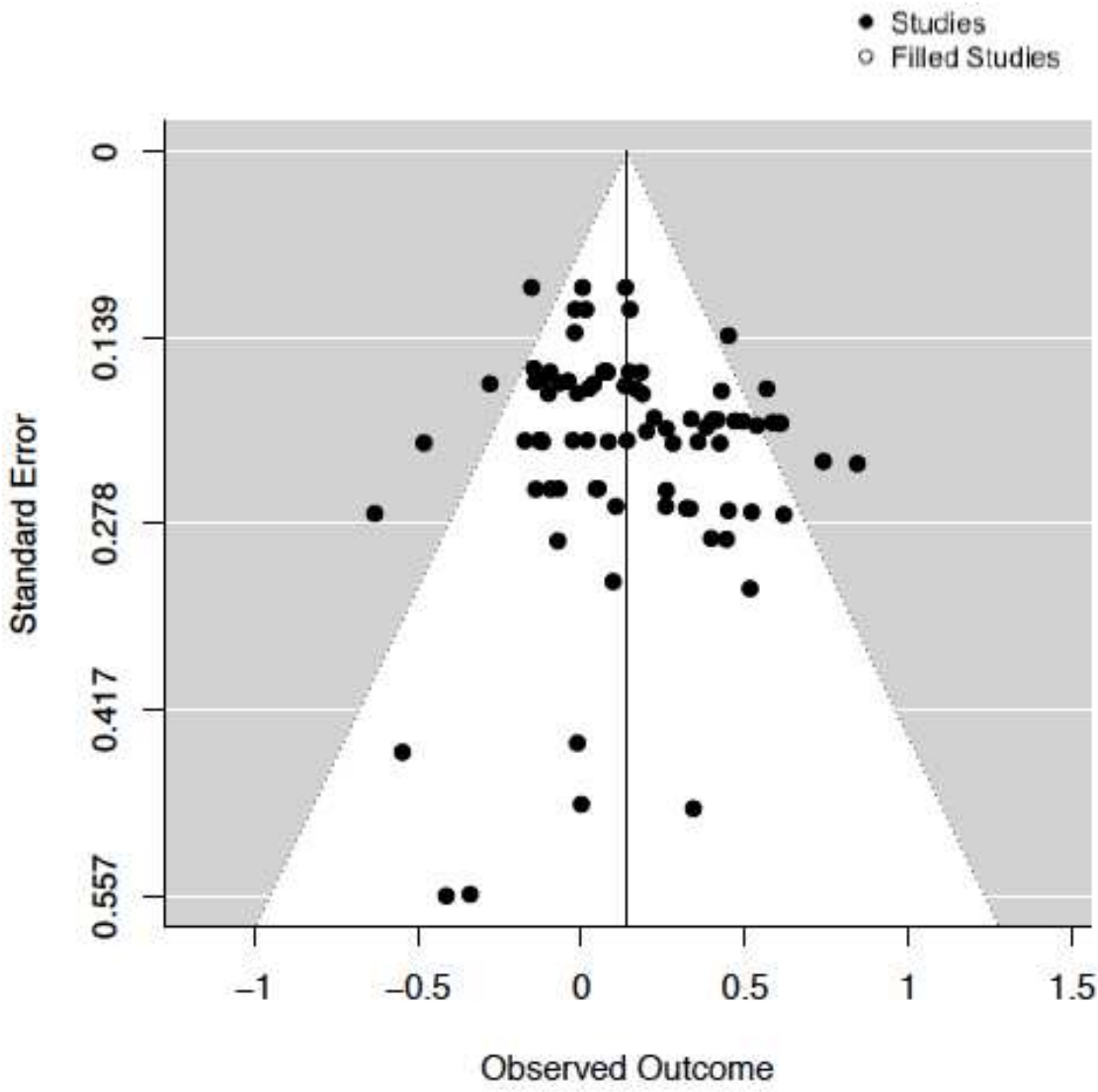
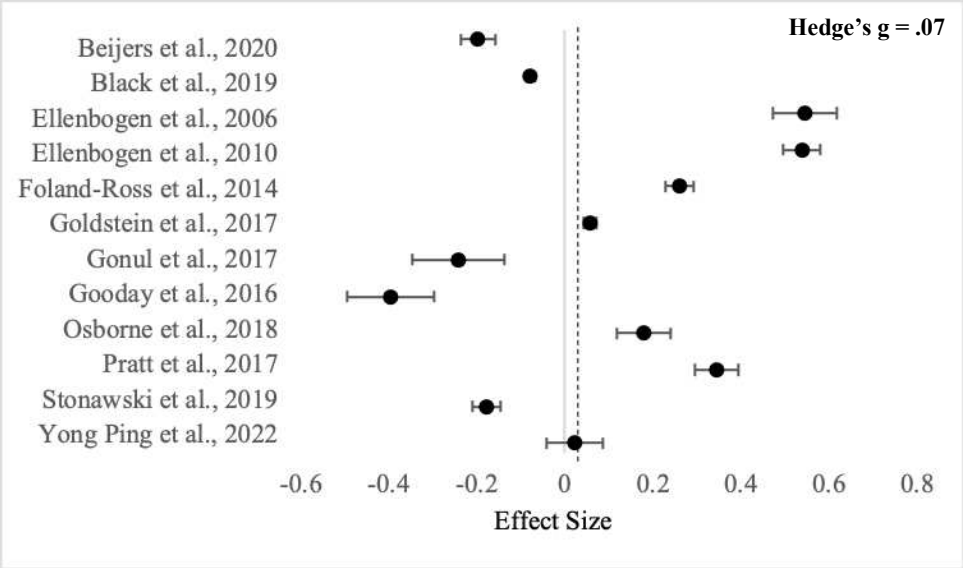


Figure 4

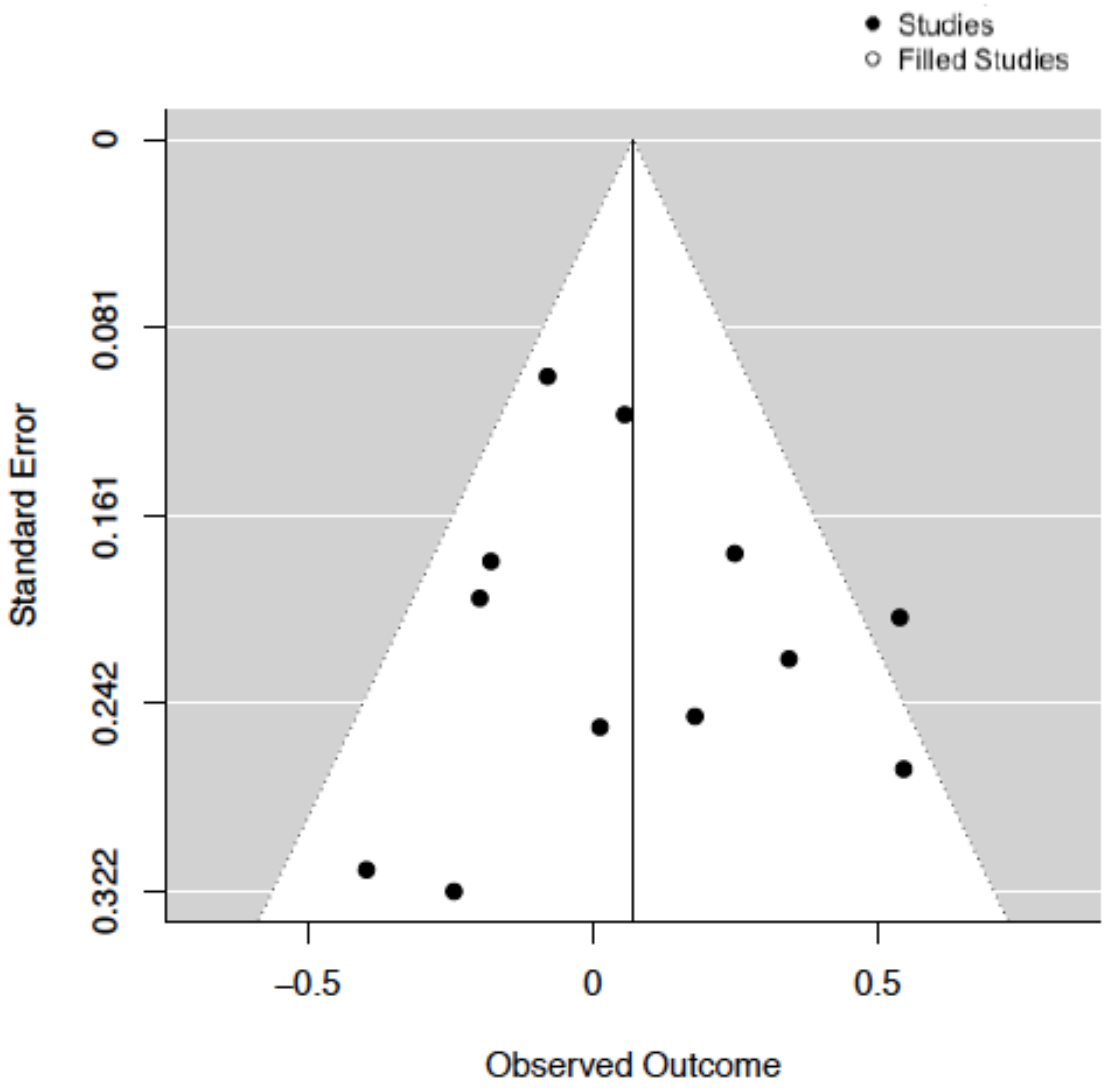
Forest plot of effect size (Hedge's g) for total daily cortisol output as measured by AUCg



Note. Offspring of parents with a mood disorder were used as the index group, therefore a positive effect size would indicate greater HPA axis activation in high-risk offspring, where as a negative effect size would indicate lower activation.

Figure 5

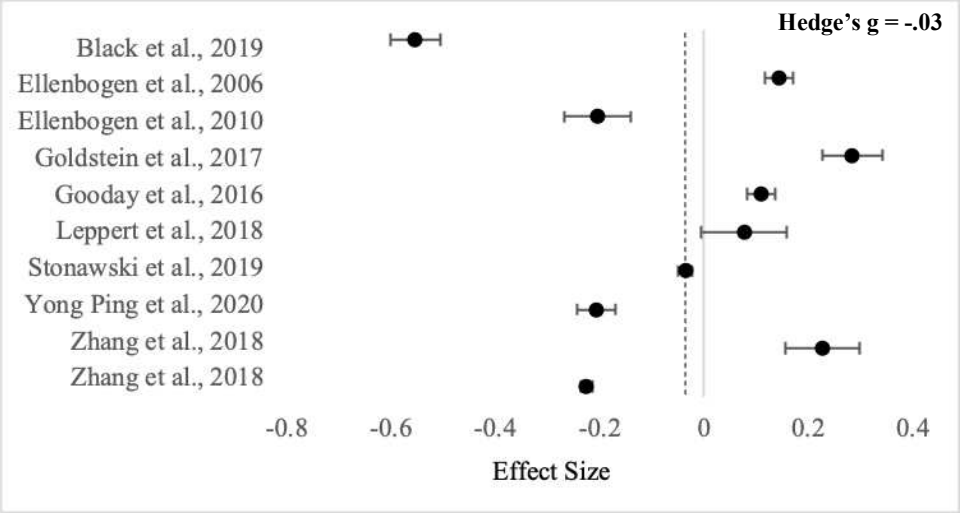
Funnel plot of each sample's mean weighted effect size by average variance to assess for publication bias for total cortisol output



Note. *Total cortisol output is measured as area under the curve from ground (AUC_g)*

Figure 6

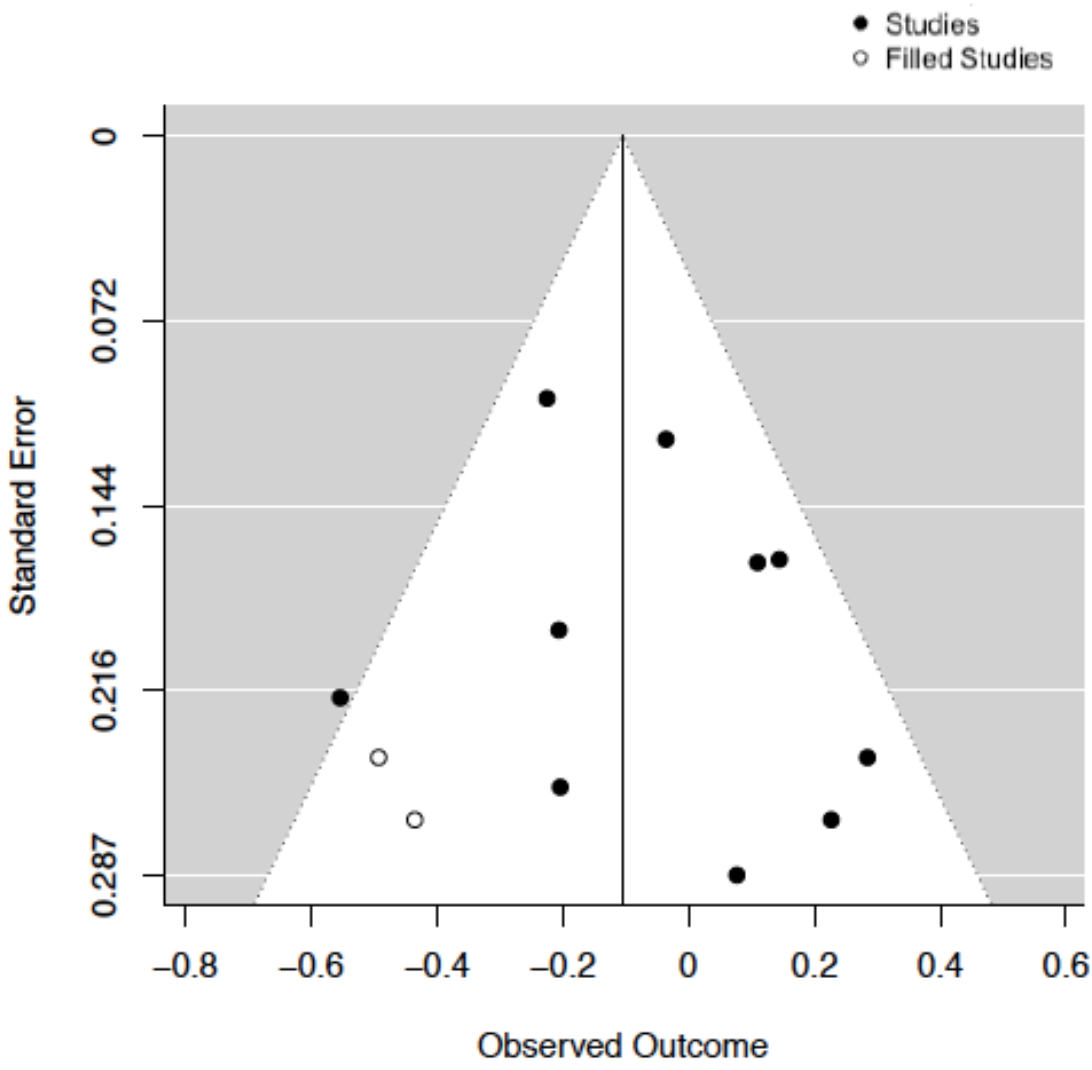
Forest plot of effect size (Hedge's g) for the cortisol awakening response (CAR)



Note. Offspring of parents with a mood disorder were used as the index group, therefore a positive effect size would indicate greater HPA axis activation in high-risk offspring, where as a negative effect size would indicate lower activation.

Figure 7

Funnel plot of each sample's mean weighted effect size by average variance to assess for publication bias for cortisol awakening response



Note. Cortisol awakening response is measured as +30 minutes awakening minus awakening.

Transition paragraph 1

The first study summarized the extant literature on HPA axis functioning in the OAD using meta-analytic statistical procedures. Consistent with meta-analyses examining HPA axis functioning in individual diagnosed with an AD (Knorr et al., 2010; Lopez-Duran et al., 2009; Murri et al., 2014, 2016; Stetler & Miller, 2011) and findings from a recent systematic review (Klimes-Dougan et al., 2022), the findings indicated the OAD had higher mean levels of cortisol at different timepoints throughout the day relative to controls. These results provide evidence that alterations in HPA function may *precede* the onset of an AD. Thus, it is possible that alterations in cortisol secretion are both a state-dependent symptom of ADs and part of its etiology. Taken together, these data add to a growing body of research that suggests abnormalities in the HPA axis play an important role in the development of ADs. There is less research available on vulnerabilities in the OAD that may lead to, or interact with, these subtle changes in HPA functioning.

At the beginning of the thesis, we discussed the importance of the caregiving environment on behavioral and emotional development in children. There is also evidence that the caregiving environment plays a significant role in the development of stress-sensitive systems. There are two models relevant to this line of work. The Adaptive Calibration Model posits that individual differences in stress responsivity are partly a result of the individual's ability to modify their developmental trajectory to match the conditions of their environment (Del Giudice et al., 2011). Boyce and colleagues (1995) were one of the first studies to illustrate the importance of biological sensitivity to context on child outcomes in two distinct samples of preschoolers. Across both samples, children who were biological responsive (cardiovascular and immune reactivity) demonstrated the greatest or lowest susceptibility to respiratory tract disease,

depending on the level of stress in their environment. Children with low biological responsivity had similar rates of respiratory illness regardless of the level of stress in their environments. It is hypothesized that heightened biological sensitivity is adaptive in both low and high stress environments given the potential for social learning/engagement in the former condition and responding appropriately to threats/dangers in the latter (Del Giudice et al., 2011). The social buffering model focuses on the influence of attachment to caregivers on offspring stress regulation. Specifically, the availability of a conspecific is thought to play a role in shaping stress-sensitive neurobiological systems, including the HPA axis (Hostinar et al., 2014; Gunnar & Hostinar, 2015). Evidence from animal and human studies suggest that the HPA axis stress response can be attenuated in supportive environments (Avellaneda & Kamenetzky, 2021).

In the context of ADs in parents, there is evidence to suggest disruptions in the early caregiving environment can lead to longstanding alterations in the HPA system (Halligan et al., 2004, 2007) and that specific aspects of the caregiving environment, name structure and consistency in the home may play an especially important role (Ellenbogen et al., 2009). Thus, disruptions in the caregiving environment may be one mechanism underlying HPA abnormalities in the OAD. The second study is based on a longitudinal dataset of families having a parent with BD and control families with parents having no history of an affective disorder. Data in parents and children were collected when the offspring were between 4 and 13 years old (Serravalle et al., 2020) and then approximately 12 years later in late adolescence or early adulthood (Nijjar et al., 2014). We intended to build on the findings of Study 1 in two ways. First, we will assess the CAR in young adults with an affective disorder (mostly OBD), OBD without an affective disorder, and control offspring without an affective disorder. Second, we examined a model of risk transmission positing that high-risk families have suboptimal caregiving practices that alter

the development of the HPA system in the OBD, and that these biological changes are associated with increased psychopathology. To our knowledge, these data would constitute the demonstration of the caregiving environment and the CAR in offspring as putative mechanisms underlying the transmission of risk for psychopathology in the OBD specifically.

Chapter 3: Structure provided by parents in middle childhood predicts cortisol levels and internalizing symptoms 12 years later among the offspring of parents with bipolar disorder

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Abstract

The offspring of parents with bipolar disorder (OBD) are at high risk for developing affective disorders. Low family structure, which refers to organization and consistency in the home, is associated with increased behavioral problems and hypothalamic-pituitary-adrenal (HPA) reactivity in the OBD, and thus may be a critical developmental mediator of outcome in these high-risk youth. In this study, we examined whether the cortisol response following awakening (CAR) is increased in the OBD with an affective disorder relative to OBD with no affective disorder. Next, we tested whether family structure in childhood and an elevated CAR in offspring mediate the relationship between risk status (i.e., having a parent with bipolar disorder) and offspring depressive symptoms in adolescence/young adulthood, 12 years later. The sample (19.3 ± 3.4 years) consisted of 68 OBD and 64 offspring of parents with no affective disorder (controls). Family structure was measured using the Parenting Dimensions Inventory. As expected, the OBD who developed an affective disorder had higher CAR than OBD who did not have an affective disorder (Cohen's d= 0.423) and controls (Cohen's d= 0.468). Bootstrapping serial mediation analyses revealed that family structure in childhood and the CAR in offspring significantly mediated the relationship between risk status and offspring depressive and anxiety symptoms 12 years later (CI: .01, .66). Low family structure in the OBD leads to changes in the HPA axis that increases the risk of developing an affective disorder. Suboptimal childrearing may have enduring consequences on mental health outcomes in the OBD.

Introduction

Social buffering is a well-documented phenomenon that suggests the presence of a conspecific plays an important role in shaping stress-regulating neurobiological systems (Hostinar et al., 2014; Gunnar & Hostinar, 2015). Much of this research has focused on the social regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, an important neuroendocrine system responsible for orchestrating the mammalian stress response. Across animal and human studies, there is ample evidence to suggest that the HPA axis stress response to threat can be attenuated with the availability of a supportive social environment (Avellaneda & Kamenetzky, 2021). Over three decades of research on social buffering has demonstrated its stress-dampening effects on the HPA axis functioning across development, from infancy (e.g., Gunnar, 1992; Gunnar et al., 1996) to middle childhood and adolescence (Bendezú et al., 2019; Perry et al., 2021; Yirmiya et al., 2020). In the earlier periods of development, attachment with parents and the caregiving environment have been found to play a particularly important role in buffering against stress in offspring (Hostinar et al., 2015). In contrast, environmental adversity has been associated with increased cortisol reactivity (see Hunter et al., 2011 for a review). Taken together, the HPA system may be calibrated by environmental influences that occur early in development.

Researchers have examined the social buffering effect in high-risk populations that often experience augmented levels of stress in early life, such as populations of youth raised by parents with childhood trauma or adopted from orphanage care (e.g., Perry et al., 2021; Senehi et al., 2021). Results from these studies have revealed risk buffering as well as risk exacerbating roles of parenting behaviour on HPA axis activity. For example, Senehi and colleagues (2021) examined the moderating effects of parental emotional availability on the relation between being

raised by a parent with a history of adverse childhood experiences (abuse, neglect, and family dysfunction) and offspring hair cortisol concentrations (an index of chronic stress). The results demonstrated that having a parent with high emotional availability buffered from the effects of parental adverse childhood experiences, as indicated by low child hair cortisol concentrations. Conversely, in the absence of parental emotional availability, parental adverse childhood experiences was a robust predictor of elevated hair cortisol concentrations in offspring. The present study aims to extend this line of research by using a sample of offspring having a parent with bipolar disorder (OBD) followed across a 12-year period. The OBD are at high risk of developing a host of mental disorders compared to offspring of healthy parents (Birhamer et al., 2021; Nijjar et al., 2014). While the intergenerational of affective disorders likely involves an interplay between many risk factors (Maciejewski et al., 2018; Remes et al., 2021; Sawyer et al., 2019), alterations in HPA axis functioning and suboptimal caregiving environments have both been independently linked to increased risk of psychopathology in the OBD (Ellenbogen et al., 2011; Iacono et al., 2018).

Indeed, HPA axis dysfunction is one of the most prominent risk factors associated with affective disorders (Bao & Swaab, 2019; Ellenbogen et al., 2019). A number of studies, including meta-analyses, have demonstrated HPA axis dysfunction in individuals with a diagnosis of major depressive disorder (MDD) or bipolar disorder (BD; Knorr et al., 2010; Lopez-Duran et al., 2009; Murri et al., 2014, 2016; Stetler & Miller, 2011). Recent systematic and meta-analytic reviews have documented a similar hyperactivation of the HPA axis in offspring of parents with an affective disorder *prior* to the onset of any mood episodes (Klimes-Dougan et al., 2022; Serravalle et al., 2023). The OBD, importantly, have higher daytime cortisol levels in the natural environment in adolescence and young adulthood than control offspring

(Ellenbogen et al., 2006, 2010). Thus, subtle changes in HPA functioning might precede the development of affective disorders.

Consistent with the literature of the effects of the caregiving environment on cortisol levels in youth (e.g., Perry et al., 2021; Senehi et al., 2021), researchers have speculated that changes in the HPA axis in the OBD might partly result from disruptions in the caregiving environment (Klimes-Dougan et al., 2022). Numerous studies indicated the OBD, relative to controls, are raised in a stressful caregiving environment. Specifically, parents with BD and their partners tend to possess maladaptive traits (Serravalle et al., 2020), demonstrate negativity and a lack of reciprocity in their relationships with their children (Doucette et al., 2016; Serravalle et al., 2020), and create home environments characterized by elevated levels of conflict, low cohesion, and poor structure/organization (Stapp et al., 2020). Despite this evidence, there are few studies who have implemented prospective longitudinal designs to investigate the relation between early exposure to stressful caregiving environment and later HPA axis functioning in youth exposed to mental illness in parents.

One prospective longitudinal study found that exposure to MDD in parents and high levels of expressed anger in the first year of the child's life predicted diurnal cortisol levels in middle childhood and adolescence (Essex et al., 2011). In the present sample of OBD and control offspring, parents' ability to provide organization and predictability (structure) within the caregiving environment was paramount in shaping cortisol reactivity in youth. That is, low levels of structure in the home during middle childhood predicted a high cortisol response to a social stressor task and following awakening in adolescents, driven primarily by the OBD (Ellenbogen & Hodgins, 2009). Halligan and colleagues (2004, 2007) added to this line of research by examining relations between HPA functioning and offspring psychopathology. Specifically, the

authors found that, compared to control offspring, youth exposed to maternal postnatal MDD had elevations and greater variability in their morning cortisol levels at 13 years old, which in turn predicted more depressive symptoms at age 16. Similarly, in the present sample of OBD, high daytime cortisol levels in late adolescence predicted the prospective development of MDD in young adulthood, even after controlling for mental disorders in adolescence (Ellenbogen et al., 2011).

In the present study, we are reporting on a new data collection focusing on the cortisol response following awakening (CAR) in the full OBD sample, who are a mean age of 19.5 years. This data collection follows up on earlier sub-sample data collected at ages 16 and 18 years of age (Ellenbogen et al., 2006, 2010). The CAR is an increase in cortisol levels (by approximately 50–60%) upon awakening that is speculated to help transition individuals from sleep to full alertness in preparation for potential challenges in the upcoming day (Clow et al., 2004; Fries et al., 2009). Although complex in nature, extra-pituitary influences, including circadian input from the suprachiasmatic nucleus and brain structures such as the hippocampus, likely play a role (Clow et al., 2010). The CAR is particularly relevant to the present study because it has been previously associated with the later development of affective disorders in pediatric populations (Adam et al., 2010). Because the sample is at an age where a substantial proportion have developed an affective disorder, it is expected that many of the OBD who have abnormal HPA functioning will have already had an affective disorder. Indeed, 33% of the OBD, compared to 12% of controls, have developed an affective disorder by the time of the present assessment (Nijjar et al., 2014). Thus, the first goal of the present study is to assess the CAR in young adults with an affective disorder (mostly OBD), OBD without an affective disorder, and control offspring without an affective disorder. In the context of research on HPA axis functioning and

affective disorders (e.g., Lopez-Duran et al., 2009; Murri et al., 2014, 2016; Serravalle et al., 2023), we hypothesize that the offspring with an affective disorder will have a stronger CAR compared to the OBD without an affective disorder and controls.

As a second goal, we will examine a model of risk transmission positing that high-risk families have suboptimal caregiving practices that alter the development of the HPA system in high-risk youth, and that these biological changes are associated with an increased risk of developing an affective disorder. The model will utilize longitudinal data of families having a parent with BD and control families collected when their offspring were between 4 and 12 years of age (Serravalle et al., 2020), and then approximately 12 years later in late adolescence and early adulthood (Nijjar et al., 2014). Based on the social buffering literature and a previous finding in the study sample (Ellenbogen et al., 2009), we hypothesize that risk status (having a parent with BD) will be associated with low levels of organization and consistency in the home (structure), and that low structure will lead to the development of an elevated CAR in offspring, which in turn will increase the risk of internalizing and externalizing symptoms. In other words, we predict that family structure in middle childhood and the cortisol response following awakening in late adolescence and early adulthood will mediate the relationship between risk status and the development of symptoms of mental disorders in youth.

Method

Participants

Participants included 132 (61 female, 71 male) offspring between the ages of 13 and 28 years (M = 19.3; SD = 3.5) from 85 families (44 OBD, 41 control). The sample was comprised of offspring who provided saliva samples from two cohorts recruited at different times. One hundred and eighteen of the offspring (74 families) were participants of a prospective

longitudinal study of families with a parent diagnosed with BD or parents with no mental disorder, taking part in a follow-up (time 2) assessment. Of the original sample (N = 176; 91 OBD and 85 controls), there was an attrition rate of 36.2% among OBD (n = 58) and 29.4% among controls (n = 60). Offspring who did not participate in the time 2 follow-up assessment did not differ from those who did on ratings of childhood internalizing and externalizing problems on the Child Behavior Checklist (Achenbach & Edelbrock, 1991) in middle childhood. The time 2 session occurred, on average, 11.6 ± 1.0 (range 10-14) and 11.5 ± 1.0 (range 10-14) years after the first one in the OBD and controls, respectively. A small number of offspring were recruited in more recent years in an effort to increase the sample size (6 OBD and 8 control from 11 families; 10.6 % of the total sample). Parents were mostly Caucasian, middle-class, and French Canadian. Demographic and clinical information in the OBD and control offspring, including a comparison of offspring with and without a lifetime affective disorder, are presented in Table 1.

Families in the longitudinal study were recruited between 1996 and 1998. Parents with a diagnosis of BD and their families were recruited from psychiatric outpatient clinics in the province of Québec, as well as from advocacy and support groups. Families in which parents had no mental disorder were recruited from the same neighbourhoods as the families with BD, through physicians' offices and community organizations. Detailed information about the original sample is described in previous studies (Ellenbogen & Hodgins; 2004; Serravalle et al., 2020). Inclusion criteria for entry into the longitudinal study were (a) adults raising at least one biological child between the ages of 4 and 14 years, fluency in either English or French, and b) children being raised and educated in Canada. Families in which either a parent or child had a chronic physical disease or handicap, and/or an IQ below 70, were excluded. The new cohort

was recruited through advertisements in local newspapers in 2006-2007. Inclusion and exclusion criteria were the same, except for the age requirement for offspring, which was set at 13 to 23 years of age. Parental diagnoses were confirmed by an experienced clinician using the Structured Clinical Interview for DSM-III-R (SCID-I; Spitzer et al., 1992) for longitudinal families and the SCID-I for DSM-IV-R (First, Spitzer, Gibbon, & Williams, 2002) for new families, as well as from an examination of psychiatric records. Parents from the control families had no current or lifetime axis-I disorder, except for past episodes of substance abuse, anxiety disorders, or eating disorders, as indicated by the SCID-I.

Measures

Time 1-offspring aged 4-13 years

Family parenting practices. Parents completed the Parenting Dimensions Inventory (PDI; Slater & Power, 1987) as a measure of levels of family 1) support (i.e., parental warmth, nurturance, and emotional expressiveness), 2) structure (i.e., organization, consistency, predictability), and 3) control (i.e., frequency and type of disciplinary strategies). Item scales ranged from one (*not at all characteristic of me*) to six (*very characteristic of me*). Scores for each subscale of the PDI were mean ratings across all parents within a family. In the current sample, the PDI showed adequate internal consistency ($a = 0.80$).

Offspring psychopathology in middle childhood. Parents also completed the Child Behavior Checklist (CBCL; Achenbach, 1991) is designed to assess children's internalizing and externalizing difficulties across eight dimensions of functioning at home. Only the overall parent-reported internalizing and externalizing symptoms in offspring were included in this study, for the purpose of controlling for potential continuity effects of psychopathology. Scores were averaged across all parents. The CBCL shows adequate test-retest reliability (k = 0.64 –

0.95) and high internal consistencies (α = 0.90; Achenbach & Rescorla, 2001). Concurrent validity has also been established between the CBCL and other parent-reported behavior scales and diagnostic interviews for children (Barkley, 1998).

Time 2-offspring aged 13-28 years

Offspring psychopathology in adolescence/young adulthood. The SCID-I for DSM-IV-R and Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL; Kaufman & Schweder, 2004) were used to assess for the number of current (past month) and past symptoms of mental disorders in adult and adolescent offspring, respectively. Interviews were conducted by experienced clinicians trained and supervised in the use of the official French and English versions of the SCID-I or K-SADS. In the present study, outcome at the follow-up was defined by the number of symptoms of MDD, anxiety disorders (generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social and specific phobia, and post-traumatic stress disorder), and substance use disorders. Given the low diagnosis rate in the current sample (see Table 1), the number of symptoms reaching the subthreshold or threshold for clinical significance was tallied for each category. Both diagnostic interview demonstrate adequate psychometric properties (Basco et al., 2000; First et al., 2002; Kaufman et al., 2004). Inter-rater reliability obtained for 15% of interviews in the current sample was excellent (k = .82 for affective disorders).

Cortisol sampling. Participants collected saliva at awakening, 30 and 60 minutes later, at 1300 h, 1500 h, 2000 h, and at bedtime on three consecutive days while following their usual daily routine. The current study will focus on the CAR, as measured by the area under the curve 'with respect to increase' (AUC_i) for the first three samples (Pruessner et al., 2003). The AUC_i assesses the magnitude of change within the first 60 minutes of awakening, using the trapezoid

formula calculated with reference to its first value (awakening). Participants were instructed to remove lipstick, to refrain from drinking water at least five minutes before sampling, and to refrain from eating, drinking (except water), smoking, and brushing teeth at least 60 min before sampling. Participants also recorded any activities prior to sampling. Saliva was expressed directly into polypropylene 6 ml vials. The vials for saliva collection were kept in larger bottles with time-stamping micro-circuitry in the cap (*Aardex Ltd., MEMS 6 TrackCap*), which automatically registered the exact time when the container was opened and closed.

Saliva samples were frozen at -20°C until assayed for cortisol by a sensitive radioimmunoassay using commercial kits from *Diagnostic Systems Laboratory* (DSL-2000; Sanofi Diagnostics, Montréal, CAN; n = 37, 20 OBD/17 OFH-) and *MP Biomedicals* (Solon, Ohio, USA; n = 85, 42 OBD/43 OFH-). DSL abruptly stopped producing radioimmunoassay kits for cortisol during the course of the study, forcing us to switch to the use of cortisol kits from MP. We compared absolute cortisol values obtained with both kits and found that the main effect of assay kit on daytime cortisol approached significance (DSL mean cortisol = 0.602 µg/dl and MP mean cortisol = 0.499 µg/dl; $p = 0.064$). We controlled for assay kit by standardizing cortisol data for each kit, so that cortisol levels for both kits had a mean of zero and a standard deviation of one (z-scores). Characteristics of the assays were similar between the two kits with a sensitivity set at 0.01 ug/dl (or 0.276 nmol/L). The inter- and intra-assay coefficients of variations for all assays were 3.4% and 4.6% for the DSL kit (on a range of 0.01-10 µg/dl dose) respectively, and 4.0% and 4.6% for the MP kit (on a range of 0.01-10 µg/dl dose) respectively.

Procedure

Following a telephone screening, parents with BD were administered the SCID-I interview in the laboratory or at their homes. Parents with BD were euthymic during testing. For

participants who partook in the longitudinal study, each parent independently completed the PDI at this first timepoint. Control parents underwent the same procedures as families with a parent having BD. Approximately 12 years later, offspring were scheduled to return to the laboratory to undergo a diagnostic assessment and partake in three days of saliva collection in their natural environment (as described above). The offspring recruited at time 2 completed the same procedures, except that their parents underwent a SCID-I assessment to determine risk status. Informed written consent was obtained from parents at time 1 and from both parents and offspring at time 2. Offspring participants received an honorarium of $150 CAN at time 2 for participating in the full data collection. All procedures at time 1 and 2 were approved by the Ethics Committee of the Université de Montréal and the Human Research Ethics Committee of Concordia University (Montréal, Canada), respectively.

Statistical Analyses

Data were first screened and corrected for outliers and distributional anomalies that violated statistical assumptions. For longitudinal analyses, cases with missing data at time 1 or 2 were deleted listwise (n = 3). Using a Statistical Package for the Social Sciences (SPSS; Version 23), an Analysis of Covariance (ANCOVA) was first conducted to examine group differences in the CAR (AUC_i) in the OBD with an affective disorder relative to OBD with no affective disorder and control offspring with no affective disorder. Specifically, a Sex (males vs females) X Risk Status (having a parent with BD vs controls) ANCOVA controlling for age and the sampling compliance was conducted. Planned simple contrasts were used to determine the source of group differences. Sex X Risk Status ANCOVA was repeated with only OBD with and without an affective disorder to explore potential differences in these clinically diverse high-risk youth.

Lastly, parallel serial mediation analyses were conducted in Mplus version 8.0 (Muthén & Muthén, 2017) to determine whether the relation between risk status and offspring psychopathology (depressive and anxiety symptoms, and substance abuse symptoms) measured at time 2 were mediated by levels of support, structure, and control in families at time 1 and offspring CAR at time 2. Parallel serial mediation analyses predicting each combination of mediator and outcome variables were ran simultaneously. Bootstrapped 95% confidence intervals were used to estimate the strength of each indirect effect. The bootstrap sample was set at 1000 iterations. Across all mediation analyses, offspring sex and offspring psychopathology at time 1 (i.e., parent-reported internalizing and externalizing symptoms) were entered as control variables. Estimates were also adjusted using the cluster function (clustered by family) to account for data dependency across siblings.

Results

Demographic and compliance measures

Demographic, diagnostic, and mean objective compliance for samples collected at 30 and 60 minutes following awakening are presented in Table 1. ANOVAs revealed a group difference in age ($F_{2, 129} = 4.9$, $p = .009$, $\eta^2 = 0.07$) but not in sampling compliance ($F_{2, 128} = .33$, $p = .722$, $\eta^2 = 0.005$). The offspring with an affective disorder were older than the control offspring (Tukey HSD, p=0.01), but no other group differences were found.

Group differences in the cortisol response following awakening

Salivary cortisol levels at awakening, and 30 and 60 minutes post-awakening are presented in Figure 1a. A Sex X Risk Status ANCOVA controlling for age and the sampling compliance was conducted on cortisol AUC_i (Figure 1b). Main effects of risk ($F_{2, 124} = 2.6$, $p = .082$, $\eta^2 = 0.04$) and sex ($F_{1, 124} = 3.0$, $p = .087$, $\eta^2 = 0.02$), and the Sex X Risk Status interaction

($F_{2, 124} = 2.4$, $p = .092$, $\eta^2 = 0.04$), were detected at a small to medium effect size, but these effects fell short of conventional levels of statistical significance. Planned simple contrasts revealed that the offspring with an affective disorder had a higher cortisol response following awakening than the OBD with no affective disorder ($p = 0.046$, *Cohen's d* = 0.423) and control offspring ($p = 0.039$, *Cohen's d* = 0.468). Follow-up ANOVAs of the Sex X Risk Status interaction revealed a robust sex difference among controls ($F_{1, 59} = 17.0$, $p < 0.001$, $\eta^2 = 0.22$) but not among the OBD with no affective disorder ($F_{1, 44} = 0.00$, $p = 0.96$, $\eta^2 = 0.00$) or offspring with an affective disorder ($F_{1, 25} = 0.17$, $p = 0.68$, $\eta^2 = 0.01$). Specifically, female control offspring had a greater CAR than male control offspring.

Because the offspring with an affective disorder included both OBD ($n = 20$) and controls ($n = 7$), the Sex X Risk Status ANCOVA was repeated excluding controls with an affective disorder ($n = 125$), thus forming "pure" groups of OBD with and without an affective disorder. The results were largely identical, with a marginally significant risk effect ($F_{2, 117} = 2.5$, $p = .084$, $\eta^2 = 0.04$) and a significant Sex X Risk Status interaction ($F_{2, 117} = 3.9$, $p = .024$, $\eta^2 = 0.06$). The OBD with an affective disorder had a larger cortisol AUC_i following awakening (z-score ± SD, 0.38 ± 0.92) than the OBD with no affective disorder (-0.11 ± 1.12; $p = 0.039$, *Cohen's d* = 0.460) and controls (-0.08 ± 0.86; $p = 0.040$, *Cohen's d* = 0.523). In sum, the cortisol AUC_i distinguishes between OBD who develop affective disorders and OBD who do not, suggesting it may be an important marker of risk for affective disorders.

Mediation of the relation between risk status and offspring psychopathology in early adolescence and young adulthood via family functioning and offspring CAR

Pearson correlations between the main study variables are shown in Table 2. Coefficients of the associations between predictor and mediator variables, and mediator and outcome

variables are presented in Table 3, as well as the coefficients for total, direct, and indirect effects. Results for the indirect effects are highlighted in the paragraph below, as a significant indirect effect is exclusively needed to establish mediation (Rucker, Preacher, Tormala, & Petty, 2011).

Among participants who had longitudinal data (N = 115; 57 OBD and 58 controls), we ran multiple serial mediation models simultaneously to examine whether risk status indirectly predicted depressive/anxiety symptoms and substance abuse in offspring 12 years later via levels of support, structure, and control in the caregiving environment during middle childhood and the AUC_i CAR in adolescence/young adulthood, while controlling for offspring sex and age. Of the three domains of the caregiving environment, family structure, along with the CAR in offspring, mediated the relation between having a parent with BD and depressive and anxiety in symptoms in youth (β = .24, SE = .18, 95% CI [.01, .66]). As depicted in Figure 2, relative to controls, the OBD were exposed to lower levels of structure in middle childhood (path a), which led to subsequent elevation in offspring CAR (path d) and depressive and anxiety symptoms in adolescence/young adulthood (path b). Across all serial mediation analyses predicting later substance abuse symptoms, the indirect effects were non-significant (all 95% CI contained zero).

Discussion

The current study first examined whether the CAR would distinguish between young adults who have a history of an affective disorder, OBD with no affective disorder, and control offspring. Consistent with our hypothesis, the CAR in offspring with an affective disorder, who are mostly OBD, was larger than both OBD and control offspring without an affective disorder. Interestingly, most of the offspring with an affective disorder were in clinical remission (i.e., met criteria for past but not current affective disorders) at the time of cortisol sampling. This is consistent with previous literature suggesting persistent alterations in cortisol rhythms

throughout different phases of affective disorders, including euthymic stages (Izakova et al., 2020; Morris & Rao, 2014; Murri et al., 2016). The present findings extend our previous reports of high CAR and daytime cortisol in the OBD, relative to control offspring, when they were younger (in adolescence), which were observed irrespective if they had an affective disorder (Ellenbogen et al., 2006). Thus, there appears to continuity from adolescence to early adulthood in terms of elevated HPA functioning in the OBD. The present distinction between OBD with and without an affective disorder is consistent with longitudinal studies showing that elevated daytime cortisol levels predict future affective disorders in the offspring of parents with an affective disorder (Ellenbogen et al., 2011; Goodyer et al., 2009; Halligan et al., 2004; Harris et al., 2000). Moreover, a prospective study of high-risk youth (oversampled for high neuroticism) shows a strong link between elevated CAR and the development of MDD (Adam et al., 2010), although this relationship waned over time (Vrshek-Schallhorn et al., 2013). Thus, the current study lends further support towards high cortisol levels, especially following awakening, as an important trait biomarker of vulnerability for developing an affective disorder.

The second part of the study tested a model of the environmental transmission of risk in the OBD, where disruptions in their caregiving environment alter the development of the HPA axis, which over time increase their risk of psychopathology. Consistent with the model, risk status (having a parent with BD) was associated with low levels of structure in the home during middle childhood, which then predicted an elevated CAR and the development of depressive/anxiety symptoms in late adolescence and young adulthood. It is important to note that this effect was independent of offspring sex and was detected even after controlling for early presentations of internalizing and externalizing symptoms in youth during middle childhood. There were no significant findings for models that including family levels of support or control,

or when substance abuse symptoms were specified as the outcome. For the latter, parental behavioural control in middle childhood and parents' satisfaction with their social support network was associated with the prospective development of substance use symptom in the OBD (Trespalacios et al., 2023).

These findings add to a growing body of literature that underline the important role parents play in shaping stress-sensitive systems in children, especially in the earlier years of development (Hostinar et al., 2014; Gunnar & Hostinar, 2015). Direct comparisons of the social buffering effect on acute psychological stress across different ages suggests that parental presence can attenuate the stress response in 9- and 10-year-old children, but not 15- and 16-year-old adolescents (Hostinar et al., 2015). The present findings are consistent with other studies of maternal depression and its longstanding effects on their offspring's cortisol levels. Halligan and colleagues (2004, 2007), for example, showed that post-natal depression in mothers prospectively predicted elevated cortisol in their 13 year old children, and that their high cortisol levels predicted MDD symptoms at age 16 years. This is in line with theories on attachment and socio-emotional development that posit early relationships with parents and the emotional climate of the family have long-lasting consequences on children's neuroendocrine function, self-regulation, adjustment, and future social relationships (Ainsworth, 1985; Morris et al., 2007; Sameroff & Fiese, 2000; Smeekens et al., 2010).

The present study is also consistent with the developmental working model of the stress-dampening effects of social support put forward by Hostinar and Gunnar (2015). This model posits that through hypothalamic oxytocin activity and safety signals given by attachment figures, early caregiving experiences determine later effectiveness of the social buffering of stress. That is, early social interactions, especially with parents, impact offspring's emotional

well-being and shape future interpersonal relationships. Indeed, childhood exposure to parents that display high levels of neuroticism and low levels of agreeableness has been shown to negatively impact offspring's mental health and interpersonal functioning both in childhood and prospectively in adolescence-early adulthood (Ellenbogen & Hodgins, 2004; Ostiguy et al., 2012). Thus, it is important to consider proximal influences (e.g., the offspring's current social relationships), in addition to early adversity effects, in shaping the HPA axis in the OBD. While not measured in the current study, it possible that the acute stress generated from negative social interactions during adolescence/young adulthood may also influence concurrent HPA axis activity and internalizing symptoms in the OBD. Given that parenting practices tend to remain consistent over time (Bornstein & Putnick, 2021), it is important to consider that the caregiving environment obtained in the present study may represent a snapshot of the prolonged exposure to the stressful caregiving environments that the OBD are exposed to throughout development. These speculations are supported by previous research demonstrating the detrimental effects of interpersonal and/or chronic stress on HPA axis functioning in the OBD (Ellenbogen et al., 2013) and the mediating effects of daily interpersonal stress in children on the relation between family stress and youth internalizing symptoms (Lecarie et al., 2022). Moreover, the OBD demonstrate a more robust HPA response to chronic and episodic stress (Ostiguy et al., 2011), which may be another factor contributing to the continuity of elevations in CAR from adolescence to early adulthood.

Family levels of structure emerged as the only aspect of the caregiving environment that predicted hyperactivation in the CAR and elevations in depressive and anxiety symptoms in the OBD. The present results replicate previous work in a sub-sample of the present cohort, where we found that low parenting structure in middle childhood predicted a high CAR and high stress

reactivity in response to the Trier Social Stress Test in adolescence (7-8 years later), which was driven largely by the OBD in the sample (Ellenbogen & Hodgins, 2009). Structure provided by parents has been identified as a distinct parenting behaviour that often promotes self-regulation and competence in children by making the environment more predictable (Grolnick & Pomerantz, 2009), and has been linked to positive outcomes in adolescents, such as academic achievement, adjustment, and self-efficacy (Ratelle et al., 2018). Conversely, consistent with the Adaptive Calibration Model, children raised in unpredictable environments have HPA systems that are calibrated upwards to allow for immediate responsivity in face of threat, despite the potential long-term costs of a sustained HPA activation (Del Giudice et al., 2011). This may be especially important in the OBD given the levels of instability associated with a diagnosis of BD (e.g., McIntyre & Calabrese, 2019). That is, parents with BD that can maintain adequate levels of structure and consistency in the home may protect their offspring from adverse outcomes. This is in line with findings from a recent studies on the efficacy of a childhood preventative intervention program for families with a parent having BD (Serravalle et al., 2023). While improvements in various aspects of the caregiving environment following treatment were noted, it was only positive changes in structure and organization in the home that predicted subsequent reductions in externalizing symptoms in the OBD relative to an assessment-only control group. Thus, structure in the home may represent an important and unique treatment target to offset adverse outcomes in the OBD.

Strengths and limitations

This the first study, to the best of our knowledge, to test a pathway of risk transmission involving the HPA axis in the OBD. It contributes to a small number of studies that have used longitudinal data to examine the associations between having a parent with an affective disorder,

the caregiving environment, and HPA axis functioning (e.g., Ellenbogen & Hodgins, 2009; Halligan et al., 2007), allowing us to better understand the underlying mechanisms that may be causally related to adverse outcomes in the OBD. The assessment of parent diagnoses and offspring depressive, anxiety, and substance use symptoms by trained clinicians, multiple cortisol sampling days, and the use of an objective method of assessing sampling compliance represent methodological strengths of the current study. Estimating all models simultaneously while controlling for the non-independence of sibling data and for offspring psychopathology in middle childhood strengthened our statistical procedures. These techniques accounted for redundancies in study variables/sibling data and the potential for the current findings to be explained by continuity of internalizing and externalizing symptoms (Larsson et al., 2008).

Several study limitations warrant further discussion. The current sample includes offspring with a large age range. It is possible that the effects of the caregiving environment on child outcomes might differ between younger and older offspring in the sample. The different aspects of the caregiving environment were measured using self-report, which could be biased by parents' mental health status (De Los Reyes & Kazdin, 2005). Attempts to reduce this bias were made by taking average ratings of family support, structure, and control across both parents and by having parents with BD complete assessment measures while in a euthymic state. It is important to consider the limitations of cortisol measurement via saliva sampling in that it only reflects cortisol levels measured during the specific days and times in which the samples were collected (Sauvé et al., 2007). Thus, assessing cortisol concentrations from hair samples, which provides an index of chronic HPA functioning over extended periods of time (Gow et al., 2010), would have been a useful supplement to the study methodology. As indicated in the recent guidelines for the assessment of the CAR (Stalder et al., 2022), even a small delay between

actual awakening time and the collection of the first salivary sample affects the reliability of the CAR estimates. The use of actigraphy technology to objectively measure awakening times and control for delays in saliva sampling time is recommended for future studies. Recent studies question the specificity of the reported links between having a parent with BD and family-environmental (Sandstrom et al., 2020; Stapp et al., 2020) and neuroendocrine risk (Adam et al., 2014). Future research might include groups of families having a parent with a different mental disorder or a physical illness. Lastly, the study sample is mostly middle-class and French Canadian; thus the findings might not generalize to a more diverse population of families with a parent having BD.

Summary and Conclusion

In conclusion, offspring who had an affective disorder, who were mostly OBD, had higher CAR compared to OBD with no affective disorder and control offspring with no history of an affective disorder. Longitudinal analyses supported the proposed model, where OBD exposed to low levels of structure in the caregiving environment during middle childhood exhibited an elevated CAR and greater depressive and anxiety symptoms in late-adolescence/young adulthood. These associations were absent when examining other aspects of the early caregiving environment, namely levels of support and control by parents. This is consistent with research demonstrating structure and consistency in the home as an important treatment target (Serravalle et al., 2023). Together, these data provide evidence of the long-term effects of the early caregiving environment on the stress-sensitive biological systems in offspring. Further research is needed to examine how this biological sensitivity may impact the effectiveness of future social relationships in buffering stress.

Table 1

Descriptive information and mental disorders in the offspring of parents with bipolar disorder (OBD) and offspring of parents with no affective disorder (control).

	Offspring with an affective disorder		**OBD with no affective disorder**		**Controls with no affective disorder**
n	27		44		61
Sex (male:female)	12:15		29:15		30:31
Mean age, years ± SD	20.7 ± 3.2		19.7 ± 3.5		18.3 ± 3.5
Sampling compliance, minutes ± SD[a]	2.4 ± 7.5		1.3 ± 4.0		1.4 ± 5.6
Number of mental disorders	**OBD**		**Control**		
n	64		68		
	Current	**Past**	**Current**	**Past**	
Affective disorders	5	15	0	7	
Major Depression	1	15	0	7	
Bipolar Disorder I	2	-	0	0	
Bipolar Disorder II	2	-	0	0	
Anxiety disorders	21	6	9	2	
Social Phobia	3	1	3	0	
Specific Phobia	10	1	4	2	
Generalized Anxiety Disorder	5	0	2	0	
Post-Traumatic Stress Disorder	0	3	0	0	
Obsessive-Compulsive Disorder	0	1	0	0	
Panic Disorder/Agoraphobia	3	0	0	0	
Externalizing disorders	13	15	7	9	
Alcohol Abuse/Dependence	3	1	3	0	
Drug Abuse/Dependence	9	13	3	7	
Attention Deficit/Hyperactivity Disorder	1	0	1	0	
Conduct Disorder/Oppositional Defiant Disorder	0	1	0	2	
Other Diagnoses[b]	1	6	1	7	
Any Diagnoses	26	17	14	13	

[a] Sampling compliance is the mean number of minutes before or after the samples taken at 30 and 60 minutes after awakening [b] Other diagnoses include anorexia nervosa (n=1, control), hypochondriasis (n=1, OBD), past adjustment disorder with depressive symptoms (controls,

n=3), past motor/vocal tic (n=1, control; n=1, OBD), past enuresis (n=1, control; n=3, OBD), past separation anxiety disorder (n=1, control; n=1, OBD), and past phencyclidine (PCP)-induced psychotic disorder (n=1, OBD).

Table 2

Pearson Correlations Between the Main Study Variables (N = 115)

	1	2	3	4	5	6	7	8	9	10	11
1) Risk Status											
2) Offspring Sex	-.13										
3) T1 Offspring Age (T1)	.20	.01									
4) T1 PDI Family Support (T1)	-.33**	.03	-.04								
5) T1 PDI Family Structure (T1)	-.31**	.13	.02	.20*							
6) T1 PDI Family Control (T1)	-.14	.06	.29**	-.28**	.23*						
7) T1 CBCL Internalizing (T1)	.05	.11	.11	.00	.03	.08					
8) T1 CBCL Externalizing (T1)	.06	.11	.11	.00	.03	.08	.22**				
9) T2 CAR (AUC_i)	-.01	.24*	.00	.09	-.20*	-.17	-.07	-.07			
10) T2 Offspring Dep/Anx Symptoms[a]	.13	.18	.20	-.01	-.02	-.04	.07	.07	.37**		
11) T2 Offspring Substance Abuse[a]	.17	-.16	.17	-.08	.04	-.17	-.12	-.12	.02	.13	

Note. Risk Status = offspring of parents with bipolar disorder vs. control; PDI = Parenting Dimensions Index; CBLC = Child Behaviour Checklist; CAR = cortisol awakening response; T1 = time 1 (middle childhood); T2 = time 2 (adolescence/young

adulthood) [a] From the Structured Clinical Interview for DSM-IV or Kiddie Schedule for Affective Disorders and Schizophrenia. [b] Includes present (past month) subclinical and clinical symptoms for each disorder. * $p < .05$; ** $p < .01$

Table 3

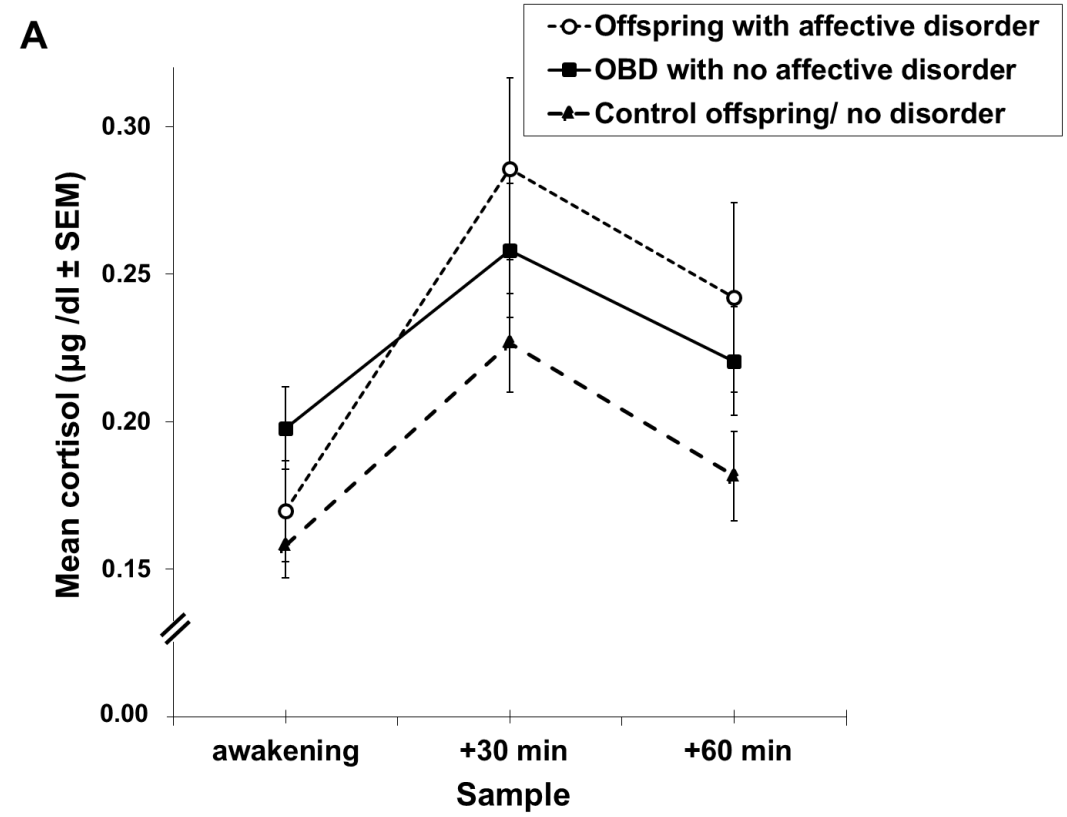
Unstandardized coefficients for the direct, indirect and total effects of parallel serial mediation models predicting offspring psychopathology from risk status via family environment and offspring cortisol awakening response (CAR).

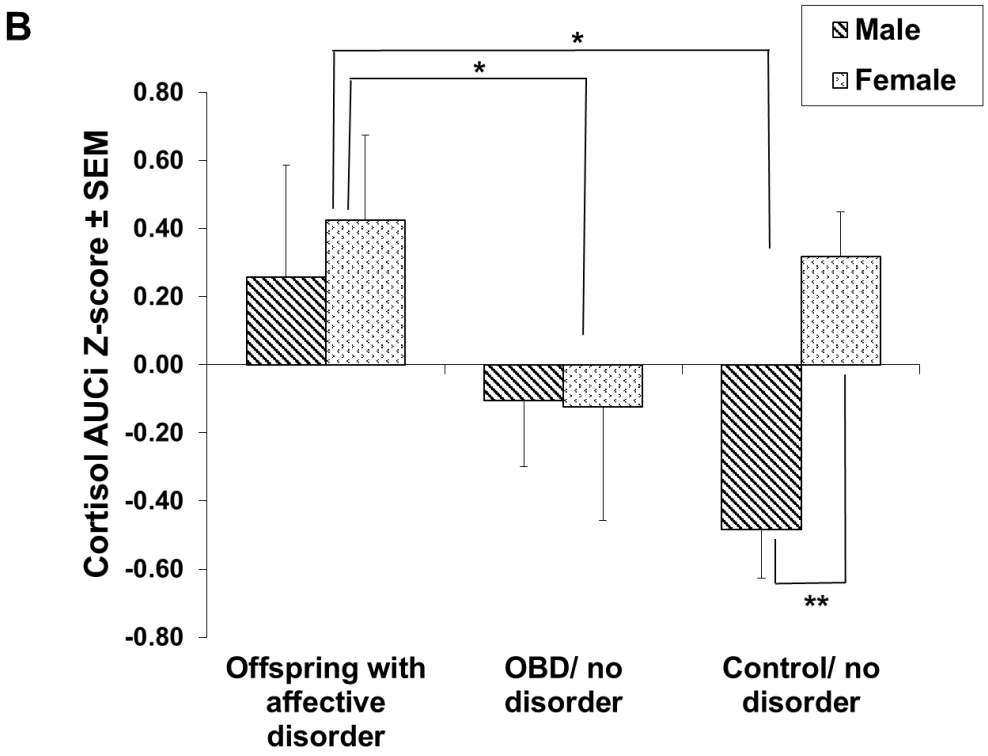
Total effects (across all models)	**β (SE)**	***p***
Predicting depressive and anxiety symptoms	1.58 (.96)	.10
Predicting substance abuse symptoms	.92 (1.09)	.40
Direct pathways	**β (SE)**	***p***
Independent[a] → Mediator 1[b] (paths a_1)		
Risk predicting family support	-.71 (.24)	.00**
Risk predicting family structure	-.64 (.23)	.01**
Risk predicting family control	-.21 (.18)	.26
Mediator 1 → Mediator 2 (paths d)		
Family support predicting CAR	.01 (.01)	.34
Family structure predicting CAR	-.01 (.01)	.05*
Family control predicting CAR	-.01 (.01)	.37
Mediator 2 → Dependent[c] (paths b_1)		
CAR predicting depressive and anxiety symptoms	33.31 (9.68)	.00**
CAR predicting substance abuse symptoms	3.41 (8.42)	.69
Indirect pathways (via both mediators)	**β (SE)**	**95% CI**
Predicting depressive and anxiety symptoms		
Risk → Family support → CAR	-.14 (.17)	[-.57, .13]
Risk → Family structure → CAR	.24 (.18)	[.01, .66]*
Risk → Family control → CAR	.05 (.09)	[-.12, .24]
Predicting substance abuse symptoms		
Risk → Family support → CAR	-.01 (.06)	[-.17, .09]
Risk → Family structure → CAR	.03 (.08)	[-.13, .22]
Risk → Family control → CAR	.01 (.02)	[-.04, .06]

Note. CAR = cortisol awakening response; [a]Across all mediation models, the independent variable is offspring risk status (having a parent with BD or not). [b]Based on Parenting Dimension Inventory (Parent-report); [c]From the Structured Clinical Interview for DSM-IV or Kiddie Schedule for Affective Disorders and Schizophrenia. Includes present (past month) subclinical and clinical symptoms for each disorder. *$p < .05$; **$p < .01$

Figure 1

Mean cortisol levels at awakening, and 30 and 60 minutes post-awakening across groups

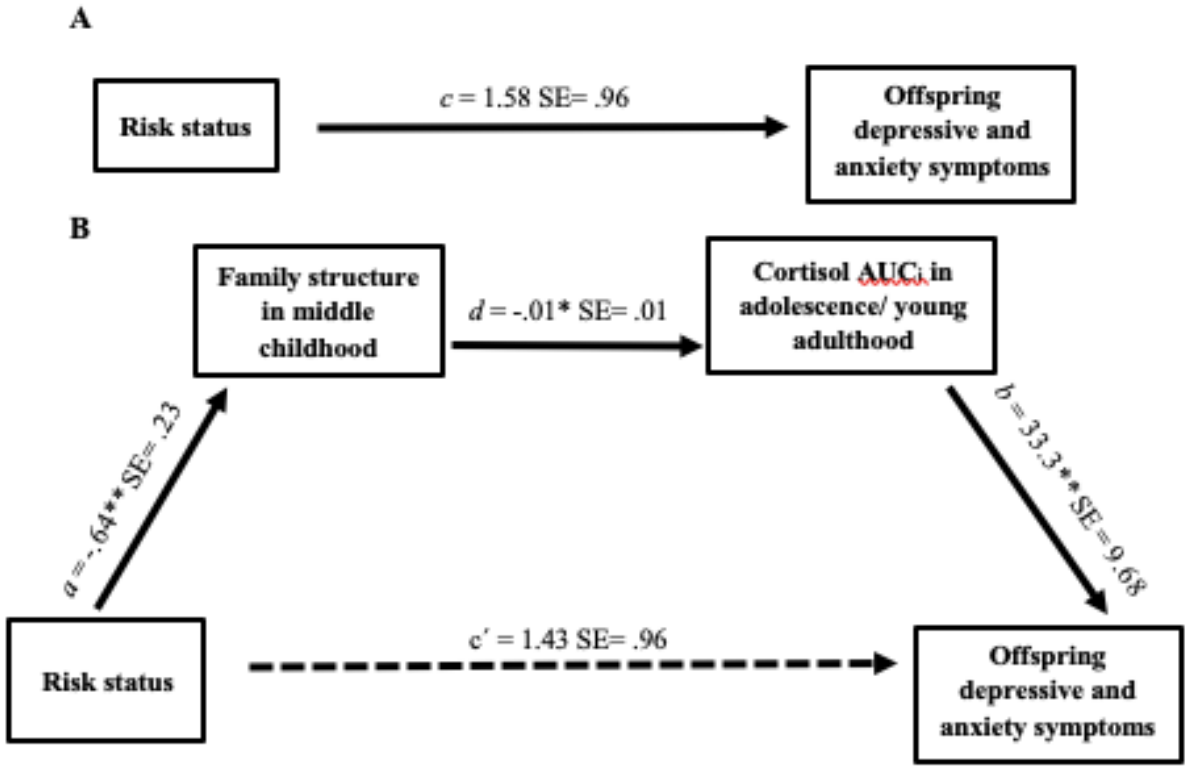




Note. **A**. Mean cortisol, in μg/dl, levels at awakening, and 30 and 60 minutes post-awakening in the offspring having an affective disorder in their lifetime, offspring having a parent with bipolar disorder (OBD) but no lifetime affective disorder, and control offspring having parents with no affective disorder and no lifetime affective disorder themselves. **B**. Standardized (z-score) area under the curve with respect to increase (AUCi) cortisol following awakening in the three groups defined above by sex of the offspring. Offspring with an affective disorder, most of whom are OBD, exhibit an increased cortisol AUCi response following awakening than high risk OBD who have not developed an affective disorder and control offspring.

Figure 2

Serial mediation model



Note. A serial mediation model testing whether family structure in middle childhood and the cortisol response following awakening in late adolescence and early adulthood mediate the relationship between risk status (having a parent with bipolar disorder) and current depressive and anxiety symptoms in youth. **A**. Path *c* is the total effect of risk status on current internalizing symptoms (sum of direct and indirect effects across all models predicting depressive and anxiety symptoms). **B**. Path *c′* is the direct effect of risk status on current depressive and anxiety symptoms, path *a* is the direct effect of risk status on family structure, path *d* is the direct effect of family structure on the area under the curve with respect to increase (AUCi) cortisol response, and path *b* is the direct effect of cortisol AUCi on current depressive and anxiety symptoms. The indirect effect (*adb*) of risk status predicting offspring internalizing symptoms through the two

mediators in sequence, family and cortisol AUCi, was significant (Confidence intervals: 0.01, 0.66). Coefficients are unstandardized regression coefficients. *p < .05; **p <.001

Transition paragraph 2

The second study investigated a model of the environmental transmission of risk in the OBD, where disruptions in their caregiving environment alter the development of the HPA axis, which over time increase their risk of psychopathology. These findings add to a growing body of literature that underline the important role parents play in shaping stress-sensitive systems in children, especially in the earlier years of development (Hostinar et al., 2014; Gunnar & Hostinar, 2015). Interestingly, we found that family structure, and not other aspects of caregiving environment, predicted increased CAR and greater internalizing symptoms in the OBD. Thus, this study builds on study 1 by highlighting the caregiving environment as an important vulnerability factor contributing to the biological development of stress-sensitive systems.

Based on the findings of Study 2, and the well-established literature on the etiological factors that confer risk to the OBD discussed at the beginning of the thesis, we created the RUSH program. As previously mentioned, the RUSH program aimed at targeting the quality of the caregiving environment in a sample of OBD aged 6 to 11 years with no past or current affective disorders. Based on analyses of secondary outcomes, the RUSH program has been shown to improve parent-child interactions (Serravalle et al., 2020) and reduce parenting stress (Resendes et al., 2022). Specifically, participation in the RUSH program resulted in improved parental positivity and negativity, and dyadic mutuality among target dyads immediately and six months post-intervention. In addition, intervention-related change in parental negativity mediated the relation between having participated in the RUSH program and lower parent-reported internalizing problems among the OBD six months later (Serravalle et al., 2020). Similarly, intervention-related improvements in self-reported parenting stress resulted in lower levels of internalizing and externalizing problems in the OBD at 6-month follow-up (Resendes et al.,

2023). We also explored the impact of the RUSH program on offspring's biological sensitivity to stress. While there were no main effects of the RUSH program on diurnal cortisol secretion in offspring from pre-treatment until 6-month follow-up, intervention-related improvements in family organization was associated with an increase in the CAR and total daily cortisol output, as well as a steepening in the diurnal cortisol slope in the OBD. Similar effects were found with regards to intervention-related changes in family cohesion, such that greater improvements in family cohesion following treatment resulted in elevations in the CAR in the OBD (Yong Ping et al., 2023). These findings are in line with the previously discussed Adaptive Calibration Model (Del Giudice et al., 2011), such that as the caregiving environment became more consistent and predictable, the OBD were able to heighten their biological responsivity in favour of social learning.

In Study 3, we examine the efficacy of the RUSH program by evaluating the primary outcomes, offspring internalizing and externalizing problems as well as various aspects of the family environment (conflict, cohesion, expressiveness, organization, and control). Specifically, we will investigate whether participating in the RUSH program decreases internalizing and externalizing problems in children and improves the quality of the family environment. We also examined a mediation model to test whether changes in the family environment resulted in reductions in internalizing and externalizing problems in the OBD following participation in the RUSH program. These data not only have the potential to further demonstrate the efficacy of one of the first selective prevention programs designed for the OBD, but would also parallel findings from Study 2 demonstrating the possible causal role of the caregiving environment in the emotional and behavioural development of the OBD.

Chapter 4: Reductions in offspring externalizing problems and improvements in the home following a prevention program for families with a parent with bipolar disorder: A pilot study.

Serravalle. L, Iacono, V., & Ellenbogen, M.A. (2023). Reductions in offspring externalizing problems and improvements in the home following a prevention program for families with a parent with bipolar disorder: A pilot study. [Manuscript submitted for publication]. Department of Psychology, Concordia University.

Abstract

The offspring of parents with bipolar disorder (OBD) are often raised in suboptimal caregiving environments, which has been linked to their increased risk for the development of psychopathology. Yet, prevention efforts among the OBD remain limited. We examined the efficacy of the 12-week *Reducing Unwanted Stress in the Home* (RUSH) program, aimed at improving communication, problem-solving and structure in the home. We recruited 26 OBD and 29 control offspring aged 6-11 years and their parents. Using a quasi-experimental design, we examined whether the OBD demonstrated decreased internalizing and externalizing problems and whether family functioning improved following the RUSH program relative to control offspring (assessment-only comparison group). Parent-reported offspring internalizing and externalizing problems, and family functioning were measured at pre- and post-treatment as well as three- and six-month follow-up. Multilevel modelling revealed reduced externalizing symptoms in the OBD and enhanced organization in the family immediately post-intervention. The gains in organization remained at the six-month follow-up, while reductions in family conflict became apparent. Bootstrapped mediation analyses indicated that treatment induced changes in organization, but not the other aspects of the family environment, were associated with reduced externalizing symptoms in the OBD. These data provide preliminary evidence of efficacy of the RUSH intervention in reducing the development of externalizing problems in the OBD. Further investigation using a randomized controlled design is warranted.

Introduction

The offspring of parents with bipolar disorder (OBD) are at risk for a host of mental illnesses and other negative psychosocial outcomes across the lifespan (Birmaher et al., 2021; De la Serna et al., 2021; Nijjar et al., 2014, 2016; Sandstrom et al., 2020). While there is evidence to suggest strong genetic contributions (Goes, 2016), environmental factors have also been shown to play an important role in the intergenerational transmission of risk for affective disorders. In a recent review of the literature, Stapp and colleagues (2020) aimed to identify key characteristics of the family environment in families of parents having bipolar disorder (BD). While the authors highlighted the heterogeneity across studies, the family environment of families with BD, compared to controls, was generally associated with lower cohesion, expressiveness, and organization, inappropriate levels of parental control, and greater conflict. Research has shown that the impact of the family environment on psychopathology in the OBD may vary across different dimensions of family functioning, and as a function of offspring sex and developmental stage (Freed et al., 2015; Iacono et al., 2018). Specifically, low structure/organization in middle childhood has been associated with elevations in concurrent internalizing and externalizing symptoms while low levels of parental control predicted greater offspring psychopathology in late adolescence, up to 12 years later (Iacono et al., 2018). Freed and colleagues (2015) found that the association between lower cohesion and offspring internalizing symptoms was strongest for younger children. In addition, the relation between higher family conflict and current affective disorder in the OBD was specific to younger males. Thus, disruptions in the family environment represents a malleable risk factor that can be targeted by interventions aimed at high risk parents and families.

Adapted Family-Focused Therapy (FFT) is an evidenced-based psychosocial intervention that has been used to treat the OBD with major depressive disorder (MDD) and/or subthreshold symptoms of BD (Miklowitz & Chung, 2016). Multiple randomized controlled trials (RCTs) have demonstrated associations between FFT and improvements in various clinical outcomes in symptomatic OBD, including shorter recovery periods from initial mood symptoms, longer intervals between depressive episodes, and more weeks in remission over the course of a year (e.g., Miklowitz et al., 2015; Miklowitz et al., 2020). Improvements in family functioning following FFT have also been shown to partially mediate improvements in depressive symptoms and suicidality (Miklowitz et al., 2020; Weintraub et al., 2022). Interpersonal and Social Rhythm Therapy is another psychosocial treatment that has been shown to optimize clinical course in similar samples (Goldstein et al., 2018). While there has been significant efforts and promising findings for interventions targeting *symptomatic* high-risk youth, preventive intervention programs focused on improving clinical outcomes among the OBD *prior* to the emergence of clinical mood symptoms are more limited.

Wirehag Nordh and colleagues (2022) compared two manual-based preventive interventions, Family Talk Intervention and Let's Talk about Children, to interventions as usual in youth (8-17 years old) of parents diagnosed with anxiety, MDD or BD using a quasi-experimental research design. Both programs include parenting strategies and skills to enhance family communication. The results revealed reductions in parent-rated mental health problems in offspring following both active treatment groups, compared to increases in offspring psychopathology in the control group from baseline to 12 months follow-up. In a pilot study, Mindfulness-Based Cognitive Therapy for Children was compared to a waitlist control group to examine longitudinal changes in anxiety and emotion regulation in the OBD (9-18 years)

diagnosed with an anxiety disorder (Cotton et al., 2020). The results demonstrated improvements in overall clinical severity in the treatment group compared to the waitlist control group, but not in clinician- or child-rated anxiety or emotion regulation. However, improvements in anxiety and emotion regulation were found in children who demonstrated increases in mindfulness in the MBCT-C condition only. In summary, there are few prevention studies targeting the OBD, and those we identified were either generalized to parents with a variety of anxiety and affective disorders, or included offspring with clinical levels of anxiety.

To the best of 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 the paucity of early prevention efforts in the OBD, we have developed the *Reducing Unwanted Stress in the Home* (RUSH) program. It is a childhood preventive intervention program designed to offset adverse outcomes in the OBD. The RUSH program is a 12-weeks, cognitive-behavioural preventative intervention program that teaches parents and their children how to cope with stress, problem-solve, and communicate more effectively, with an additional focus for parents to better manage child behavior and improve organization and consistency in the home. The RUSH program differs from other existing preventive interventions for this specific population in that it includes both parents and their offspring to *simultaneously* target (1) challenges in the family system, a well-established environmental risk factor associated with BD (Miklowitz, 2007), and (2) stress and anxiety symptoms in offspring, commonly observed in the early stages of the clinical course in BD (Duffy et al., 2019). Including both parent and children in the treatment approach is consistent with evidence based FFT intervention programs for affected offspring (Miklowitz & Chung, 2016). Importantly, the RUSH program is designed as an *early* preventive intervention as it exclusively targets children in middle

childhood (6-11 years old), an age range where few children will have developed an affective disorder. Based on analyses of secondary outcomes, the RUSH program has been shown to improve parent-child interactions and reduce parenting stress, both of which were associated with decreased internalizing or externalizing problems among the OBD (Resendes et al., 2022; Serravalle et al., 2020). It has also been shown to alter hypothalamic-pituitary-adrenal (HPA) axis functioning as a function of changes in family functioning (Yong Ping et al., 2023). The current study focused on the primary clinical outcomes: offspring internalizing and externalizing problems, and the family environment.

The present study was meant to be a proof-of-concept clinical trial comparing OBD to offspring of parents with no affective disorders (i.e., control offspring) across four time points (pre- and post-intervention, and 3- and 6- month follow-up). The present study had two goals: (1) to determine if the RUSH program elicited immediate (T2) and long-term (T3 and T4) improvements in offspring internalizing and externalizing and the family environment (conflict, cohesion, expressiveness, organization, and control), and (2) to assess if positive changes from pre- to post-intervention within these five aspects of the family environment mediated the association between participating in the RUSH program (for families having a parent with BD) and offspring's internalizing and externalizing problems at T4. Offspring of parents with no affective disorder (control) did not participate in RUSH program but served as a comparison group to the OBD by completing all four assessments. Thus, we could control for the effects attributable to the passage of time or participating in a research project.

We hypothesized that the OBD at T1 would display more internalizing and externalizing problems and be exposed to greater levels of difficulties in the family environment than the control offspring. Participating in the RUSH program was expected to yield positive changes in

offspring internalizing and externalizing problems as well as in the family environment for the OBD, including reduced conflict and control, and increased cohesion, expressiveness, and organization. We anticipated that the gains would be sustained up to six months post-intervention (T4). Lastly, via the use of statistical mediation, we hypothesized that participation in the RUSH program would decrease offspring's internalizing and externalizing symptoms at T4 by way of improvements in the family environment from T1 to T2.

Method

Participants

After the screening process and attrition across the study (see Figure 1), the final sample consisted of 26 OBD (60% female) and 29 control offspring (62% female) and an index parent who completed the assessments (BD group: 73% mothers; 86% with a diagnosis of BD; Control group: 89% mothers). Offspring were aged from 6 to 11 years old (OBD: M = 8.2 years; SD = 1.6 years; Control: M = 8.67 years; SD = 1.68). The current sample was mostly Caucasian, middle-class, and French-Canadian. Further details about the demographic characteristics of the sample are presented in Table 1. There were no significant group differences in offspring age, sex, ethnicity, and socio-economic status (all $p < .05$). The six OBD that discontinued participation at T4 did not differ from the original sample in terms of the above demographic variables, offspring internalizing and externalizing problems at T1, and baseline scores in family functioning (all $p > .05$).

Ninety percent and 10% of parents with BD met diagnostic criteria for BD-I and BD-II, respectively. Most of the parents with BD were stable (not in an episode) at the time of the baseline assessment; two individuals with BD met criteria for a current manic episode. All parents with BD were receiving pharmacological treatment (see Serravalle et al., 2020 for

details). Two partners of parents with BD met criteria for a clinical major depressive episode at baseline. Among the OBD, one met criteria for an anxiety disorder, two for enuresis, one for oppositional defiant disorder, and six for attention deficit hyperactivity disorder (all treated with psychostimulant medication) at baseline. The control offspring did not have any mental health diagnoses at T1. None of the OBD were receiving additional psychosocial treatments while completing the RUSH program.

Families with a parent having BD and control families were recruited using online and local newspaper advertisements as well as local clinics and patient support groups within Montréal, Québec. Parents' diagnosis of BD were confirmed using a structured clinical interview. In the control group, parents were included if they did not meet criteria for a current axis-1 diagnosis or a past episode of major depressive disorder, mania, or hypomania. Families must also have at least one biological child between the ages of 6-11 years and be fluent in English or French to be included. Children who presented with an intellectual or pervasive developmental disorder, a chronic physical disorder, or a past or present affective or psychotic disorder were excluded from the study.

Measures

The Structured Clinical Interview for DSM-IV-R (SCID-I; First et al., 2002) and Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL; Kaufman & Schweder, 2004) were used to assess past and present mental disorders of parents and their offspring. Interviews were conducted by senior graduate students in clinical psychology. Both diagnostic interviews demonstrate good psychometric properties (Basco et al., 2000; First et al., 2002; Kaufman et al., 2004).

The Family Environment Scale (FES; Moos & Moos, 2013) is a 90-item self-report questionnaire that was completed by the index parent to assess *current* characteristics of the family environment. The five characteristics of the family environment examined in the current study were conflict (the amount of openly expressed anger and conflict) cohesion (the amount of commitment/support), expressiveness (the degree to which emotional expression is encouraged), organization (the amount of planning that goes into family activities/responsibilities) and control (the degree to which set rules and procedures are respected). Items are answered as true/false and reflect important aspects of family functioning (e.g., "We fight a lot in our family"; "Family members really help and support each other"; "Each person's duties are clearly defined in our family"). The FES has demonstrated adequate internal consistency (Cronbach $\alpha = .71$) and test-retest reliability (Moos & Moos, 1994).

The Behavior Assessment System for Children, Second Edition (BASC-2; Reynolds & Kamphaus, 2004) was used to assess children's internalizing (anxiety, depression, and somatic complaints) and externalizing (hyperactivity, aggression, and conduct problems) symptoms at home (Parent Rating Scales, PRS) and school (Teacher Rating Scales, TRS). The BASC-2 demonstrates adequate test-retest reliability ($k = .64$ - $.95$; Merydith, 2001) and high internal consistency (Cronbach $\alpha = .80$ - $.90$; Tan, 2007). The BASC-2 has also been shown to be sensitive to changes in children's symptoms when used as a treatment outcome measure (McClendon et al., 2011).

Procedure

Following a telephone screening, eligible parents were invited to participate in a diagnostic interview at the laboratory to report on their current and past mental health (SCID-I) as well as the mental health of their children (K-SADS). As the current project was developed as

a proof-of-concept, a quasi-experimental design was adopted. That is, only families with a parent having BD participated in the RUSH program while the control families served as a comparison group for the assessments.

The RUSH program is a 12-session, manual-based preventive intervention program aimed at improving the family environment. Parents participated in 2-hour weekly sessions that followed four modules: stress psychoeducation, problem-solving, communication skills, and organization and consistency in the home (including parenting skills). Child sessions consisted of one-hour sessions that ran separately but in parallel to parent groups. These sessions focused on teaching stress-coping skills to youth, including thought restructuring, problem-solving, emotion labeling, relaxation, and assertiveness training (see Table 2 for session breakdown). The study protocol was based on a number of empirically based treatments for stress management, child anxiety, and marital/family dysfunction (Abramowitz, 2012; Kendall & Hedtke, 2006; Severe, 2000; Shapiro & Sprague, 2009). Groups were made up of five to ten parents or children, and were run by senior graduate students in clinical psychology. Amongst the families that participated in the RUSH program, nine families had only the parent with BD attend, three had only the non-BD partner attend, and nine had both partners attend. The number of sessions attended varied between 8-12 (M = 11.15, SD = 1.18). Scores from observer coding of video-recorded therapy sessions revealed strong therapist competence and adherence to treatment protocol across all parent and child groups (see Serravalle et al., 2020 for more details).

Index parents and their offspring completed four assessments: baseline/pre-treatment baseline (T1), immediately post-treatment (T2), 3-months post-treatment (T3), and 6-months post-treatment (T4). At these assessments, parents completed questionnaires about their child's internalizing and externalizing symptoms (BASC-2 PRS) and characteristics of the family

environment (FES). Similar questionnaires about offspring internalizing and externalizing problems (BASC-2 TRS) were sent to teachers (approximately 70% were returned). These assessments also comprised of other parent questionnaires/interviews, child neuropsychology testing and cortisol sampling, and a parent-child interaction paradigm (not reported here). Participants were remunerated after each assessment ($100 CAN at T1 and T4, and $80 CAN at T2 and T3). All procedures were approved by the Human Research Ethics Committee at Concordia University, Montréal.

Statistical Analysis

Missing data (6 OBD who discontinued participation at T4) was imputed using full maximum likelihood estimation for all analyses. The main efficacy analyses examining the longitudinal changes in offspring internalizing and externalizing scores, and the family environment across the four timepoints were conducting using hierarchical linear modelling techniques (HLM 8.0). Two separate multivariate linear mixed models were estimated to examine pre- to post-treatments (T1-T2) and pre-treatment to six-month follow-up (T1-T4) changes in offspring internalizing and externalizing scores. Level-1 predicted the variability in four measures of offspring internalizing and externalizing problems (parent- and teacher-reported) from an intercept, within-person variation of time (either T1-T2 or T1-T4), and a residual term. The intercepts represented baseline (i.e., pre-treatment) levels of offspring internalizing and externalizing scores. Next, Level-2 estimated the between-person effects of risk status (OBD vs. controls) and relevant covariates (offspring sex and age). Covariates were entered first followed by risk status to obtain the amount of variance risk status accounted for after controlling for offspring sex and age. The same analyses were repeated to examine pre- to post-treatment effects (T1-T2) and long-term changes (T1-T4) in the family environment

(conflict, cohesion, expressiveness, organization, and control). We explored various treatment-related variables (e.g., parent reported motivation prior to treatment, number of sessions attended) as potential covariates but no significant effects were found. Thus, these variables were removed from the analyses to preserve statistical power.

Parallel mediation analyses were then conducted in Mplus version 8.0 (Muthén & Muthén, 2017) to determine if pre-to-post-intervention gains in the family environment (conflict, cohesion, expressiveness, organization, and control) yielded improvements in offspring's internalizing and externalizing symptoms at T4 (see Figure 2). For each of the five family environment measures, a change score was calculated by subtracting scores obtained at T2 from those obtained at T1. Parallel mediation analyses predicting each of the four outcomes, parent- and teacher-reported internalizing and externalizing symptoms at T4, were run simultaneously. Bootstrapped 95% confidence intervals were used to estimate the strength of each indirect effect. The bootstrap sample was set at 1000 iterations. Across all mediation analyses, offspring sex and levels of parent-reported externalizing and internalizing symptoms at T1 were entered as control variables. Estimates were also adjusted using the cluster function (clustered by family) to account for data dependency across siblings.

Results

Multivariate linear mixed model analyses predicting the OBD's growth trajectories over time

Comparisons (OBD vs. controls) of the means and standard deviations for all outcomes across the four timepoints are presented in Table 3. Pearson correlations between the main study variables are shown in Table 4.

Within-subject (level 1) models of parent- and teacher-reported offspring internalizing and externalizing scores, and the five family environment measures (mean scores of conflict, cohesion, expressiveness, organization and control), were assessed from pre- to post-intervention (T1 to T2) and over the course of the study (T1 to T4) among the OBD. The models included linear and curvilinear (quadratic, cubic), if applicable, predictors of change for all outcomes. The growth trajectories in parent- and teacher-reported internalizing and externalizing problems from T1-T2 and from T1-T4 in the OBD were not significant (data not shown). For measures of the family environment, the growth trajectories followed a significant linear trend for family cohesion and organization, such that families with a parent having BD demonstrated increases in cohesion (B = .81, SE = .29, p = .010) and organization (B = .89, SE = .34, p = .010) from T1 to T2. Similar linear increases in family cohesion (B = .79, SE = .28, p = .009) and organization (B = .96, SE = .34, p = .009) were observed from T1 to T4. Changes in family expressiveness followed a cubic curve (B = .65, SE = .16, p = <.001); families who participated in the RUSH program demonstrated an increase in expressiveness in the home from T1 to T2, followed by a decrease at T3, which then improved by T4. No statistically significant growth trajectories were observed for family conflict or control or for family expressiveness from T1 to T2 (data not shown). Visual depictions of changes in offspring internalizing and externalizing scores, and family functioning over time can be found in Figure 3 and 4, respectively.

Multivariate linear mixed model analyses predicting between-group differences in offspring internalizing and externalizing problems over time

Baseline (T1)

Differences in pre-treatment levels of offspring internalizing and externalizing scores between the OBD and control offspring were first examined. The average amount of variability

in the intercept was significant for all measures of offspring internalizing and externalizing problems; parent-reported internalizing (χ^2 = 224.56, p = <.001) and externalizing (χ^2 = 251.97, p = <.001), and teacher-reported internalizing (χ^2 = 194.10, p = <.001) and externalizing symptoms (χ^2 = 148.28, p = <.001). The results revealed a significant effect of risk on baseline levels of parent-reported externalizing symptoms (95% CI *B* [.28, 9.84]), indicating the OBD had higher levels of externalizing problems than control offspring. After controlling for the offspring sex and age, risk accounted for an additional 2.2% in the variance of parent-reported externalizing symptoms at baseline. Offspring sex was found to be a significant predictor of teacher-reported externalizing symptoms (95% Cl *B* [-2.07, -14.50]), indicating female offspring exhibited significantly less teacher-reported externalizing symptoms at baseline compared to male offspring. No other significant effects were observed. Results are summarized in Table 5.

Linear effect of time

Two multivariate models were conducted separately to examine pre- to post-treatment effects (T1-T2) and the effects across all timepoints (T1-T4). The variability in the slopes across time was significant from T1-T4 for all outcomes; parent-reported internalizing (χ^2 = 91.12, p = <.001) and externalizing symptoms (χ^2 = 186.12, p = <.001), and teacher-reported internalizing (χ^2 = 160.13, p = <.001) and externalizing symptoms (χ^2 = 79.55, p = .007). There was considerably less variability in the time slopes across all outcomes from T1-T2 (all results non-significant; data now shown). Given the effects from pre-to post-treatment may be smaller than the more long-term effects and the relatively small sample size, these analyses may have been underpowered. Considering that the change from T1-T2 is of theoretical interest and a core study hypothesis, a Level-2 model was estimated for both pre- to post-treatment effects (T1-T2) and across all timepoints (T1-T4).

When predicting parent-reported externalizing symptoms, there was a significant effect of risk status on the time slope for T1-T2 (95% CI *B* [-1.42, -10.95]). After controlling for the covariates, participation in the RUSH program accounted for an additional 14% of the variance in parent-reported externalizing symptoms from T1-T2. Participating in the RUSH program reduced parent-reported externalizing symptoms from pre- to post-treatment in the OBD relative to the control group. However, these effects were not maintained at 6-month follow-up. No other significant effects emerged (summarized in Table 5).

Multivariate linear mixed model analyses predicting between-group differences in the family environment over time

Baseline (T1)

Differences in pre-treatment levels of different aspects of the family environment between the OBD and control offspring were first examined. The average amount of variability in the intercept was significant for all measures of the family environment; conflict ($\chi^2 = 262.17$, $p = <.001$), cohesion ($\chi^2 = 114.40$, $p = <.001$), expressiveness ($\chi^2 = 84.67$, $p = .003$), organization ($\chi^2 = 224.33$, $p = <.001$), and control ($\chi^2 = 212.39$, $p = <.001$). Risk status was a significant predictor of the intercept for all aspects of the family environment except for cohesion. Specifically, the OBD were exposed to higher levels of conflict (95% CI *B* [0.91, 3.05]) and lower levels of expressiveness (95% CI *B* [-.15, -1.39]), organization (95% CI *B* [-.37, -2.11]) and control (95% CI *B* [-.13, -1.84]) at baseline compared to controls. After controlling for the covariates, risk status accounted for an additional 10.8%, 17%, 11.5% and 1.4% of the variance in baseline levels of conflict, expressiveness, organization, and control in the family home, respectively. Age was found to be a significant predictor of organization (95% Cl *B* [.01, .05]), indicating families with older children exhibited significantly greater organization in the

home at baseline compared to those with younger children. No other effects of age and sex on family functioning at baseline were observed. Results are summarized in Table 6.

Linear effect of time

Two multivariate models were conducted separately to examine pre- to post-treatment effects (T1-T2) and the effects across all timepoints (T1-T4). The variability in the slopes of within-person variation of time was significant from T1-T4 for conflict ($\chi^2 = 132.87$, $p = <.001$), control ($\chi^2 = 97.94$, $p = <.001$), and organization ($\chi^2 = 120.45$, $p = <.001$). The variability in the slopes of within-person variation of time was not significant cohesion and expressiveness from T1-T4, and for all outcomes from T1-T2. For the same reasoning as stated above, a Level-2 model was estimated for both pre- to post-treatment effects (T1-T2) and across all timepoints (T1-T4).

In the second step, risk status was a significant predictor of the time slope for organization from pre-to post-treatment (95% CI *B* [-1.42, -10.95]) as well as across the follow-up period (95% CI *B* [-1.42, -10.95]). After controlling for the covariates, participation in the RUSH program accounted for an additional 8.5% and an additional 0.3% of the variance in organization from pre- to post-treatment and until 6-month follow-up, respectively. Thus, the majority of improvement in family organization occurred between T1 and T2. Risk status was also a significant predictor of the time slope for conflict from pre-treatment to 6-month follow-up (95% CI *B* [-.01, -.84]) and accounted for an additional 3.7% of the variance. Taken together, families with a parent having BD demonstrated more organization in the home immediately post-intervention and at 6-month follow-up, and less conflict by the end of the follow-up period, compared to the control offspring.

The analysis revealed a significant effect of offspring sex on the time slope for cohesion (95% CI *B* [-.12, -1.44]) and expressiveness (95% CI *B* [-.07, -1.40]) from pre-to post-treatment, and for conflict (95% CI *B* [-.02, -.80]) from pre-treatment to 6-month follow-up. Specifically, female offspring had greater decreases in cohesion and expressiveness from T1 to T2 and greater decreases in conflict from T1 to T4 compared to male offspring.

Parallel mediation analyses predicting offspring internalizing and externalizing symptoms at T4 via changes in family functioning

Pre-to-post-intervention gains (T2-T1) in family conflict, cohesion, expressiveness, organization and control were tested as potential parallel mediators of the relation between having participated in the RUSH program and levels of offspring internalizing and externalizing symptoms at T4. Coefficients of the associations between predictor and mediator variables (paths a in Figure 2), mediator and outcome variables (paths b in Figure 2), and for direct, indirect, and total effects (paths c, and ab in Figure 2) are summarized in Table 7.

Changes in organization partially mediated the relation between having participated in the RUSH program and the number of parent-reported externalizing symptoms at T4 (β = -2.88, SE= 2.03, Cl = -7.92, -.12). Pre-to-post-intervention changes in family conflict, cohesion, expressiveness, and control were not significant mediators in the mediation models. There were no significant findings for mediation models (data not shown) nor when predicting parent-reported internalizing behaviours or teacher-reported symptoms.

Discussion

The present study examined changes in offspring internalizing and externalizing problems, and family functioning following participation in the RUSH program, a 12-week preventive intervention aimed at improving the family environment and teaching stress-coping

techniques to families with a parent with BD. RUSH participants were compared to families with parents having no history of an affective disorder who completed all assessments, but not the intervention program. Consistent with previous research (Linnen et al., 2009; Sandstrom et al., 2020; Stapp et al., 2020), the OBD had greater levels of externalizing behaviours, and were exposed to more conflict and lower levels of expressiveness, organization and control in the home, at baseline compared to the control offspring. In terms of treatment outcomes, participation in the RUSH program resulted in reduced externalizing symptoms in the OBD and enhanced organization in the family environment immediately post-intervention (T2). The gains in organization in the home remained at the six-month follow-up assessment (T4), while reductions in family conflict not evident at post-intervention were observed at the six-month follow-up. Lastly, pre-to-post-intervention improvements (T2-T1) in organization mediated the relation between having participated in the RUSH program and lower rates of parent-reported externalizing problems six months later.

The main benefit of the RUSH program on offspring was a decrease in externalizing problems from pre- to post-intervention, which was over and above natural changes expected with the passage of time and being enrolled in a research study. There was no concomitant change in internalizing behaviors. The result is consistent with the fact that the OBD in this sample and other samples (Linnen et al., 2009; Maoz etal 2014) showed elevated externalizing but not internalizing problems in childhood. Rates of disruptive behavioural disorders in the OBD are high both in childhood (Birmaher et al., 2009) and at follow-up assessments in young adulthood (Nijjar et al., 2014; Mesman et al., 2013). In the Pittsburgh Bipolar Offspring Study, the OBD were already twice as likely to be diagnosed with a disruptive behavioural disorder than control by the mean age of 12 years (Birhamer et al., 2009). Thus, the positive effects of the

RUSH program on externalizing problems in middle childhood might have important clinical significance given its continuity across development. While the reduction in externalizing problems in the OBD appeared to persist to the 3-month follow-up (T3), the intervention effects on externalizing problems were no longer apparent by 6-month follow-up (T4) in the full sample. However, mediation analyses showed that, at the six-month follow-up, reduced externalizing problems were maintained in those families who most benefitted from improved organization following the RUSH intervention. Thus, positive behavioural changes in offspring were maintained in families who were highly responsive to the RUSH program.

Although no intervention-related change in internalizing problems was found in the present study, reduced internalizing problems in the OBD was observed among families who showed robust improvements in parent-child interactions and reductions in parenting stress following the RUSH program (Resendes et al., 2022; Serravalle et al., 2020). The difference across studies likely reflects the RUSH program's focus on structure and consistency in the home, including behavioural management techniques, which likely had direct effects on externalizing behaviours in children. The observed indirect changes in areas of functioning not directly targeted by RUSH, such as the quality of parent child interactions, seemed to improve internalizing problems.

As described above, long-term reductions in externalizing problems were observed in families who made improvements in structure and consistency in the home. The robust effects of the RUSH program on family organization were expected given the module on implementing structure and consistency in the home. This module partly focused on behavioural contingency strategies, which are typically used to manage child disruptive behaviours (Steiner & Remsing, 2007). Similar findings were found in a separate study demonstrating associations between

improvements in family organization following the RUSH program and various indices of diurnal cortisol levels (Yong Ping et al., 2023). These finding are in line with previous research demonstrating strong associations between structure/organization in the home during middle childhood and offspring psychopathology and stress reactivity (Ellenbogen et al., 2009; Iacono et al., 2018). Indeed, we recently reported having a parent with BD was associated with low levels of structure in the home during middle childhood, which then predicted an elevated CAR and the development of depressive/anxiety symptoms in late adolescence and young adulthood (Serravalle et al., 2023). Taken together, it appears that structure and consistency in the home represents an important environmental factor associated with adverse outcomes in the OBD.

The second aspect of the family environment that improved following the RUSH program was family conflict. In contrast to the improvements in organization following the intervention, positive changes in family conflict only emerged at the 6-month follow-up (T4). This may be partly explained by inherent differences in the therapeutic skills taught for system maintenance and relational aspects of the family system. The former involves concrete skills focused on behaviour change (e.g., setting a routine, implementing a behaviour chart) while the latter involves more abstract techniques (e.g., identifying thoughts and emotions to communicate more effectively). Moreover, while we demonstrated immediate changes following the RUSH program in the parent-child relationship (Serravalle et al., 2020), it may take time for these effects to impact the overall family functioning as it involves multiple dyadic relationships. Research has also shown greater impact on parents and children who are active participants in an intervention than the overall family system (Cornett & Bratton, 2014). Another possibility is the potential evocative effects of improvements in externalizing behaviour on family dynamics. Research has highlighted the negative impact child behaviour problems can have on parent and

family functioning (Pu & Rodriguez, 2023; Yan et al., 2021). Thus, we can speculate that early treatment effects of the RUSH program on externalizing problems in the OBD may have contributed to later reductions in overall family conflict.

Notably, with the exception of family expressiveness, the observed effects of the RUSH program were specific to offspring externalizing problems and family environment factors with the largest baseline differences between the OBD and controls. Previous literature has suggested that family functioning in families with a parent having BD are heterogeneous (Stapp et al., 2020). While the intention of the RUSH program was to act as a broad-based prevention program for the OBD with varying emotional and behavioural difficulties, these findings suggest that tailoring intervention programs to specific family needs may enhance treatment effects. While the RUSH program appeared to respond to difficulties with structure/organization and conflict in families, no treatment effects were observed for family expressiveness, an important environmental risk factor associated with BD (Miklowitz, 2007). In existing family-based treatments, emotional expression is addressed using much of the same skills taught in the RUSH program (e.g., active listening, assertive communication) but are typically practiced in-vivo with the whole family (Miklowitz & Chung, 2016). Thus, to respond to families with this need, future implementations of the RUSH program in high-risk samples should include parent-child components, in which all family dyads are given the opportunity to practice various therapy skills (e.g., effective communication) in session.

Strengths and limitations

The current study is a proof-of-concept pilot project using a quasi-experimental design. Therefore, the observed benefits from participating in the RUSH program were compared to natural changes that occur over time and/or the effects of being enrolled in a research study.

Thus, we cannot compare our intervention effects with a more stringent control, which would be OBD enrolled in a waitlist or active control group. Another limitation of the study is the small sample size, although the effects of this problem were minimized to some degree by the use of non-parametric statistical procedures. It will be important to replicate the present findings using a randomized controlled trial (RCT) and a larger, more diverse sample of families with a parent having BD. Adopting a RCT design would reduce the effects of regression to the mean (i.e., the tendency for extreme baseline scores to approach the mean in subsequent measurements), a common concern in intervention research (Linden, 2013).

In terms of outcome measurement, one strength of the study is the use of multiple informants to assess offspring internalizing and externalizing problems across four timepoints. However, the family environment was assessed using parent-report, thus the results should be interpreted as parent perceptions of changes in family functioning. As discussed by Stapp and colleagues (2020), this represents a limitation in the field and future studies may want to include perspectives from other family members, including the OBD. Another strength of the study is that offspring and family functioning outcomes were examined simultaneously, accounting for potential overlap across variables. Given that improvement in relational aspects of the family environment, namely family conflict, were only observed at the end of the study, we cannot determine whether such changes are stable and whether the positive impact of the intervention would persist for longer than six months. It will be important for future studies to include longer follow-up periods, as some family-based treatments for pediatric BD have done (see Miklowitz & Chung, 2016 for a review).

Summary and conclusion

The RUSH program is the first of its kind, to the best of our knowledge, to target OBD in childhood *prior* to the emergence of affective symptoms and to incorporate parents and their children simultaneously in the prevention program. The present results provide preliminary evidence that the RUSH program, a preventive intervention aimed at reducing stress in the family environment, can be effective at reducing child behaviour problems, particularly in those families who were able to increase structure and organization in the home. The present findings are in line with growing evidence that family-based treatments can offset adverse outcomes in symptomatic offspring of parents with BD (e.g., Miklowitz et al., 2015; Miklowitz et al., 2020). Given these promising preliminary findings, future research implementing an RCT design with a larger sample size is warranted to shed light on the utility of the RUSH program in improving the family environment and reducing adverse mental health outcomes in the OBD.

Table 1

Session descriptions for the parent and youth groups of the RUSH program

Session #	Brief description
Parent group	
1	Orientation to the program and fostering motivation for change
2	Identification and management of stressors
3	Problem solving: Individual applications
4	Problem solving: Family applications
5	Enhancing communication: Active listening
6	Enhancing communication: Assertive communication
7	Enhancing communication: Expressing emotions and needs
8	Implementing structure and consistency: Time management and organization
9	Implementing structure and consistency: Family routines and household rules
10	Implementing structure and consistency: Management of child misbehaviors
11	Implementing structure and consistency: Management of child misbehaviors
12	Review and maintenance
Youth group	
1	Orientation to the program and fostering motivation for change
2	Understanding and recognizing stress
3	Identifying emotions
4	Expressing emotions to cope with stress
5	The body's reaction to stress
6	Breathing techniques to cope with stress
7	Recognizing thoughts
8	Modifying negative self-talk to cope with stress
9	Introduction to problem solving
10	Using problem solving to cope with stressful situations
11	Assertive communication
12	Review and maintenance

Table 2

Demographic information presented by risk status

Variable	OBD	Control Offspring
Mean offspring age at first timepoint in years (SD)	8.2 (1.6)	8.7 (1.7)
Offspring sex (female:male)	12:14	17:12
Family ethnicity		
Aboriginal	1	0
Black	0	4
Asian	1	2
Hispanic/Latino	1	3
Middle Eastern, North African, Central Asian	2	3
Caucasian	21	17
Parental marital status		
Single	5	2
Married	19	19
Separated/ Divorced	2	8
Parental education level		
Highschool Diploma	1	0
CÉGEP Diploma	4	4
Some university attainment	1	3
University degree	20	22
Family annual income		
Less than $25,000	4	4
$25,001-$50,000	8	8
$50,001-$75,000	5	5
$75,001-$100,000	1	7
More than $100,000	8	5
Mean Family SES composite[a] (SD)	9.44 (2.10)	9.48 (1.67)

[a]Family SES Composite = socioeconomic composite score, which combines both parental educational attainment and family annual income

Table 3

Means and standard deviations (SD) for offspring internalizing and externalizing problems*, and family functioning across the four timepoints*

	T1	T2	T3	T4
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Offspring PRS symptoms[a,b]				
Internalizing symptoms				
OBD	25.12 (10.01)	22.78 (12.36)	23.31 (13.51)	21.75 (11.35)
Controls	21.48 (11.14)	19.10 (10.31)	19.62 (11.53)	17.69 (11.03)
Externalizing symptoms				
OBD	19.46 (11.69)	17.58 (11.12)	17.62 (10.32)	18.40 (11.25)
Controls	13.76 (7.74)	15.28 (8.05)	14.62 (8.10)	13.83 (7.80)
Offspring TRS symptoms[a,c]				
Internalizing symptoms				
OBD	13.52 (11.33)	11.28 (10.68)	12.37 (10.36)	10.29 (10.62)
Controls	7.96 (6.87)	9.23 (7.39)	10.95 (9.31)	6.67 (10.10)
Externalizing symptoms				
OBD	13.19 (11.28)	12.94 (14.39)	11.11 (13.90)	14.43 (11.71)
Controls	10.69 (13.10)	9.64 (8.24)	9.85 (13.53)	10.78 (14.39)
Family functioning[d]				
Conflict				
OBD	3.81 (2.42)	3.71 (2.44)	2.77 (2.14)	2.52 (2.86)
Controls	2.07 (1.89)	1.31 (1.47)	1.79 (1.88)	1.93 (1.82)
Cohesion				
OBD	6.62 (1.30)	7.42 (1.59)	7.67 (1.37)	7.68 (1.29)
Controls	7.17 (1.20)	8.00 (1.25)	7.93 (1.33)	7.56 (1.69)
Expressiveness				
OBD	6.15 (1.12)	6.67 (1.27)	5.42 (1.50)	6.59 (1.05)
Controls	7.00 (1.13)	7.24 (.95)	6.00 (1.09)	6.88 (1.27)
Organization				
OBD	5.00 (2.23)	5.96 (2.44)	5.92 (2.28)	6.27 (1.28)
Controls	6.76 (1.35)	6.55 (1.48)	6.89 (1.29)	6.40 (1.63)
Control				
OBD	3.58 (1.90)	3.21 (1.56)	3.33 (1.55)	3.72 (1.86)
Controls	4.28 (1.62)	4.28 (1.46)	4.43 (1.64)	4.04 (1.93)

Note. OBD = offspring of parents with bipolar disorder; Controls = offspring of parents with no affective disorder; PRS = parent report scale; TRS = teacher report scale; T1 = pre-intervention; T2 = post-intervention; T3 = 3-month follow-up; T4 = 6-month follow-up. a From the Behavior Assessment Schedule for Children (BASC-2). b T1 (n = 21 OBD, 26 controls), T2 (n = 18 OBD,

22 controls), T3 (n = 19 OBD, 20 controls), T4 (n = 14 OBD, 18 controls). c T1 (n = 34 OBD, 32 controls), T2 (n = 26 OBD, 29 controls), T3 (n = 26 OBD, 29 controls), T4 (n = 20 OBD, 29 controls). d From the Family Environment Scale (FES).

Table 4

Pearson Correlations Between the Main Study Variables (N = 55)

	1	2	3	4	5	6	7	8	9	10	11	12
1) Risk Status												
2) Offspring Sex	-.13											
3) Offspring Age	-.34	-.00										
4) PRS Internalizing Symptoms	.17	.10	-.01									
5) PRS Externalizing Symptoms	.28*	-.15	-.17	.19								
6) TRS Internalizing Symptoms	-.12	.03	.06	-.02	.03							
7) TRS Externalizing Symptoms	-.12	.01	.06	-.03	.04	.19						
8) FES Conflict	.38**	.05	-.26	.33*	.49**	-.14	-.13					
9) FES Cohesion	-.22	.28*	.04	-.03	-.20	.14	.13	-40**				
10) FES Expressiveness	-.36**	.26	.15	-.23	-.26	.04	.04	-.30*	.17			
11) FES Organization	-.44**	.00	.36**	-.15	-.29*	.06	.07	-.46**	.06	.21		
12) FES Control	-.20	-.03	.08	.04	.12	.18	.19	.28*	-.18	-.23	.22	

Note. Variables were measured at time 1 (pre-intervention). Risk Status = offspring of parents with bipolar disorder vs. control; PRS = parent report scales; TRS = teacher report scales; FES = family environment scale; Variables 4-12 represent levels at baseline (pre-treatment). * $p < .05$; ** $p < .01$

Table 5

Results from HLM analyses examining the effects of between-subject factors on changes in offspring internalizing and externalizing problems over time (N = 55)

	Baseline levels (Intercept)		Change over time (T1-T2) (Slope)		Change over time (T1-T4) (Slope)	
	Coefficient (SE)	*T-Ratio*	*Coefficient (SE)*	*T-Ratio*	*Coefficient (SE)*	*T-Ratio*
Parent-reported internalizing problems						
Risk status	4.07 (3.33)	1.22	-1.50 (3.10)	-.49	-.56 (.85)	-.66
Offspring sex	2.37 (3.10)	.76	1.08 (2.80)	.39	.34 (.83)	.42
Offspring age	.03 (.08)	.44	-.10 (.07)	-1.32	-.02 (.02)	-1.01
Parent-reported externalizing problems						
Risk status	5.06 (2.44)	2.07*	-6.18 (2.43)	-2.54*	-.07 (.71)	-.10
Offspring sex	-2.37 (2.41)	-.98	-.18 (2.19)	-.08	.38 (.69)	.55
Offspring age	-.07 (.06)	-1.25	-.09 (.06)	-1.55	-.02 (.02)	-1.29
Teacher-reported internalizing problems						
Risk status	5.33 (2.73)	1.95	-3.42 (2.27)	-1.51	-1.28 (.89)	-1.43
Offspring sex	1.12 (2.54)	.44	1.77 (2.05)	.86	-.59 (.87)	-.67
Offspring age	.02 (.06)	.44	-.02 (.05)	-.34	-.02 (.02)	-1.05
Teacher-reported externalizing problems						
Risk status	.50 (3.40)	.15	.92 (3.24)	-1.07	.76 (1.02)	.74
Offspring sex	-8.29 (3.17)	-2.61*	5.31 (2.92)	1.82	3.42 (1.00)	3.42
Offspring age	-.04 (3.40)	-.55	-.04 (.08)	-.54	-.01 (.02)	-.61

Note. Analyses were conducted separately for pre-to post-treatment changes (T1-T2) and changes from pre-treatment to 6-month follow-up (T1-T4). Risk coded as OBD = 1, Controls = 0, and Offspring Sex as Female = 1, Male = 0. *Df*s = 51. * $p < .05$; ** $p < .01$.

Table 6

Results from HLM analyses examining the effects of between-subject factors on changes in the family environment over time (N = 55)

	Baseline levels (Intercept)		Change over time (T1-T2) (Slope)		Change over time (T1-T4) (Slope)	
	Coefficient (SE)	*T-Ratio*	*Coefficient (SE)*	*T-Ratio*	*Coefficient (SE)*	*T-Ratio*
Conflict						
Risk status	1.98 (.55)	3.62**	.51 (.43)	1.20	-.42 (.21)	-2.01*
Offspring sex	.48 (.52)	.92	-.60 (.41)	-1.47	-.41 (.20)	-2.04*
Offspring age	-.02 (.01)	-1.54	-.01 (.01)	-.52	.01 (.01)	1.64
Cohesion						
Risk status	-.61 (.36)	-1.70	.04 (.36)	.13	.23 (.13)	1.70
Offspring sex	.32 (.34)	.93	-.78 (.34)	-2.31*	.06 (.13)	.45
Offspring age	.01 (.01)	.64	.01 (.01)	1.32	-.01 (.01)	1.64
Expressiveness						
Risk status	-.77 (.32)	-2.44*	.09 (.36)	.24	.12 (.15)	.78
Offspring sex	.27 (.30)	.89	-.74 (.34)	-2.17*	-.22 (.14)	-1.55
Offspring age	.01 (.01)	.35	-.01 (.01)	-.51	-.01 (.01)	-.57
Organization						
Risk status	-1.24 (.44)	-2.79**	1.18 (.38)	3.06**	.40 (.20)	2.13*
Offspring sex	-.51 (.42)	-1.22	-.40 (.37)	-1.10	.30 (.18)	1.65
Offspring age	.03 (.01)	2.75**	.01 (.01)	.74	-.01 (.01)	-1.41
Control						
Risk status	-.99 (.44)	-2.26*	-.42 (.39)	-1.07	.14 (.18)	.76
Offspring sex	-.24 (.41)	-.58	.10 (.37)	.28	.17 (.17)	1.01
Offspring age	-.01 (.01)	-.44	-.01 (01)	-.45	.01 (.01)	1.03

Note. Analyses were conducted separately for pre-to post-treatment changes (T1-T2) and changes from pre-treatment to 6-month follow-up (T1-T4). Risk status coded as offspring of parents with bipolar disorder (OBD) = 1, Controls = 0; Offspring Sex coded as female = 1, male = 0. *Df*s = 51. * $p < .05$; ** $p < .05$

Table 7

Parallel mediation model results examining the effects of participating in the RUSH program on parent- and teacher-reported internalizing and externalizing symptoms at T4 via pre-to-post-intervention change in the family environment.

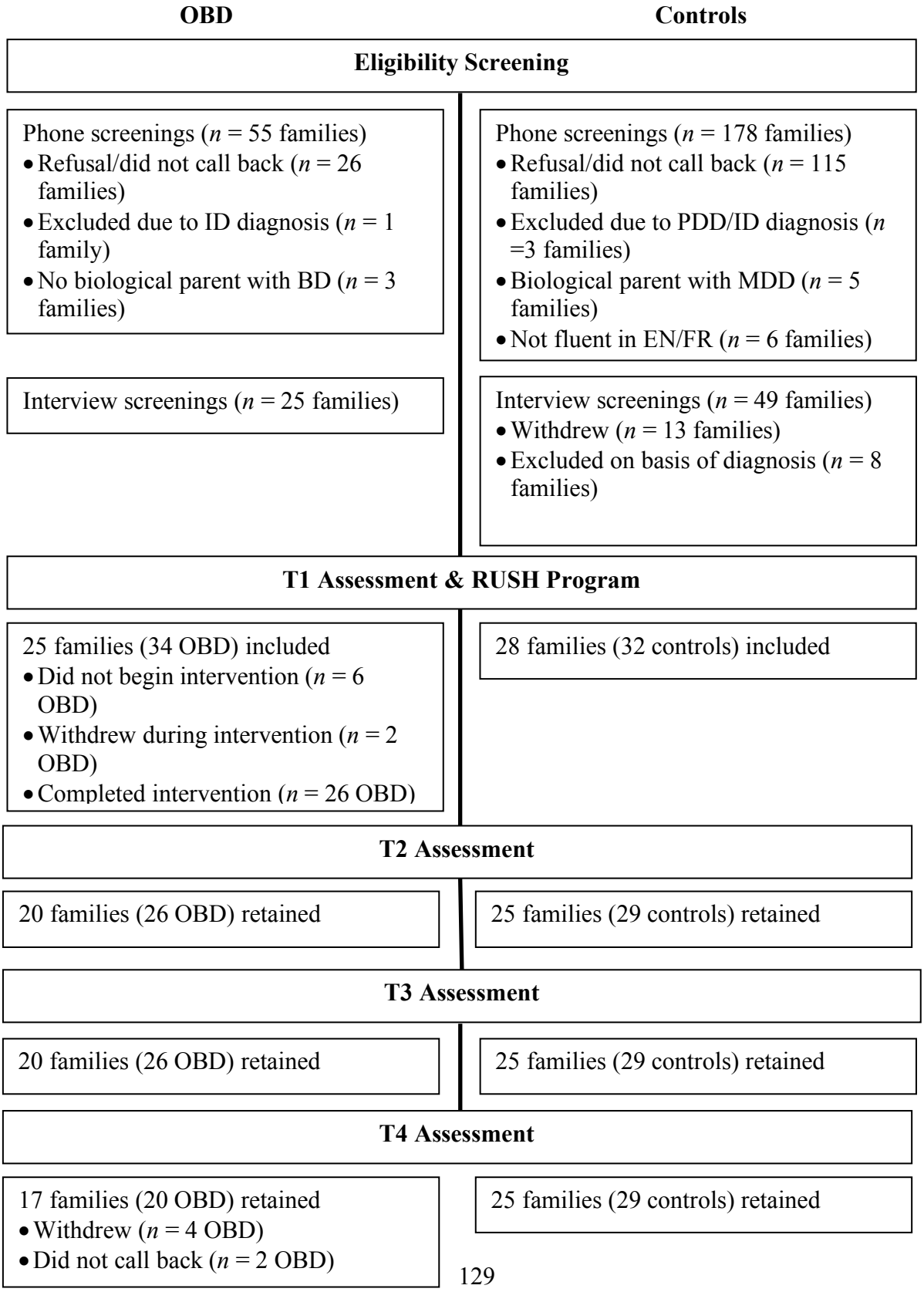
Independent[a] → Dependent (paths c)					
	Mediators				
	Conflict	Cohesion	Expressiveness	Organization	Control
	β (SE)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Independent → Mediator (paths a)[a]	.83 (.49)	.06 (.35)	-.12 (.39)	1.04 (.40)*	-.39 (.42)
Mediator → Dependent (paths b)					
Offspring PRS symptoms[b]					
Internalizing symptoms	.74 (1.14)	-1.12 (1.04)	.16 (1.42)	-.56 (1.56)	.38 (1.67)
Externalizing symptoms	.99 (1.03)	-1.09 (1.18)	1.10 (.84)	-2.78 (1.30)*	.60 (.94)
Offspring TRS symptoms[b]					
Internalizing symptoms	.17 (1.48)	.72 (1.58)	.86 (1.93)	.20 (1.64)	.05 (1.67)
Externalizing symptoms	1.39 (1.85)	.11 (2.08)	.13 (2.45)	-3.15 (2.18)	-2.70 (1.68)
Direct, Indirect, and Total Effects	**β (SE)**	**95% CI**			
Direct Effects (paths c)					
Offspring PRS symptoms[b]					
Internalizing symptoms	4.01 (3.58)	[-2.77, 11.43]			
Externalizing symptoms	6.17 (2.87)*	[1.04, 12.13]			
Offspring TRS symptoms[b]					
Internalizing symptoms	3.68 (5.05)	[-6.54, 13.13]			
Externalizing symptoms	4.96 (5.97)*	[-7.40, 14.78]			
Total Effects (across all mediators)					
Offspring PRS symptoms[b]					
Internalizing symptoms	3.82 (3.18)	[-2.70, 9.93]			
Externalizing symptoms	3.68 (3.10)	[-2.43, 9.61]			
Offspring TRS symptoms[b]					

Internalizing symptoms	3.94 (3.96)	[-4.08, 12.30]
Externalizing symptoms	3.87 (5.32)	[-6.98, 14.13]
Indirect Effects (via mediators)		
Predicting PRS internalizing symptoms[b]		
FES Conflict	.62 (1.10)	[-1.92, 2.71]
FES Cohesion	-.07 (.49)	[-1.01, 1.07]
FES Expressiveness	-.02 (.57)	[-1.56, .85]
FES Organization	-.58 (1.85)	[-5.24, 2.34]
FES Control	-.15 (1.03)	[-3.20, 1.04]
Predicting PRS externalizing symptoms[b]		
FES Conflict	.82 (1.06)	[-1.39, 2.99]
FES Cohesion	-.06 (.56)	[1.55, .88]
FES Expressiveness	-.13 (.57)	[-1.33, .93]
FES Organization	-2.88 (2.03)*	[-7.92, -.12]
FES Control	-.23 (.61)	[-1.81, .97]
Predicting TRS internalizing symptoms[b]		
FES Conflict	.14 (1.47)	[-2.95, 2.90]
FES Cohesion	.04 (.61)	[-1.39, 1.18]
FES Expressiveness	-.10 (.88)	[-2.01, 1.70]
FES Organization	.21 (1.90)	[-3.92, 4.40]
FES Control	-.02 (1.02)	[-1.93, 2.61]
Predicting TRS externalizing symptoms[b]		
FES Conflict	1.15 (2.19)	[-1.08, 7.21]
FES Cohesion	.01 (.71)	[-1.47, 1.47]
FES Expressiveness	-.02 (.98)	[-2.00, 2.42]
FES Organization	-3.27 (2.83)	[-9.80, 1.69]
FES Control	1.04 (1.59)	[-1.20, 5.25]

Note. a The independent variable is whether or not a family participated in the RUSH program, which should be considered synonymous with having a parent with BD or not; b From the Behavior Assessment Schedule for Children (BASC-2); FES = Family Environment Scale; CI = confidence interval; *$p < .05$. Estimates are presented as unstandardized coefficients.

Figure 1

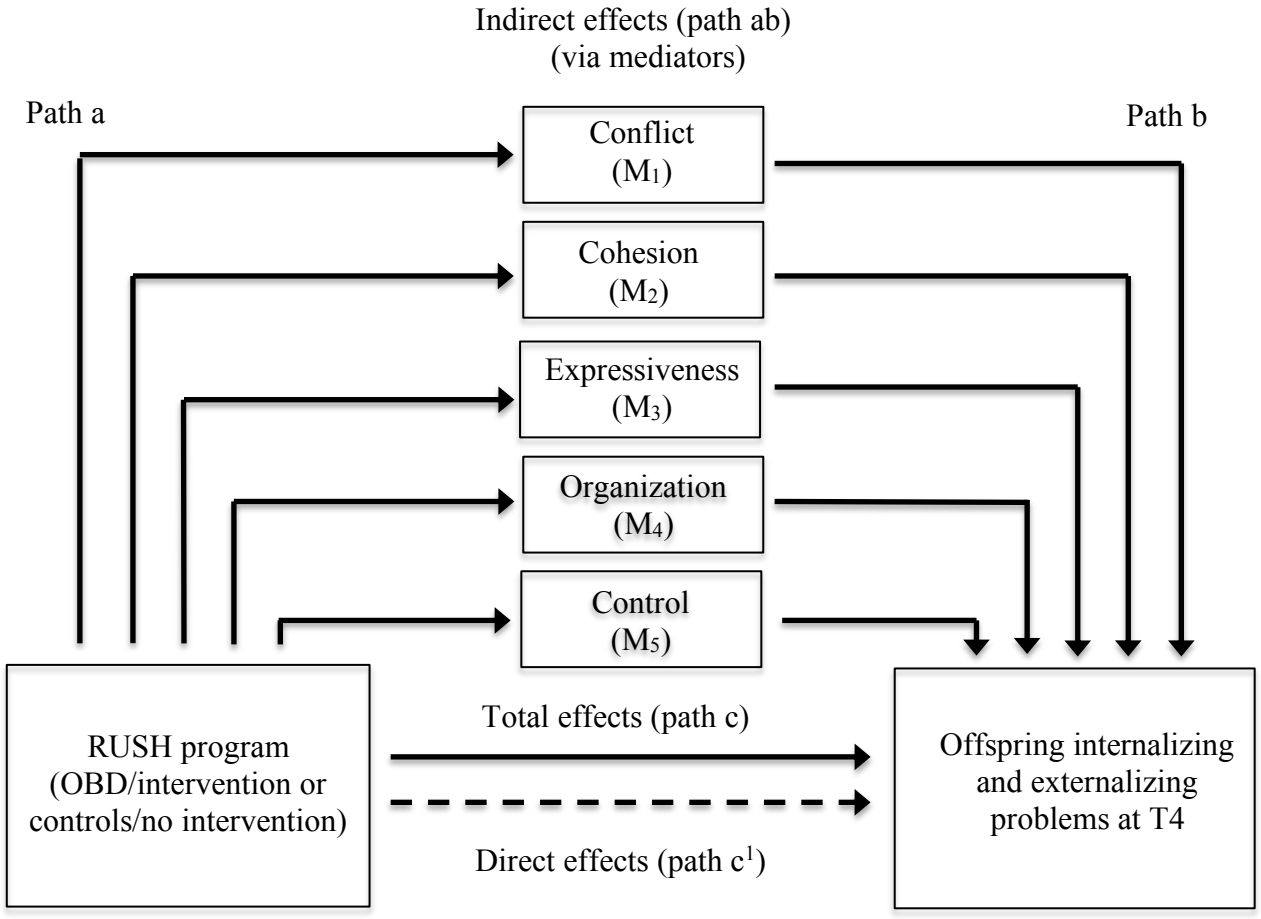
Sample retention by group



Note. OBD = offspring of parents with BD; Controls = offspring of parents with no affective disorder; BD = bipolar disorder; MDD = major depressive disorder; PDD = pervasive developmental disorder; ID = intellectual disability; EN = English; FR = French; T1 = pre-intervention; T2 = post-intervention; T3 = 3-month follow-up; T4 = 6-month follow-up

Figure 2

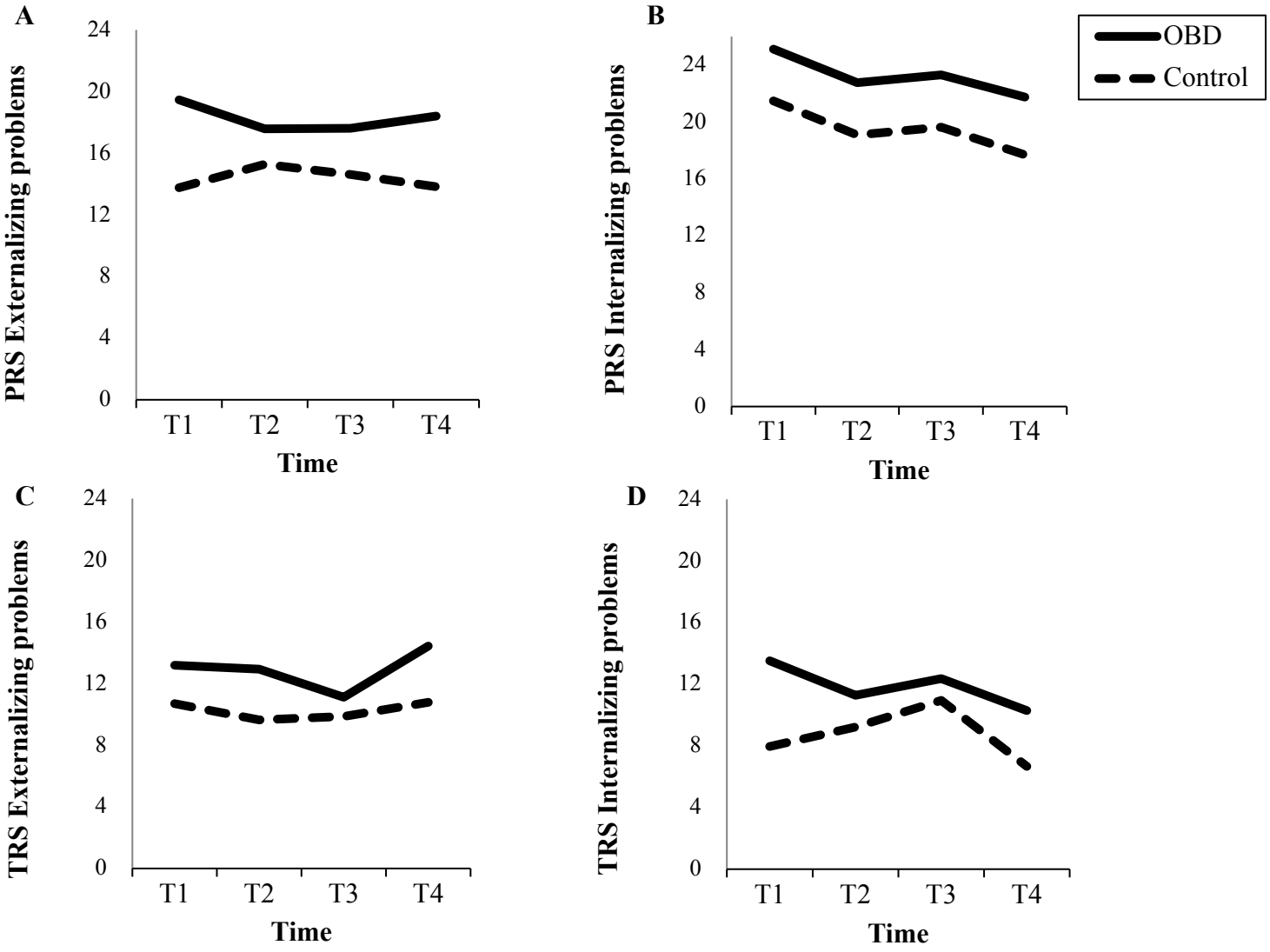
Parallel mediation model



Note. Mediators (M_1–M_5) represent changes in the family environment from pre- to post-treatment (T2 – T1).

Figure 3

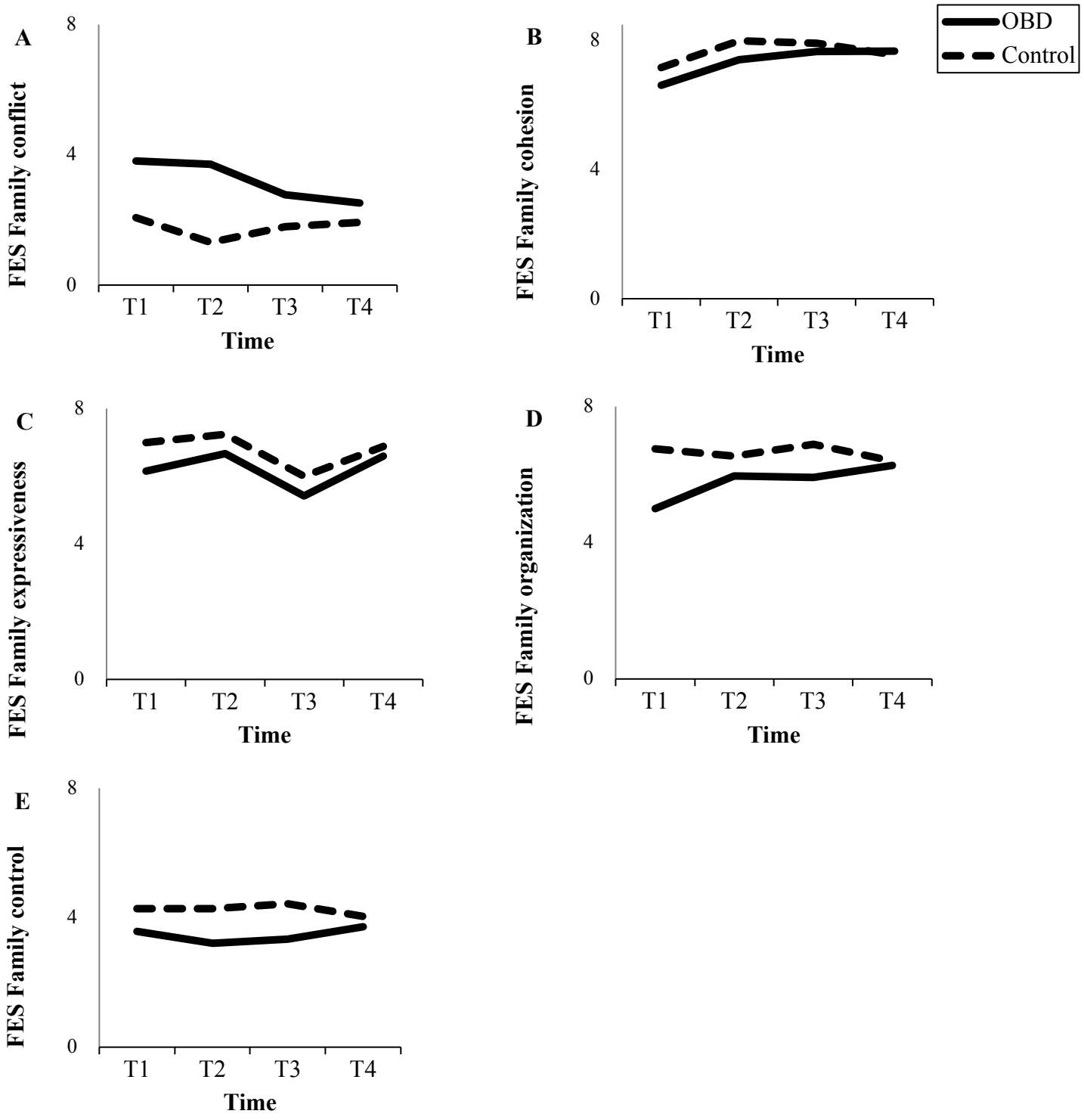
Average growth rates in parent- and teacher-reported externalizing and internalizing scores for the OBD and control offspring across the four measurement points



Note. PRS = parent report scales; TRS = teacher report scales. T1 = pre-intervention; T2 = post-intervention; T3 = 3-month follow-up; T4 = 6-month follow-up.

Figure 4

Average growth rates in parent-reported aspects of the family environment for the OBD and control offspring across the four measurement points



Note. FES = family environment scale. T1 = pre-intervention; T2 = post-intervention; T3 = 3-month follow-up; T4 = 6-month follow-up.

Chapter 5: General Discussion

The OAD represent an at-risk population by virtue of increased mental health challenges (Lau et al., 2018; Mesman et al., 2013; Vandeleur et al., 2012) and various functional impairments (e.g., Nijjar et al., 2014) across their lifespan. Pathways of the intergenerational transmission likely involve a complex interaction between genetic, biological, and environmental factors (Maciejewski et al., 2018; Remes et al., 2021; Sawyer et al., 2019). Various preventive intervention programs have been developed to reduce risk in offspring of parents with MDD (Loechner et al., 2018) and similar efforts have begun to increase over the last decade for the OBD (Cotton et al., 2020; Jones et al., 2014; Wirehag Nordh et al., 2022). To this end, the current thesis used various methodologies to further our understanding of the biological and environmental factors contributing to the risk of psychopathology in the OAD. Namely, the first study adopted a meta-analytic approach to quantitatively summarize the literature on HPA axis activity in the OAD. Consistent with previous meta-analyses on individuals diagnosed with an AD (Knorr et al., 2010; Lopez-Duran et al., 2009; Murri et al., 2014, 2016; Stetler & Miller, 2011) and findings from a recent systematic review (Klimes-Dougan et al., 2022), the overall findings indicated a hyperactivation in the HPA axis system in the OAD. The next two studies focused on the OBD specifically, as there is less research available for this population in comparison to offspring of parents with MDD. The main goal of the second study was to examine the influence of the caregiving environment on the development of the HPA system and its cascading effects on the development of psychopathology in the OBD. The results of Study 2 revealed that the relation between having a parent with BD and offspring internalizing symptoms was mediated by poor structure provided by parents in middle childhood and subsequent elevations in offspring CAR. These data replicate previous findings showing how structure and

consistency in the home can shape the developing HPA system in ways that increase the risk of developing an AD (Ellenbogen & Hodgins, 2009; Ellenbogen et al., 2011). It also furthers this model by incorporating offspring psychopathology as an outcome and is the first study, to the best of our knowledge, to implement a longitudinal, prospective design to replicate similar results found in offspring of parents with MDD (Halligan et al., 2007). The third study of the current thesis tested whether a preventive intervention program could reduce adverse outcomes in the OBD by targeting quality of the caregiving environment, a well-known risk factor for the OAD that is amenable to change. It builds on the findings from Study 2 by demonstrating that participation in the 12-week RUSH prevention program led to immediate improvements in offspring externalizing symptoms and family structure/organization, with the latter maintained at 6-month follow-up. Reductions in family conflict also became apparent at 6-month follow-up. Mediation analyses revealed that offspring from families that were able to increase structure/organization in the home from pre- to post-treatment demonstrated significantly fewer externalizing symptoms at the 6-month follow-up, compared to an assessment-only control group. While it is important to acknowledge that these interpretations are limited by the quasi-experimental design of the study, the results provide preliminary evidence of the efficacy of a unique preventive intervention program designed for the OBD *prior* to the onset of any significant mood symptoms. In combination with the findings of Study 2, these results also highlight structure and consistency in the home as an important risk and protective factor in the OBD.

Alterations in hypothalamic-pituitary-adrenal axis functioning in affective disorders as a correlate of disease, a biomarker of risk, and a result of exposure to early social stress

As previously alluded, HPA axis dysregulation has long been considered a key facet in the pathogenesis of ADs (Bao & Swaab, 2019; Ellenbogen et al., 2019). With regards to diurnal cortisol secretion specifically, several meta-analyses have demonstrated alterations in HPA axis functioning as a correlate of disease in AD. Specifically, higher cortisol levels have been observed in persons diagnosed with an AD compared to healthy controls (Hedge's g = .38 – 60; Murri et al., 2016, 2014; Stetler & Miller, 2011). Hyperactivation of the HPA axis have also been documented in children and adolescents with MDD (Lopez-Duran et al., 2009). Similar findings were found in Study 2 of this thesis, namely the greatest elevations in the CAR were found in adolescents with an AD compared to the OBD and control offspring with no history of an AD. Interestingly, most of the offspring with an AD were in clinical remission (i.e., they met criteria for an affective disorder in the past but not at the time of assessment). This is consistent with evidence that suggests levels of cortisol may fluctuate but subtle elevations in cortisol in affected youth persist through different phases of the disorder. Indeed, Murri and colleagues (2016) found that, relative to controls, patients with BD displayed cortisol levels that were highest during manic (Hedge's g = .64) and depressive (Hedge's g = .44) episodes but remained elevated during euthymic phases (Hedge's g = .28). Similar findings have been observed in the context of MDD, with evidence suggesting that cortisol rhythms remain dysregulated during periods of clinical remission (e.g., Izakova et al., 2020; Morris & Rao, 2014). Together, the continued elevations of cortisol secretion throughout periods of remission suggest HPA axis dysregulation may represent more than an epiphenomenon of ADs.

While ample evidence to suggest HPA axis functioning is severely disrupted in individuals with an AD, there has much more uncertainty surrounding potential abnormalities in this stress-mediating system prior to the onset of illness. Further examination of the latter

remains an important research endeavor, as it would imply HPA axis dysfunction is not only a symptom presentation of ADs but also part of the etiology. This has been partly investigated by tracking large community samples over time, such as the Tracking Adolescents' Individual Lives Survey (TRAILS; e.g., Zandstra et al., 2015). The current thesis focused on a different approach to examining HPA axis functioning prior to the onset of ADs; the study of high-risk populations. By quantitatively summarizing the extant literature comparing diurnal cortisol levels in the natural environment between the OAD and healthy control offspring, the first study provided preliminary evidence that alterations in HPA axis may precede the onset of an AD. While we could not account for levels of depressive/internalizing symptoms as these were not consistently reported across studies, efforts were made to include mostly unaffected OAD (only about 5% of offspring had a history of an AD, mostly from studies on parental BD). Interestingly, the elevated levels of diurnal cortisol observed in the OAD observed in Study 1 (Hedge's g = .21) were comparable to the effect size obtained in the meta-analysis comparing youth with MDD and controls (Hedge's g = .20; Lopez-Duran et al., 2009) and approached levels seen in euthymic adult patients with BD (Hedge's g = .28; Murri et al., 2016). Taken together, data from Study 1 and 2 contribute to the existing literature by providing additional support for alterations in HPA axis activity as not only a state-dependent feature of ADs, but also a trait-like biomarker of the disorder. Further evidence of trait-like presentations of HPA axis disruptions emerged in a study that measured children's and adolescents' cortisol reactivity twice over an 18-month interval (Hankin et al., 2015). They found that patterns in stress reactivity in this general community sample remained stable over time, especially in susceptible youth who presented with the high-risk genetic variants of certain genes associated with stress sensitivity (5-HTTLP and CRHR1). This is in line with data from previous reports (Ellenbogen et al., 2006) and results from Study 2

that show elevations in CAR from adolescence until early adulthood in a sample of OBD (Ellenbogen et al., 2006) and that collected in Study 2. These findings are also of clinical importance, given that detection of HPA abnormalities may help determine the likelihood of an AD developing.

There is growing evidence to suggest abnormalities in the HPA axis play an important role in the development and clinical trajectory of ADs. Less is known about how other vulnerabilities in the OAD may lead to, or interact with, subtle changes in HPA function. Research on the social buffering of stress-sensitive systems have highlighted the pivotal role parents play in regulating offspring's biological stress systems during earlier periods of development, revealing both risk buffering and risk conferring effects (Hostinar et al., 2015; Perry et al., 2021; Senehi et al., 2021). In line with this research, Study 2 depicted a longitudinal model in which suboptimal caregiving environments led to elevations in the CAR and mental health problems in the OBD during adolescence/young adulthood. This is consistent with studies demonstrating elevations in morning cortisol, stress reactivity, and diurnal cortisol rhythms following exposure to parental ADs (Ellenbogen & Hodgins, 2009; Halligan et al., 2007; Mackrell et al., 2014). Similar to the study linking maternal postnatal depression and family expressed anger to elevations in cortisol secretion (Essex et al., 2011), Study 2 examined specific aspects of the caregiving environment that are found to often be disrupted in the OBD (Stapp et al., 2020). While population-wide primary prevention efforts, such as screening measures for post-partum depression (Vasta et al., 2018), remain warranted, longitudinal studies of the effects of parenting practices or aspects of overall family functioning on the OAD have the potential to inform secondary prevention. By identifying modifiable aspects of the caregiving environment

that confer risk in the OAD, preventive intervention programs can be tailored to the *specific* needs of this high-risk population and potentially increase effectiveness of such interventions.

Structure and organization in the home: an important environmental risk and protective factor in the OBD

As discussed at the beginning of this thesis, the chronic and often debilitating nature of the clinical features of BD tends to introduce elevated levels of disruption and instability to their families (e.g., Desai et al., 2020; Grover et al., 2021; Lépine & Briley, 2011; McIntyre et al., 2019). Difficulties in the marital and parent-child relationships (e.g., Anke et al., 2019; Doucette et al., 2016; Serravalle et al., 2020), and overall family functioning (see Stapp et al., 2020 for a review) have also been well-documented in families with a parent having BD. As demonstrated in a recent longitudinal study (Shalev et al., 2019), parents' general psychosocial functioning may be one mechanism by which parents' diagnosis of BD disrupts family functioning. Specifically, parents with BD and non-BD psychopathology demonstrated diminished general psychosocial functioning, which in turn led to lower levels of family cohesion and higher levels of family conflict. Child psychopathology played a similar mediating role, but to a lesser extent. The authors also found that family functioning tended to worsen over the 4-year follow-up period (Shalev et al., 2019). In terms of the specific relation between the caregiving environment and psychopathology in the OBD, there are few studies outside those presented in this thesis that have investigated this research question using broad-band measures of family functioning.

Based on cross-sectional data, low levels of cohesion and high levels of conflict have been linked to greater levels of internalizing and externalizing symptoms in the OBD (Freed et al., 2015). Calam and colleagues (2012) found that the regression equation in their proposed model only became significant when family chaos (another construct in the literature that

captures instability and lack of organization) was entered as the sole predictor of emotional and behaviour problems in the OBD. There is also evidence that associates parental history of BD with child BD via lower levels of overall family functioning (Du Rocher Schudlich et al., 2008). In contrast, Lau and colleagues (2018) did not find a mediating role of the caregiving environment in the relation between having a parent with BD and offspring psychopathology. While these studies provide some insight into the impact of the caregiving environment and mental health well-being in the OBD, the cross-sectional nature of the data does not allow us to infer directionality. Recently, studies implementing longitudinal designs have begun to address this question. In the sample reported in Study 2, the impact of the early caregiving environment on offspring psychopathology varied depending on developmental stage of the OBD (Iacono et al., 2018). Based on the longitudinal analyses, parental control (i.e., adequate supervision and role boundaries, setting appropriate expectations, limits, and consequences of child misbehaviour) provided in middle childhood emerged as the strongest predictor of psychopathology in the OBD approximately 12 years later. Conversely, a separate study found that family functioning, as reported by mothers, did not predict the onset of affective disorders in the OBD at 12-year follow-up (Koenders et al., 2020).

Overall, these studies are partly consistent with the results of the current thesis. Specifically, in Study 2, family structure emerged as the only aspect of the caregiving environment to predict the CAR and depressive/anxiety symptoms in the OBD. Similarly, in Study 3, change in family levels of structure/organization following the RUSH prevention program was the only improvement from pre- to post-treatment in the caregiving environment that resulted in reductions in offspring psychopathology at 6-month follow-up. This is in contrast to the literature on parental MDD, which repeatedly highlight the association between parental

warmth/support and various child outcomes, such as cognitive/intellectual functioning and general psychopathology (see Goodman et al., 2020 for a meta-analysis). The caregiving environment might be a key factor that differentiates risk trajectories of the OBD from offspring of parents with MDD. Further evidence that parental warmth may not play as significant a role in the OBD as it does in the offspring with parent having MDD can be found in evaluations of the RUSH program. While intervention-related changes in parental positivity within parent-child interactions were observed, these changes did not mediate the relation between participating in the RUSH program and internalizing/externalizing problems in the OBD (Serravalle et al., 2020). Thus, the robust effects of family structure/organization, rather than parental warmth/support, on mental health in the OBD highlights how the impact of different aspects of the caregiving environment on risk for psychopathology may be partly related to the nature of the vulnerabilities inherent to the population of high-risk youth of interest.

There are several potential explanations of the particularly detrimental effects on the OBD's mental health resulting from a paucity of structure/organization in the home. First, as demonstrated in this thesis and in previous research (Ellenbogen & Hodgins, 2009), a lack of family structure/organization, but not parental control or support, has been shown to increase offspring CAR. Thus, exposure to low levels of structure/organization specifically may introduce high levels of instability and unpredictability in the OBD's daily living, which has been associated with a biological responsivity to stress (Del Giudice et al., 2011). Other neurobiological abnormalities, such as weakened fronto-striatal connectivity and reduced expression of brain-derived neurotrophic factor gene (Park et al., 2015; Singh et al., 2014), have also been linked with high levels of family chaos and dysfunction, and may thus represent other vulnerability factors contributing to offspring psychopathology. As previously mentioned, the

OBD are at increased risk of disorders that come with deficits in executive functioning (e.g., ADHD), including poor impulse control, low cognitive flexibility, and difficulties with self-regulation (Birmaher et al., 2021; De la Serna et al., 2021; Propper et al., 2023). Even in typically developing children, executive functioning has been strongly linked to influences of the caregiving environment (Bernier et al., 2010, 2012; De Cock et al., 2017). In positive caregiving environments, children learn how to modulate their behaviour and other skills that promote successful school integration (Bernier et al., 2015; Vernon-Feagans et al., 2016). In contrast, home chaos has been bi-directionally linked with ineffective parenting and child behavioural problems in the context of ADHD (Farbiash et al., 2014; Mokrova et al., 2010). Lastly, the OBD demonstrate a more robust HPA response to chronic and episodic stress than control offspring (Ostiguy et al., 2011). Thus, not only are the OBD exposed to more stress via low levels of structure/organization in the caregiving environment, but they are also more biologically sensitive to it. It is therefore possible that the OBD, who are at heightened risk of neurobiological abnormalities, are especially vulnerable to chaos and instability in the home.

In keeping with discussions of identifying specific targets of treatment, the findings from the current thesis lend further support for structure/organization provided by parents as a unique and important environmental mechanism that may heighten biological sensitivity as well as confer and buffer against risk of mental illness in the OBD. Given the limited number of studies examining the effects of the caregiving environment on psychopathology in the OBD, and the heterogeneity of family environments in which the OBD are raised (Stapp et al., 2020), additional longitudinal studies with larger sample sizes are needed to gain a better understanding in this area of research.

Linking findings from observational studies of the intergenerational transmission of ADs and preventive intervention efforts

As outlined at the beginning of the current thesis, a growing number of studies have examined a variety of potential risk factors that contribute to the elevated levels of psychopathology observed in the OAD, including alterations in the HPA axis (e.g., Ellenbogen et al., 2011; Halligan et al., 2007) and suboptimal caregiving environments (e.g., Iacono et al., 2018; Russotti et al., 2022). As employed in Study 2, longitudinal, prospective studies, in contrast to cross-sectional designs, allow researchers to infer directionality and explore causal mechanisms underlying the development of mental illness in the OAD. While discussions thus far have centered around factors that confer risk to the OAD, it is important to recognize that many, if not the majority, of these youth display positive mental health functioning as they grow up. Indeed, results from a longitudinal study have shown that about one in five offspring of parents with recurrent MDD sustained positive mental health functioning over a 4-year period (Collishaw et al., 2016). Resilience in the face of significant adversity has been of long-term interest in the field of developmental psychopathology (Luthar & Cicchetti, 2000; Masten, 2001). Nevertheless, studies on the risk factors for negative outcomes in the OAD have historically taken precedence over understanding the circumstances in which youth demonstrate resilience (Hammen, 2003), with studies on the latter remaining limited to this day.

There are different approaches to studying resilience in youth (Hammen, 2003). Some researchers have examined the main effects of the absence or low levels of previously identified risk factors on child functioning. Similarly, researchers have examined protective factors that do not simply reflect the opposite extreme of risk factors, but individual characteristics that typically contribute to adaptive functioning in youth. For example, positive expressed emotion,

adequate co-parent support, good-quality social relationships, self-efficacy, and frequent physical activity have all been longitudinally associated with sustained mental health in adolescents of parents with MDD (Collishaw et al., 2016). Interestingly, these data also suggested that the more protective factors present, the better the mental health outcomes in high-risk youth.

Another approach to resilience research is to examine the interactive effects between protective factors and having a parent with a history of an AD. Specifically, it would be expected that those at high-risk for ADs would benefit from the protective factor whereas it would have little to no effect on those at low-risk. Brennan and colleagues (2003) adopted this approach in a cross-sectional study using a community sample. The results indicated that maternal MDD interacted with low levels of parental psychological control, high levels of maternal warmth, and low levels of maternal overinvolvement to predict of resilient outcomes in adolescents exposed to maternal MDD. Taken together, future studies should examine *both* risk and protective factors using longitudinal designs and incorporate these findings in the design of treatment programs would best promote positive mental health outcomes in the OAD. The RUSH program is an example of such an approach, by targeting risk factors in the caregiving environment while promoting resilience in youth by teaching stress-coping techniques.

In addition to informing the content of preventive interventions, findings from observational studies on risk and resilience in the OAD have the potential to shed light on which factors moderate treatment efficacy. Belsky and van Ijzendoorn (2015) outlined the importance of considering the match between and individual and a proposed intervention, and to be cautious about attributing low treatment efficacy solely to poor program implementation. The authors conceptualized this idea within a differential susceptibility framework, which posits that certain

individuals are more susceptible to both positive and adverse effects of their environment while others are relatively unaffected by their surroundings (Belsky, 1997). As mentioned by Belsky and van Ijzendoorn (2015), it is important to acknowledge the potential ethical issues with regards to not providing equal access to available treatments across the population. However, this is not to say that individuals who are less responsive to the *currently available* treatments would not benefit from *all* treatments, thus creating opportunities to further tailor interventions to specific subgroups of high-risk youth. There is evidence to suggest that certain individual and family characteristics moderate treatment effects in the OAD. For example, Weersing and colleagues (2016) found that the effects of a cognitive-behavioural prevention program for adolescent offspring of parents with MDD on youth depressive symptoms were less strong when parents were in a depressive episode at baseline or had a history of hypomania, or when adolescents reported more internalizing symptoms and hopelessness as well as lower functioning at baseline. Based on findings from the RUSH program, the OBD with a lower CAR and decreased total daily cortisol output, as well as a flatter diurnal cortisol slope, at baseline benefitted the most from the intervention, as indexed by the greatest decreases in internalizing symptoms (Yong Ping, 2023). Together, this suggests that there may be an optimal time for prevention in the OAD (i.e., when youth and parents are clinically stable) and those with putative biomarkers of risk, such as a dysregulated HPA axis, might most benefit. Future studies should continue to explore potential moderating factors of the efficacy of prevention programs for the OAD to better understand how diverse high-risk youth respond to treatment.

Preventive intervention studies also provide further opportunity to replicate findings from observational studies on risk and resilience factors. Specifically, one would expect that changes in a risk or resilience factor following the intervention would result in reductions of

psychopathology in youth. Similar to one of the study goals of Study 3, future studies should explore whether changes in risk or resilience factors following an intervention mediate the outcomes on offspring psychopathology.

Strengths, limitations, and additional recommendations for future research

The three manuscripts that comprise the current thesis add to the growing body of literature examining the role of HPA axis dysfunction and the caregiving environment in the transmission of risk in the OAD. This was accomplished by using a variety of research designs and approaches, including meta-analytic procedures, replication of previous data, longitudinal study designs, and a proof-of-principle preventive intervention project. To the best of our knowledge, Study 1 was the first to quantitatively summarize HPA axis functioning, as indexed by diurnal cortisol levels in the natural environment, in the OAD. This allowed for comparisons with similar meta-analyses demonstrating hyperactivation in the HPA axis in individuals with a diagnosis of an AD across the lifespan (e.g., Lopez-Duran et al., 2009; Murri et al., 2016, Stetler & Murri, 2011). The second study replicated previous finding in the OBD sample of study 2, in which low parenting structure in middle childhood predicted a high CAR and high stress reactivity in response to the Trier Social Stress Test in adolescence (7-8 years later), which was driven largely by the OBD in the sample (Ellenbogen & Hodgins, 2009). The importance of structure in the caregiving environment was further highlighted in Study 3, which introduced a novel preventive intervention program for the OBD. The RUSH program remains one of the few prevention programs that exist for the OBD *prior* to the onset of clinically significant mental health challenges. Other commons strengths in the studies included using multiple assessment tools (i.e., questionnaires, clinical interviews, saliva sampling) and well-controlled statistical procedures (e.g., accounting for correlations between saliva samples or sibling data).

Simultaneously including multiple indexes of diurnal cortisol levels and aspects of the caregiving represents another strength across studies.

Several limitations need to be considered when interpreting the results presented in the current thesis. First, there are important characteristics of the parents that were not consistently evaluated across the three studies. There is evidence to suggest child outcomes may vary depending on whether it is the mother or father having a mental illness (Connell & Goodman, 2002). For example, during earlier periods of development, MDD in mothers seems to have a larger impact (Bagner et al., 2010), while father with MDD seem to gain greater influence during adolescence (Reeb et al., 2015). Consistent with a phenomenon known as assortative mating, individuals with an AD also often choose romantic partners with similar mental health challenges (Nordsletten et al., 2016). This not only heightens the genetic risk (Rietschel et al., 2017) but further exposes the OAD to the psychosocial dysfunction that has been observed in partners of parents with an AD (Serravalle et al., 2020). While we attempted to account for parent sex in Study 1, many of the studies included in the meta-analysis focused on maternal AD. In Study 2 and 3, the sample was too small to investigate the effects of parent sex on the results, despite including both mothers and fathers with BD in our sample. Therefore, future studies should include both parents in their assessments and investigate how different patterns of parental AD (i.e., the presence of an affective disorder in the mother, father or both) may influence child outcomes.

Similarly, the clinical features of ADs, including the severity (e.g., number of hospitalizations), the chronicity, and the timing within child's lifetime can have a significant impact on child outcomes (Hammen & Brennan, 2003; Mars et al., 2012). For example, having an anxiety disorder or the timing of the mood episode both influenced cortisol levels in infants of

mothers with MDD (Brennan et al., 2008). We attempted to include such variables in our meta-analysis, but this information was rarely reported in the included studies. We also recruited individuals with BD who were relatively stable and conducted assessments when parents were in euthymic states in Study 2 and 3, but more formal measures of the clinical features of the ADs is warranted in future studies.

While Study 2 and 3 both had the strength of using longitudinal designs, there several ways in which these research procedures can be improved in future studies. First, including more assessment timepoints would allow researchers to explore which aspects of the caregiving environment may be important for offspring outcomes across development. Based on our findings, it seems that structure/organization is important in middle childhood, but this may differ once offspring enter adolescence. Given parenting measures were not collected at time 2 of Study 2, we cannot be certain whether parentings practices remained stable or changed over time. While we spoke about potential transactional effects in our discussions, our data did not allow for formal testing of such hypotheses. Thus, increasing the number of assessment timepoints would also allow the application of cross-lagged statistical procedures to further elucidate the transactional nature between youth and their environment (Hails et al., 2018). In terms of Study 3 specifically, it would be important to include longer follow-up periods. We found that changes in family conflict only changed at 6-month follow-up. This is not uncommon in the treatment, and thus it is possible that some treatment effects were not able to be observed given the relatively short follow-up period. Conversely, longer follow-up periods would allow us to determine whether the observed treatment effects are maintained over time. It is important to note that the RUSH program is still in its early stages of development, and that using an RCT

design over a longer post-intervention timeframe will be considered in its future implementations.

Conclusions

In sum, the findings from the studies included in this thesis contribute to a growing body of literature on the biological and environmental factors that confer risk for psychopathology in the OAD. It further highlights a specific aspect of the caregiving environment, namely family structure/organization in middle childhood, that plays an especially important role in future mental health well-being in the OAD. Finally, these findings provide evidence that changing levels of family structure/organization via preventive intervention can lead to subsequent reductions in child behaviour problems. Thus, we can limit the intergenerational transmission of risk for psychopathology in the OAD by providing targeted, developmentally-informed treatments tailored to the specific needs of this high-risk population.

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