FAMILY ENVIRONMENT AND POLYGENIC RISK IN THE BIPOLAR HIGH-RISK CONTEXT

by
Emma Kilvington Stapp

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ABSTRACT

Objective: The overarching goal of this project was to investigate the role of family environment (FE) in youth at high familial risk for bipolar disorder (BD), a severe and impairing mood disorder associated with genetic and environmental risk—what about the FE is particularly salient, and does it confer risk for psychopathology in offspring, alone or with genetic burden for BD? The specific aims were to: 1) systematically review prospective studies of parental BD, FE, and offspring psychiatric disorders, identifying characteristics of FE associated with risk for psychiatric disorders among offspring of parents with and without BD (Chapter 2); 2) take a person-centered approach to modeling FE among offspring at high or low familial risk for bipolar disorder, by a) identifying latent patterns (classes) of child-perceived FE; and b) testing for demographic and clinical characteristics associated with FE (Chapter 3); and 3) test the main effects of offspring-perceived latent FE and the interaction of polygenic risk (BD-PRS) with FE on offspring mood diagnoses in offspring at high or low familial risk for BD (Chapter 4).

Methods: Aim 1: Four databases were searched to identify studies on offspring of BD parents. We followed PRISMA guidelines for best practices in systematic reviews and assessed for risk of bias. Aims 2 and 3: We used data from a multi-site prospective study of adolescents at high or low familial risk for BD in the US and Australia. We focused on a subset of offspring (266 high-risk, 175 controls). In Aim 2, we conducted exploratory factor analysis, latent class analysis, and latent class regressions to develop a person-centered model of offspring-perceived latent FE. In Aim 3, we used a three-step approach to modeling distal outcomes (main effects of latent FE and its interaction with BD-PRS), accounting for the effect of covariates on both the latent variable and offspring diagnosis.

Results: Aim 1: We identified 12 studies covering FE domains of family nurturance, communication, system maintenance, and values. Families with a BD parent versus no parental psychiatric disorders reported lower cohesion, and offspring had higher prevalence of psychiatric disorders. Family environment was not different between parents with BD parents and other major psychiatric or physical illnesses, nor was prevalence of offspring psychiatric disorders elevated. Families in which a child was diagnosed with BD had higher conflict than families without a child with BD. Children's perceptions were infrequently reported. Aim 2: Offspring perceived three patterns of FE: one large 'well-functioning' class characterized by nurturance, flexibility, and low conflict, and two smaller classes with high conflict and low warmth and cohesion, with separation based on high conflict with the father or very high conflict and rigidity in the mother-child relationship. Girls were more likely to be in the High Conflict with Mother class. Aim 3: Youth in the conflict classes were more likely to be diagnosed with BD, though the increased risk was only significant for youth in the High Conflict with Father class. High Conflict with Father was significantly and inversely associated with BD in interaction with BD-PRS; among those perceiving High Conflict with Father, increasing BD-PRS was associated with lower risk of BD.

Conclusions: Family environment in BD-parented families is heterogeneous, and it is important to assess offspring directly. High-risk youth experiencing FE that is high in conflict and low in warmth and flexibility are also more likely to themselves have BD. Researchers and clinicians working with BD high-risk families may reduce morbidity by attending to family cohesion and communication. Understanding the genetics of intergenerational transmission of BD may be facilitated by taking into account environmental influences, such as the family, which impacts the full spectrum of child development including mental health.

DISSERTATION COMMITTEE

Committee Members:

Peter P. Zandi, Professor, Mental Health (Advisor)

Holly C. Wilcox, Associate Professor, Psychiatry and Behavioral Sciences (Co-Advisor)

Donna Strobino, Professor, Population, Family and Reproductive Health (Chair)

Rashelle J. Musci, Assistant Professor, Mental Health

Alternates:

Tamar Mendelson, Associate Professor, Mental Health

Beth Renee Dail Marshall, Assistant Scientist, Population, Family and Reproductive Health

Robert L. Findling, Professor, Psychiatry and Behavioral Sciences

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CHAPTER 1: Introduction and Specific Aims

Part 1. Bipolar Disorder: The Public Health Problem

Definition. Bipolar disorder (BD) is a mood disorder defined by the presence of mania and depression (American Psychiatric Association [APA], 2000). Diagnosis of bipolar type I (BD-I) requires at least one manic episode, marked by elevated, expansize, or irritable mood for at least one week (or significant enough to require hospitalization), and at least three additional symptoms (four, for primarily irritable mood) including grandiosity, decreased need for sleep, pressured speech, flight of ideas or racing thoughts, distractibility, increased goal-directed activity or psychomotor agitation, and 'risky pleasures' (excessive involvement in activities with high potential for painful consequences, like buying sprees, promiscuity). There is marked impairment and symptoms are not due to medical problems, pharmacologic agents, or substances. A diagnosis of bipolar type-II (BD-II) involves at least one hypomanic episode and at least one major depressive episode. Hypomania has the same symptoms (and medication and substance-induced rule-outs) as mania, but shorter duration (at least four days). It is distinctly different from the individual's usual non-depressed mood and is observable by others, activities are usually organized rather than bizarre, and hypomania does not typically result in the level of impairment associated with mania. A major depressive episode (required for BD-II) involves at least five of the following symptoms over a two-week period: at least one must be dysphoria or anhedonia, plus appetite or weight change, sleep change, psychomotor retardation, fatigue, worthlessness or guilt, trouble thinking or concentrating or being indecisive, and suicidal ideation. Mixed episodes involve concurrently meeting criteria for mania and depression; this is typically associated with BD-I. In this dissertation, we will largely refer to BD as a broad phenotype

including BD-I, BD-II, and BD-not otherwise specified, where a person meets some but not all criteria or meets all criteria except duration.

Public health burden. Bipolar disorder is highly persistent and impairing, and associated with excess morbidity and mortality compared to the general population (Kessler, Merikangas, & Wang, 2007). In the United States (US), lifetime prevalence among adults is 1% for BD-I and 1.1% for BD-II (Kessler et al., 2007), and 0.6% and 0.4%, respectively, internationally (Merikangas et al., 2011). Among US adolescents aged 13-18 years, lifetime prevalence of BD-I or II combined is 2.9% (Merikangas et al., 2010), and when combining US and international estimates of youth aged 7-21 years the prevalence of BD spectrum is 1.8% (Van Meter, Moreira, & Youngstrom, 2011). Prevalence of BD does not consistently differ by sex, race, or socioeconomic status. Peak age of onset is 18 years for BD-I and 20 for BD-II (Kessler et al., 2007; Merikangas et al., 2011). In a nationally representative sample, approximately 10% of BD cases report onset before age 13 and one-third before age 18 (Merikangas et al., 2007), with higher prevalence of early onset reported in clinical samples (Birmaher et al., 2009; Danner et al., 2009; Perlis et al., 2004). Index episodes are frequently depressive (Perlis et al., 2004), and onset in childhood or adolescence is associated with worse prognosis and significantly more clinical correlates compared to adult-onset BD (Holtzman et al., 2015; Perlis et al., 2004).

The World Health Organization (WHO) ranks BD among the top 10 disabling disorders globally (Goodwin & Jamison, 2007). The majority of cases of BD are in the severe range, and annually, BD is associated with an estimated 96.2 million lost workdays and $14.1 billion salary-equivalent lost productivity (Kessler et al., 2007). Based on retrospective reports, the mean number of years that persons are in-episode is over 10, and the average number of lifetime episodes per person is over 60 (Kessler et al., 2007).

Between three-quarters and 97% of those with a bipolar spectrum disorder meet criteria for at least one comorbid psychiatric disorder, with anxiety disorders and substance use disorders being very common (Goodwin & Jamison, 2007; Kessler et al., 2007; Merikangas et al., 2011). Additionally, BD is associated with increased risk of cardiovascular disease, obesity, diabetes, and premature mortality (Crump, Sundquist, Winkleby, & Sundquist, 2013), with the relative risk of all-cause mortality for BD being at least twice that of the general population (Eaton et al., 2008; Walker, McGee, & Druss, 2015). As many as 10-15% of persons with BD die by suicide (APA, 2000) and attempted suicide is troublingly common among persons with BD, occurring at a rate of 1 in 4 with BD-I and 1 in 5 with BD-II (Merikangas et al., 2011). These numbers far exceed the annual international population suicide rate of 0.015% (Baldessarini, Pompili, & Tondo, 2006) and underscore the burden of severity experienced by individuals affected by this disorder.

Etiology. Both genetics and environment are associated with BD, although the exact causes remain unknown. There is heterogeneity of presentation of BD, which is likely reflected by heterogeneity in etiology.

Early genetics studies and heritability. Decades of genetics studies have demonstrated the bipolar disorder (BD) aggregates in families and that genetics play a substantial role in conferring risk (Craddock & Sklar, 2013). Having a family history of BD is the strongest known predictor of developing the disorder (Goodwin & Jamison, 2007), with offspring of BD parents at 8–10 fold increased risk of developing BD (Craddock & Sklar, 2013) and increased risk of developing mood and psychiatric disorders in general (Hodgins, Faucher, Zarac, & Ellenbogen, 2002; Rasic, Hajek, Alda, & Uher, 2014), compared to offspring of parents without psychiatric disorders. Monozygotic twin

concordance for BD is estimated to be 40–70% and heritability estimates range from 63–93% (Bearden, Zandi, and Freimer, 2016; Craddock & Sklar, 2013).

Genome-wide association studies and Psychiatric Genomics Consortium. Genetics studies have not produced one particular risk gene; rather, the results from a growing body of genome-wide association studies (GWAS) paint a more complex picture for the role of genetic inheritance involving the accumulation of risk across many genes (Purcell et al., 2009; Wray et al., 2014). Results from the Psychiatric Genomics Consortium (PGC) have demonstrated that the single-nucleotide polymorphisms (SNPs) associated with BD are common genes of small effect individually, which additively increase risk (i.e., polygenic risk), and are estimated to account for 25% of the variance in risk for BD (Lee et al., 2013; Sklar et al., 2011; Smoller et al., 2013). It is unclear exactly how many genes or which genes may serve as a tipping point in the pathway of developing BD, and the gene effects need not be the same in individuals and the overall gene action may not be additive, though some components may be (Visscher & Wray, 2016). Genetic susceptibility may vary for an individual depending on both gene expression and the environment to which he or she is exposed. Additionally, monozygotic twin concordance is substantially lower than 100% (Craddock & Sklar, 2013). That, combined with increasing attention to epigenetic mechanisms in risk for complex diseases (Rutten & Mill, 2009), points to the importance of non-genetic influences on development of BD.

Polygenic associations and liability-threshold model. One model that has been proposed for inheritance of complex disorders is the multifactorial liability threshold model. The assumption, building on diathesis-stress models, is that liability for a disorder is a continuum, and that when an individual's combined liability from multiple factors crosses some unobserved (latent) threshold, he or she will develop the disorder (Gottesman &

Shelds, 1967; McGue, Gottesman, & Rao, 1983). The recent findings related to polygenic risk and BD may support this model, as opposed to single locus or candidate gene models. There is not a large literature on the interaction of polygenes and environmental effects on liability (Visscher & Wray, 2016).

Environment. Among non-genetic influences, the family environment children experience is predominant, holding potential to be a key source of support or stress. Stress—both as it is appraised psychologically and experienced physiologically—has been implicated in the onset, recurrence, severity, and excess morbidity associated with BD (Bender & Alloy, 2011; Brietzke, Mansur, Soczynska, Powell, & McIntyre, 2012; Miklowitz & Chang, 2008; Post & Leverich, 2006). However, most offspring of parents with BD do not develop the disorder. Therefore, aspects of the environment may protect against development of psychiatric disorder in those at risk due to family history. Alternatively, correlates of lower (or not significantly elevated) risk for psychiatric disorders may represent the absence of risk factors, rather than the presence of protective factors (Weintraub, 1987).

Resilience theory focuses on strengths rather than deficits – on understanding healthy development despite exposure to risk (Fergus & Zimmerman, 2005). Supportive parenting is an example of a resource that may contribute to adolescents' resilience in the context of familial risk for BD. Family cohesion has been shown to have positive effects on recovery from substance abuse and management of depression, and family flexibility influences children's coping behaviors, social acceptance, and academic competence (Kouneski, 2000). Fowler and Christakis (2008) found that being connected to more happy persons increased the likelihood of future happiness among a cohort of over 4700 residents of Framingham, Massachusetts; this social contagion of happiness has implications for

families, such that happy and well-adjusted family members could increase other family members' likelihood of being or becoming happy.

Defining what is known about the family environment in the context of BD parents and their offspring is an important step toward understanding risk pathways to BD and potential targets for intervention.

Part 2. Family Theory and Child Development

The family environment is commonly understood as having a central role in children's physical, psychological, and socio-emotional development. Many well-supported theories exist regarding the relationship of family environment and child development, including healthy and abnormal trajectories. Family theories tend to emphasize the parent-child relationship (Ainsworth, 1985; Bowlby, 1969; Bretherton, 1992), the interparental relationship (Cummings & Davies, 2010; Grych & Fincham, 1990), or the transactional nature of family interactions (Sameroff & Fiese, 2000; Schermerhorn & Cummings, 2008). In the main aims of this dissertation, we focus largely on parent-child relationships and the transactional nature of family dynamics, as opposed to the interparental relationship, however they are all briefly introduced below.

Attachment theory, the work of Bowlby and Ainsworth, focuses on the importance of the child-caregiver relationship with a special focus on a stable and responsive mother-infant bond (Bretherton, 1992). Proximity to an attachment figure (attachment behavior) serves an evolutionary purpose–protection from danger ('predators') (Bowlby, 1969). The attachment figure serves as a secure base from which the infant explores the environment, and a safe haven upon return (Ainsworth, 1985). The ability of an attachment figure to serve effectively in that role is affected by their sensitivity to the child's signals, providing comfort and protection while also providing room for independence (Bretherton, 1992). Bowlby

posits that the combination of nurturing supportiveness with encouragement of autonomy is likely to promote the child's development of an internal working model of the self as valued and reliable (Bretherton, 1992). That working model promotes overall development of stability and self-reliance, and, along with open dialogue showing that working models are open to revision, contributes to the intergenerational transmission of attachment (Bowlby, 1973). From this perspective, parent-child relationships, as a component of family environment, play an essential role in the transmission of mental health and illness.

Davies and Cummings (1994) present a theory of 'emotional security' (EST), which holds that "maintaining a sense of protection, safety, and security is a central goal for children in family settings" (Cummings & Davies, 2010, p. 30). Departing from traditional attachment theory, EST argues that maintenance of security in the interparental relationship, in addition to the parent-child relationship, is an important goal. This includes the context of marital conflict, which, based on a large and long-ranging literature, is linked to children's adjustment (Emery, 1982). Emotional security is a process that happens within children. As a theory, it provides a conceptual model for understanding direct effects of exposure to marital conflict, as well as indirect effects of marital conflict such as changes in parenting and family relationships and new or worse family problems such as parental depression or substance use disorders. Exposure to destructive interparental conflict directly influences children's adjustment by undermining their emotional security in the interparental relationship, and hence, their ability to preserve stable family relationships (including the parent-child relationship), which increases children's vulnerability.

Grych and Fincham (1990) argue that the process by which marital conflict has an impact on children's adjustment is mediated by children's understanding of that conflict, which in turn is influenced by characteristics of the conflict, context, and cognitive and

developmental factors. Their review of studies of families in the U.S. from the 1970s to 1980s indicates that overt conflict, more so than covert conflict or marital dissatisfaction, is associated with children's maladjustment. Certain characteristics of conflict episodes are particularly salient and associated with negative consequences: higher frequency and duration; higher intensity (e.g., physical aggression, hostility and negative affect); the content (children as young as two years are sensitive to the topic and emotional valence, and disagreements about childrearing may be indicative of inconsistent discipline); and, whether and how the conflict is resolved (Grych & Fincham, 1990). Implications of this framework include the child's development of attributions for events and others' behavior, coping strategies, and social skills, particularly the ability to develop positive and healthy peer relationships.

Sameroff and Fiese (2000) set forth a transactional model of child development in which "the context of development is as important as the characteristics of the child in determining successful development" (p. 135). Child outcomes are therefore a result of the mutual, continuous, dynamic interactions between child and context. Sameroff and Fiese (2000) propose that a 'family code' regulates child development across generations and provides a sense of belonging. The family code organizes beliefs and behaviors in pursuit of fulfillment of the basic tasks of the family, including physical, emotional, social, cognitive, moral, and cultural development as well as health. The transactional model, as an ecological model, considers different disciplines' explanations for problems during child development as complementary rather than competing, so that a child's trajectory is influenced by economic concerns, community, family structure, education and within-family and within-individual psychological processes. Sameroff and Fiese (2000) underscore that the power of

risk and promoting factors lies in their accumulation, and assert that no single factor is determinant. Child and environmental effects are emphasized equally.

Whereas Sameroff's transactional model of development is ecological, and includes family dynamics, Schermerhorn and Cummings (2008) build on 50 years of family and development theory to propose transactional family dynamics as a framework specifically for understanding mutual influences and processes within families over time. Again, the focus is on the dynamic influence of individuals on each other and on family relationships as well as the influence of the family on individuals, rather than unidirectional pathways, and acknowledges how these influences evolve over time, both short and long-term.

What constitutes 'family environment' ranges across theories and certainly across individual research studies, with different components of family dynamics assuming key roles. A healthy family environment provides for children's emotional security, physical safety and wellbeing, and social integration, ultimately facilitating children's self-regulation and acquisition of behaviors that allow them to maintain wellbeing independent of caregivers (Bowlby, 1951; Repetti et al., 2002). Caregiving behavior affects offspring physical and psychological development, and is the foundation for socialization (Basic Behavioral Science Task Force of the National Advisory Mental Health Council [NAMHC], 1996). Key components of positive caregiving involve warmth, nurturance, and acceptance, as well as structure and control (Basic Behavioral Science Task Force of the NAMHC, 1996). Warmth, firmness, and psychological autonomy granting are particularly important domains in families with adolescents (Steinberg, 2001). Caregiver warmth and discipline influence children's perceptions of caregiver behavior, and, in turn, the impact of caregiving (Basic Behavioral Science Task Force of the NAMHC, 1996).

In contrast to a healthy family environment, families characterized by conflict and aggression, and cold, unsupportive, neglectful relationships are considered especially risky to child development (Repetti et al., 2002). These characteristics may create vulnerabilities in offspring and interact with preexisting vulnerabilities (for example, high burden of genetic risk) to put children at risk in both the short- and long-term for problems in emotional regulation, cognitive development, psychosocial functioning, and biological health (Johnson, Riley, Granger, & Riis, 2013; Repetti et al., 2002).

Parenting while adults negotiate their own mental health concerns is not a rare phenomenon. A substantial proportion of the population experiences at least one lifetime psychiatric disorder, and most adults fill the role of parent during their lifetime. In the context of genetically high-risk groups, the importance of the family environment grows in its potential for either increasing vulnerability or attenuating risk for developing psychiatric disorders (or more general patterns of maladjustment) among offspring. The ability to identify unique features of the family environment that are malleable and to harness that knowledge for development and application of interventions that may prevent, lessen, or heal intergenerational family environment risk processes is a public health priority.

Part 3. Specific Aims

The goal of this study was to investigate the role of family environment in youth at high familial risk for BD—what, if anything, is particularly salient in their family environment compared to other families (what is currently known, and if there is a BD-high-risk family environment 'signature'?); how might it contribute to or protect against psychopathology in individuals at high risk for BD (and for which); and how does genetic burden modify these associations? The specific aims of this project were:

Aim 1: Systematically review prospective, non-experimental studies of parental BD, family environment, and offspring psychiatric disorders, with the objective of identifying characteristics of family environment associated with risk for psychiatric disorders among offspring of parents with and without BD.

Aim 2: Model child-perceived family environment, using a person-centered approach, among a sample of adolescent and emerging adult offspring at high or low familial risk for BD. Specifically, a) identify latent patterns (classes) of child-perceived family environment; and b) test for predictors of family environment class membership, including demographic and clinical characteristics.

Aim 3: Test the main effects of offspring-perceived latent family environment and the interaction of polygenic risk with family environment on offspring mood diagnoses in offspring at high or low familial risk for BD.

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Chapter 2: Parental bipolar disorder, family environment, and offspring psychiatric disorders: A systematic review (Aim 1)

ABSTRACT

Objective: Our objective was to systematically review prospective, non-experimental studies of parental bipolar disorder (BD), family environment, and offspring psychiatric disorders, to identify characteristics of family environment associated with risk for psychiatric disorders among offspring of parents with and without BD.

Method: CINAHL, Embase, PsycINFO, and PubMed were searched using MeSH terms to identify potentially relevant studies on offspring of parents with BD published through September 2015. We followed PRISMA guidelines for best practices in systematic reviews. We used the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) to facilitate assessment of risk of bias within and across studies. We calculated prevalence ratios and 95% confidence intervals to compare offspring psychiatric disorders within and across studies.

Results: Of 8,844 unique documents retrieved, we identified 12 studies for inclusion covering domains of family nurturance, communication, system maintenance, and values. The most consistent finding from these studies was lower parent-reported cohesion in families with a BD parent versus no parental psychiatric disorders. Family environment was not different between BD parents and parents with other major psychiatric or physical illnesses. Children's perceptions were infrequently reported. Offspring of BD parents had higher prevalence of psychiatric disorders than offspring of parents without psychiatric disorders, but not compared to offspring of parents with other major disorders. Families in

which a child was diagnosed with BD had higher conflict than families without a child with BD.

Conclusions: Family environment in families with a BD parent is heterogeneous. Comparison to families without parental psychiatric disorders may identify problems with parental psychiatric illness generally, as opposed to parental BD in particular. Given the association between higher family conflict and offspring mood disorders, studies of children's perceptions of the family environment in the BD high-risk context merit further consideration.

Key Words: high-risk, bipolar disorder, family environment, parenting, family climate

Bipolar disorder (BD) is a persistent and impairing mood disorder associated with severe public health burden and individual suffering (Crump, Sundquist, Winkleby, & Sundquist, 2013; Eaton et al., 2008; Goodwin & Jamison, 2007; Kessler, Merikangas, & Wang, 2007; Merikangas et al., 2011). Offspring of parents with BD have greater risk of developing BD and other psychiatric disorders than offspring of parents without psychiatric history (Delbello & Geller, 2001; Hodgins, Faucher, Zarac, & Ellenbogen, 2002; Rasic, Hajek, Alda, & Uher, 2014). Indeed, decades of genetics studies have shown that BD aggregates in families, and that much of the variance in risk for the disorder is due to genetics (Bearden, Zandi, and Freimer, 2016; Craddock & Sklar, 2013). However, BD is a complex disorder, the etiology of which is attributable to some combination of genes and environment (Alloy et al., 2005; Craddock & Sklar, 2013; Miklowitz & Chang, 2008; Post & Leverich, 2006; Rutten & Mill, 2009; Wray, Byrne, Stringer, & Mowry, 2014). The gap in understanding intergenerational transmission of BD and related sequelae limits opportunities for effective treatment or possible prevention. It is imperative to identify sources or pathways of increased risk for developing psychiatric disorders among offspring of BD parents, as well as factors associated with resilience against developing psychiatric disorder in the BD high-risk context.

The family environment is one avenue of particular interest in the BD high-risk context due to its great importance in child development. This environment includes family climate, the timbre and functional quality of family relationships, as well as family system maintenance, including components such as organization and control. It is commonly understood as having a central role in children's physical, psychological, and socio-emotional development. Many well-supported theories exist regarding the relation of family environment with child development, including healthy and abnormal trajectories. Family

theories tend to emphasize the parent-child relationship (Ainsworth, 1985; Bowlby, 1969; Bretherton, 1992), the interparental relationship (Cummings & Davies, 2010; Grych & Fincham, 1990), or the transactional nature of family interactions (Sameroff & Fiese, 2000; Schermerhorn & Cummings, 2008).

Attachment theory, the work of Bowlby and Ainsworth, focuses on the importance of the child-caregiver relationship with a special focus on a stable and responsive mother-infant bond (Bretherton, 1992). Proximity to an attachment figure (attachment behavior) serves an evolutionary purpose–protection from danger ('predators') (Bowlby, 1969). The attachment figure serves as a secure base from which the infant explores the environment, and a safe haven upon return (Ainsworth, 1985). The ability of an attachment figure to serve effectively in that role is affected by their sensitivity to the child's signals, providing comfort and protection while also providing room for independence (Bretherton, 1992). Bowlby posits that the combination of nurturing supportiveness with encouragement of autonomy is likely to promote the child's development of an internal working model of the self as valued and reliable (Bretherton, 1992). That promotes overall development of stability and self-reliance, and, along with open dialogue showing that working models are open to revision, contributes to the intergenerational transmission of attachment (Bowlby, 1973).

Davies and Cummings (1994) present a theory of 'emotional security' (EST), which holds that "maintaining a sense of protection, safety, and security is a central goal for children in family settings" (Cummings & Davies, 2010, p. 30). Departing from traditional attachment theory, EST argues that maintenance of security in the interparental relationship, in addition to the parent-child relationship, is an important goal for children. This includes the context of marital conflict, which, based on a large and long-ranging literature, is linked to children's adjustment (Emery, 1982). Emotional security is a process that happens *within*

children. As a theory, it provides a conceptual model for understanding direct effects of exposure to marital conflict, as well as indirect effects such as changes in parenting and family relationships and new or worsening family problems such as parental depression or substance use disorders. Exposure to *destructive* interparental conflict directly influences children's adjustment by undermining their emotional security in the interparental relationship, and hence, their ability to preserve stable family relationships (including the parent-child relationship), increasing children's vulnerability.

Grych and Fincham (1990) argue that the process by which marital conflict has an impact on children's adjustment is mediated by children's understanding of that conflict, which in turn is influenced by characteristics of the conflict, context, and cognitive and developmental factors. Their review of studies of families in the U.S. from the 1970s to 1980s indicates that overt conflict, more so than covert conflict or marital dissatisfaction, is associated with children's maladjustment. Certain characteristics of conflict episodes are particularly salient and associated with negative consequences: higher frequency and duration; higher intensity (e.g., physical aggression, hostility and negative affect); the content (children as young as two years are sensitive to the topic and emotional valence, and disagreements about childrearing may be indicative of inconsistent discipline); and finally, whether and how the conflict is resolved (Grych & Fincham, 1990). Implications of this framework include the child's development of attributions for events and others' behavior, coping strategies, and social skills, particularly the ability to develop positive and healthy peer relationships.

Sameroff and Fiese (2000) set forth a transactional model of child development in which "the context of development is as important as the characteristics of the child in determining successful development" (p. 135), and, therefore, child outcomes are a result of

the mutual, continuous, dynamic interactions between child and context. Sameroff and Fiese (2000) propose that a 'family code' regulates child development across generations and provides a sense of belonging. The family code organizes beliefs and behaviors in pursuit of fulfillment of the basic tasks of the family, including physical, emotional, social, cognitive, moral, and cultural development and health. The transactional model, as an ecological model, considers explanations by different disciplines for problems during child development as complementary rather than competing, so that a child's trajectory is influenced by economic concerns, community, family structure, education, and within-family and within-individual psychological processes. Sameroff and Fiese (2000) underscore that the power of risk and promoting factors lies in their accumulation, and assert that no single factor is determinant. Child and environmental effects are emphasized equally.

Whereas Sameroff's transactional model of development is ecological, and includes family dynamics, Schermerhorn and Cummings (2008) build on 50 years of family and development theory to propose transactional family dynamics as a framework specifically for understanding mutual influence processes within families over time. Again, the focus is on the dynamic influence of individuals on each other and on family relationships as well as the influence of the family on individuals, rather than unidirectional pathways. It acknowledges how these influences evolve over time, both short and long-term.

Given the burden associated with BD, there is a need to understand for whom, when, on what, and how to intervene, informed by knowledge of cause and trajectory. A key source of knowledge on BD has been studies of high-risk samples. These studies, which focus on subgroups at increased risk for a disorder due to one or more causes, such as family history, provide the opportunity to prospectively assess individuals, gathering biological and/or environmental data and charting the prevalence or emergence of disorder. In these

studies, comparisons are made between those with and without familial risk for a given disorder, and between high-risk persons who develop a condition of interest and high-risk persons who remain free of the condition. Studying offspring of persons with BD may aid detection of etiologic factors (such as harsh family environment or gene-environment interaction); highlight timeframes most appropriate for interventions; and identify children who are experiencing distress or impairment (pointing to a need for services for the child, while identifying a potential source of stress for the parents) (Chang, Steiner, Dienes, Adleman, & Ketter, 2003; Hodgins et al., 2002).

To increase understanding of malleable risk processes in the intergenerational transmission of BD, it would be useful to identify signature features of the family environment of BD parents and link those features to offspring outcomes, taking into account the quality of the literature. Oyserman and colleagues (2000) presented a thoughtful review of studies addressing mothering in the context of serious mental illness, but their review does not include fathers and ends with papers published in 1999. More recently, several groups of researchers (e.g., Alloy et al., 2006; Jones & Bentall, 2008; Miklowitz & Johnson, 2009) have reviewed characteristics of family environment (e.g., expressed emotion, parenting) among persons with BD, but did not follow systematic procedures for identifying and assessing relevant literature, uniformly present rates of high-risk offspring psychiatric diagnosis, or focus on current (rather than retrospective) reports. To our knowledge, there has been no systematic review that characterizes family environment, measured prospectively, of families with a BD parent in contrast to families without a BD parent, while reporting and contrasting the rates of offspring psychiatric disorders in the offspring of those families. Our objective was to systematically review prospective, non-experimental studies of parental BD, family environment, and offspring psychiatric

disorders, identifying characteristics of family environment associated with risk and resilience to psychiatric disorders among offspring in families with BD parents compared to families without BD parents.

Methods

Eligibility Criteria

We approach our criteria by focusing on participants, exposures, comparisons, outcomes, and study design (PICOS; Liberati et al., 2009). The **participants** are families parented by a BD-affected parent (probands may be *parents with BD* and/or *offspring of parents with BD*), with parent diagnostic group established based on clinical diagnostic interviews. The **exposure** is an assessment of family environment using established self-report questionnaires or behavioral observation procedures. We acknowledge that there is great heterogeneity in the measurement of family environment. In many studies, family environment was treated as a dependent measure in the analytic phase, with parent diagnosis providing 'exposure' groups; however, in the context of studying the relation of parental BD, family environment, and offspring psychiatric disorder, family environment is ultimately an exposure. The *process* by which these constructs relate is outside the scope of this review. While parents' psychiatric disorder can be considered an exposure, we assess parent diagnostic group in the context of study samples and sampling. The **comparators** include at least one comparison group of families who were not parented by a BD-affected parent. This could include parents with no psychiatric disorder, a psychiatric disorder other than BD, or a chronic medical illness, for example. There is further heterogeneity in this regard, which we discuss when interpreting and comparing individual studies. For our **outcome**, we focus on psychiatric diagnoses in the offspring, requiring that diagnoses were assessed via clinical diagnostic interviews. We acknowledge that psychiatric diagnoses are not the only

important developmental outcome for youth, and indeed many studies additionally assessed other indices of functioning or symptomatology. It is with an eye toward prevention, as well as reliability across studies, that we focus on diagnosis as an outcome. The **study design** must be non-experimental (i.e., observational), and may be prospective longitudinal or cross-sectional. Retrospective reports of family environment (e.g., adult offspring reporting on their childhood) are excluded due to potential for recall bias.

Studies were included in the review if they met the aforementioned PICOS criteria and were an original research paper published in a peer-reviewed journal in English by September 2, 2015. In cases of multiple papers from a larger longitudinal study or data source, a single study meeting all aforementioned inclusion criteria was selected. In the event of more than one paper meeting all inclusion criteria, the paper reporting results with older offspring was selected due to peak onset of BD beginning in late-adolescence (Merikangas et al., 2011).

Search Strategy and Review Process

Four databases were searched for this review: CINAHL, Embase, PsycINFO, and PubMed. In PubMed, draft search strings using MeSH terms were tested and refined to maximize identification of articles about the target population of offspring of parents with bipolar disorder. The other 3 databases (CINAHL, Embase, and PsycINFO) were searched with comparable terms, calibrating the search strings until they were conceptually equivalent. We did not limit our searches by outcome terms, with the goal to reduce risk of publication bias by capturing a wider range of full-text documents including studies with unpublished results (Song, Hooper, & Loke, 2013). Appendix A lists the final search strings, which covered publications through September 2, 2015. We searched the references of the studies included in the review, as well as those in key background articles, applying the

aforementioned eligibility criteria. Additionally, we contacted authors to clarify information and identify additional studies when relevant.

Metadata from the electronic searches was reviewed in RefWorks, and coding for each paper was saved in the RefWorks 'User' fields. Each paper was assessed for inclusion according to the criteria listed above, by first reading the title, and, as necessary, the abstract and full text of the paper. Inclusion in the analytic set was agreed on by consensus of all authors. A protocol was not registered for this review. In order to compare prevalence of psychiatric disorders in the offspring across studies, we calculated prevalence ratios and 95% confidence intervals.

Assessment of Risk of Bias

Based on recommendations for best practices in systematic reviews (Liberati et al., 2009; Moher et al., 2009), we assessed risk of bias within and across studies. The workgroup that developed the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement did so as a broader version of the QUOROM (quality of reporting of meta-analysis) statement. They point out that the utility of a systematic review is directly related to the methodologic rigor with which it is conducted, its findings, and the clarity with which the methods and results are reported. They note that failure to report the assessment of risk of bias in the context of a systematic review may be a marker of poor conduct (Moher et al., 2009). Per PRISMA, a systematic review must have a clearly defined objective and use explicit, systematic methods to identify, select, assess, and present data from a set of studies that are relevant to the objective. Although application of the PRISMA statement is more straightforward for a review of interventions, the guidelines may be modified to accommodate the different features of a review that addresses diagnoses (e.g., the spectrum

of patients and verification of disease status are essential areas of concern) or disease etiology (Liberati et al., 2009; Moher et al., 2009).

To assess the risk of bias of an individual study in the analytic set of papers included in this systematic review, we used the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS; Kim et al., 2013). RoBANS includes assessments of six domains: selection of participants (selection bias due to the inadequate selection of participants), confounding variables (selection bias due to the inadequate confirmation or consideration of confounding variables), exposure measurement (performance bias due to the inadequate measurement of intervention/exposure), blinding of outcome assessments (detection bias due to the inadequate blinding of outcome assessments), incomplete outcome data (attrition bias due to the inadequate handling of incomplete outcome data), and selective outcome reporting (reporting bias due to the selective reporting of outcomes). Some domains (e.g., selective reporting) also speak to bias across studies.

To further assess the risk of bias across studies, we consider publication bias. Family environment is assessed through multiple methods, and, at times, non-overlapping measures, so a quantitative synthesis (meta-analysis) is not appropriate; nor do we include a funnel plot (Lau, Ioannidis, Terrin, Schmid, & Olkin, 2006). In an attempt to find unpublished outcomes (i.e., by not reporting psychiatric disorders in the offspring) in studies that would otherwise meet inclusion criteria, we contacted authors when relevant (Song et al., 2013). We did not contact authors of studies focused on infants, for example. In an attempt to find unpublished studies, we followed up on the status of conference abstracts and dissertations/theses initially excluded during our criteria review, searching the literature and contacting authors as needed to identify subsequent papers in peer-reviewed journals (Song et al., 2013).

Additionally, we considered how differences in study design and modeling affected the ability to draw inferences and compare quality across studies. The six domains of RoBANS, as well as consideration of other potential sources of bias, facilitate taking a PICOS approach to assessing the risk of bias in studies. These assessments are included in the presentation of data extraction and considered in the interpretation of results.

Results

Of the 11,967 articles identified through database and manual searching, 8,844 remained after removing duplicates using a reference manager program. We excluded 8,679 documents in the first round of screening. After assessing 164 papers for eligibility in the second round of screening (see **Figure 2.1** for PRISMA flow diagram), 12 papers published between 1987 and 2015 were included in this review. Essential components (including PICOS characteristics) of the 12 papers in the analytic set are summarized in **Table 2.1**, including study sample, study design, age of offspring, diagnostic assessments of parents and offspring, measures used to assess family environment, differences in family environment by parent diagnosis group, prevalence of offspring psychiatric diagnoses, and, if reported, associations between family environment and offspring diagnosis. Main findings are presented below, with RoBANS in **Table 2.2**.

Characteristics Across Studies

Across 12 studies, there were 1773 total offspring, with sample size ranging from 47 to 544 in the number of offspring studied. Offspring ranged in age across studies from 5–21 years old. Most studies covered ages ranging from 6, 7, or 8 through 17 or 18 years. For studies reporting a mean age of offspring, it was typically between 10 and 13 and consistently younger than the mean age of onset of BD.

Of the studies in which parent bipolar type was specified, 3 sampled parents with BD-I (Ferreira et al., 2013; Petti et al., 2004; Romero, DelBello, Soutullo, Stanford, & Strakowski, 2005) and 3 sampled parents with BD-I or -II (Chang, Blasey, Ketter, & Steiner, 2001; Doucette, Horrocks, Grof, Keown-Stoneman, & Duffy, 2013; Park et al., 2015). The six remaining studies did not specify type of BD (Burge & Hammen, 1991; Du Rocher Schudlich, Youngstrom, Calabrese, & Findling, 2008; Ellenbogen & Hodgins, 2009; Tarullo, DeMulder, Martinez, & Radke-Yarrow, 1994; Vance, Jones, Espie, Tai, & Bentall, 2008; Weintraub, 1987). For several of these studies, the reason was due to DSM-III not separating BD-I from BD-II. Families under study were largely of White race and middle to middle-high socioeconomic status.

Comparison groups consisted of parents with depression, schizophrenia, chronic medical illness, or no psychiatric disorders; offspring of parents with the aforementioned diagnoses; or, a normative U.S. sample. Comparison groups free of parental psychiatric disorder were most common. Studies presented findings across domains of family nurturance, communication, system maintenance, and, to a lesser extent, values. While some studies presented both parent and child reports, most findings were based on parent-reported family environment. Individual studies are presented below, with synthesis in our Discussion.

Findings and Risk of Bias of Individual Studies

Studies using behavioral observation. Using a sample drawn from the UCLA Family Stress project, **Burge and Hammen (1991)** reported on 57 mother-child dyads in which the mother has BD, unipolar depression, a chronic medical illness, or no psychiatric history (normal controls). Participants were mostly White and middle or upper-middle SES. Based on direct behavioral observation of an unstructured discussion of a mother-child-

identified conflict issue, they coded two core dimensions of family interaction: a) communication clarity or task productivity/involvement (creating an index of maternal task productivity/focus), and b) affective quality (creating an index of maternal positivity). They assessed offspring psychiatric diagnosis using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS), then created 4-point affective (0-3 on depression: none, nondiagnosable, minor, major depression) and nonaffective scales, which they analyzed as dependent variables. They found that maternal communication characteristics contributed together to child affective (depressive) symptoms (but not nonaffective symptoms), driven by maternal positive affect as opposed to task productivity. Additionally, they found that maternal chronic stress predicted maternal positivity, while maternal depressive symptoms (measured by the Beck Depression Inventory) predicted task focus. Thus, they found that stress predicts maternal positive affect, which in turn predicts child depressive symptoms. When they tested maternal psychiatric diagnosis as a dichotomous variable, it did not make a significant contribution, indicating that current symptoms, rather than diagnostic status, may be more important for understanding mother-child interactions. This group also found that child-reported perceptions of the mother on the Parent Perception Inventory were associated with lower diagnostic scores among the high-risk children (Conrad & Hammen, 1993).

An earlier paper from this study, using slightly different coding and group sizes, reported between-group differences on the behavioral interaction task (Gordon et al., 1989). Mothers with BD scored higher on task productive verbal behavior, lower on off-task and negative/disconfirming verbal behavior, and no different on positive/confirmatory statements than depressed mothers. Hammen, Burge, Burney, and Adrian (1990) reported lifetime psychiatric diagnosis (rather than scaled K-SADS) among the offspring, with

prevalences of 72%, 82%, 43%, and 32% for children of BD, depressed, chronically medically ill, and normal control mothers, respectively.

This is generally a high quality study, particularly in its longitudinal design, thorough assessment and interviewer training, and psychometrics, but there may be some potential bias related to sampling and attrition. The sample size was relatively small, generated from convenience patient populations and school-based controls. There was incomplete measurement of exposure and/or outcomes of 16% of the sample, and the authors do not explain whether there were between-group differences in attrition, or provide sensitivity analysis. Family interaction behavior was brief, and coded for verbal interactions resulting in summary scores, but the coding was standardized with good interrater reliability, and the findings are in line with now well-established literature on family interactions and depression (although it is possible that a bias toward publishing significant findings may reduce the weight of this type of accumulative evidence). Findings may not be generalizable to fathers, non-White races, or families of lower SES.

Tarullo and colleagues (1994) reported on mothers with BD, unipolar depression, or no psychiatric history, and each of their two children, from the NIMH Childrearing Study. At this paper's time point (Time 3), one child was a preadolescent (8-11 years) and the other an adolescent (12-16 years). Mothers and children were observed in informal discussion using questions randomly selected from a set as a starting point. Both maternal and child behaviors were coded and factor analyzed separately. BD mothers were less engaged with preadolescents than were well mothers, but maternal critical/irritable behavior with preadolescents was not significantly different by maternal diagnosis. While preadolescents' engagement and critical/irritable behavior were not significantly different by maternal diagnosis, the preadolescent children of BD and well mothers displayed higher

levels of comfort/happiness than did the preadolescent children of unipolar depressed mothers. In mothers' interactions with their adolescent children, maternal diagnosis was not associated with any of the mother or child factors. Offspring diagnoses were analyzed as presence or absence of one or more psychiatric disorders in the past year. When only considering disruptive, mood, or anxiety disorders, roughly half of the offspring of BD mothers had 'any' psychiatric problem, compared to two-thirds of offspring of mothers with unipolar depression, and one-third of offspring of mothers with no psychiatric disorder (Radke-Yarrow, 1998).

The selection of participants and thoughtful modeling in this study are high quality, although some results may need to be interpreted with caution due to small cell sizes. Also related to sample size, the authors do not address attrition in the study. We would expect 166 offspring (1 preadolescent and 1 adolescent for 83 mothers), but only 147 children were analyzed, and this discrepancy is seen particularly in the adolescents. Mothers participating were required to be primary caretakers without major disruptions of care and the majority of families were White, which may reduce generalizability.

Studies using the self-report Family Environment Scale (FES). The FES (Moos & Moos, 1994) measures Family Relationships (cohesion, expressiveness, conflict), System Maintenance (organization, control), and Personal Growth (independence, achievement orientation, intellectual-cultural orientation, active-recreational orientation, moral-religious emphasis). Normative FES scores are based on a sample from across the US in the 1970s, and treated as population means for comparison.

Chang and colleagues (2001) examined the relationship of parent-reported family environment and offspring psychiatric disorders in a sample at high risk for BD. They compared 36 families with a parent with BD-I or -II, recruited in the San Francisco Bay area

in the late-1990s, to the FES normative controls. While use of normative controls is efficient, the groups under study do not come from the same source population and we cannot be sure that the control group does not contain parents with BD. Prevalence of psychiatric disorders is unknown in the normative sample (Moos, personal communication), so prevalence of offspring psychiatric disorders cannot be made between groups.

Chang and colleagues (2001) found that, compared to normative controls, the BD parents scored higher on conflict, control, and intellectual-cultural orientation; lower on cohesion, organization, independence, and achievement orientation; and not significantly different on expressiveness, active-recreational orientation, and moral-religious emphasis. At the time of assessment, offspring of BD parents were aged 6-18 years (mean 10.4 years). Over half received a DSM-IV Axis I diagnosis, and 9 of the 56 children received a diagnosis of BD-I or -II or cyclothymia, which is much higher prevalence than in the population (Merikangas et al., 2010), though not inconsistent with other BD high-risk studies. Given that the children were young compared to peak onset years of BD, it is possible that more will go on to develop BD. Children's reports on family environment were not obtained, and it is possible that offspring diagnosis could be significantly related to children's perceptions of family environment even when not related to parent-reported family environment.

Romero and colleagues (2005) compared parent-report FES scores between 24 families with at least one parent with BD-I and 27 'healthy families' (parents without any psychiatric disorders). One parent in each family completed the FES and in over half of the BD families the parent with BD completed the questionnaire, but they were not in-episode and there were no significant differences within BD families based on which parent completed the FES. BD parents scored their families as lower on cohesion and expressiveness than healthy families; the groups were not different on other FES subscales.

Within the BD families, those with two parents with BD (n=11 of 24) scored higher on cohesion compared to those with one parent with BD. Over two-thirds of the 8-12 years old offspring of parents with BD were diagnosed with a mood disorder (n=17 or 71% total; n=9 diagnosed with BD), compared to only one child (3.7%) of parents without psychiatric disorder.

Romero and colleagues (2005) also compared their BD families' scores to the normative FES data, and found a higher number of significant differences on FES subscales than when comparing BD to the healthy families. Compared to the Moos normative sample, BD families scored lower on cohesion and independence, and higher on conflict, control, intellectual-cultural orientation, and moral-religious emphasis. Interestingly, they also compared their healthy families' scores to the normative data, and found significantly higher scores on cohesion, expressiveness, intellectual-cultural orientation, active-recreational orientation, and moral-religious emphasis among their healthy families.

More recently, **Ferreira and colleagues (2013)** used the FES to measure parent-reported family environment in Brazilian families, studying 47 families with at least one parent with BD-I and their offspring with or without psychiatric disorders compared to 30 families in which neither parents nor children had psychiatric disorders. Although cases and controls are clearly defined in this study, it is unclear whether they represent the same source population. The authors do not mention whether interviewers were blinded to participant group status or study objective. As with the aforementioned studies using the FES (Chang et al., 2001; Romero et al., 2005), Ferreira and colleagues (2013) did not obtain child reports.

Compared to families with no axis I disorders, BD parents scored higher on conflict and control; lower on cohesion, organization, intellectual-cultural orientation, active-recreational orientation, and moral-religious emphasis; and not significantly different on

expressiveness, independence, and achievement orientation. Within the BD families, those with two parents with BD (n=6 of 47) scored higher on moral-religious emphasis compared to those with one parent with BD. Offspring were aged 6–17 years, with a mean of 12 among BD families and 13 among Controls. For BD offspring diagnosed with a psychiatric disorder (a total of 47% of the sample), mean age at onset was 13 years. Approximately 23% were diagnosed with BD or major depressive disorder.

Studies using other measures of family environment. Vance and colleagues (2008) studied a group of 20 parents with BD and their 23 offspring compared to an age- and sex-matched control group of 20 parents without current psychiatric disorder and their 24 offspring in the United Kingdom. Two parents in the control group met criteria for a past major depressive episode, however their data were retained because results did not change when excluded. Authors Vance and Espie performed all diagnostic interviews (Y. Vance, personal communication), which means outcome assessments may not have been blinded. Parents and children reported on the Parental Attributions for Children's Events questionnaire (PACE) and Family Relationships Inventory (FRI).

The PACE is a self-report questionnaire designed to assess parents' inferential communication and attribution style, presenting a range of hypothetical negative events with a list of statements of possible causes and consequences of those events happening to their child. Parents rate how likely they would be to communicate each statement, and children rate their parents' likely responses. Compared to control parents, BD parents communicated more negative consequences—a more negative inferential communication style—as a result of hypothetical negative interpersonal events happening to their children, but the authors did not present findings specific to negative achievement events. The FRI is a self-report questionnaire assessing family cohesion, expressiveness, and conflict, derived from the FES

relationship domain (Holahan & Moos, 1983). As in the FES, cohesion is the degree to which family members are helpful and supportive of each other, expressiveness is the extent to which family members are encouraged to act openly and to express their feelings; and conflict refers to the extent to which anger, aggression, and conflictual interactions are characteristic of the family (Holahan & Moos, 1983). Compared to controls, BD parents endorsed lower expressiveness. The authors did not report findings on cohesion or conflict, leaving the reader to assume they were non-significant. Child reports on the PACE and FRI were not significantly different between BD-parented and control families. Offspring were aged 12-20 years (mean not provided). Mood disorders were diagnosed in 6 (26%) BD offspring and 1 (4%) control offspring.

Park and colleagues (2015) compared a group of offspring of BD parents and offspring of healthy control families selected for lack of psychiatric diagnosis, symptoms, medication, and family history, aged 9-18 years. By requiring BD offspring to have at least moderate mood symptoms, while the healthy controls were highly selected for lack of psychiatric morbidity, the comparisons being made may be more of a reflection of active mood symptoms, rather than diagnosis or risk status. Additionally, although 100 BD families and 60 healthy controls were recruited, 36 BD offspring and 9 healthy control offspring were excluded for incomplete data on an anxiety measure. Of the remaining 64 BD offspring and 51 healthy controls, data on the Family Adaptability and Cohesion Evaluation Scales, version IV (FACES-IV) were available for 22 BD offspring and 28 healthy controls. The authors report that there were no statistically significant demographic or clinical differences between those with versus without complete FACES-IV data; however, there is differential loss to follow-up between groups and the remaining small

samples (22 of 100 BD families recruited, 28 of 60 healthy control families recruited) may not represent their source or target populations. All FACES-IV data were parent-report.

In contrast to the research-oriented FACES-II, which measures adaptability/flexibility and cohesion linearly (high levels are better), the FACES-IV considers balanced (moderate) versus unbalanced (too high or too low) levels of flexibility and cohesion (Kouneski, 2000). Park and colleagues (2015) measured two additional FACES-IV scales: family communication and family satisfaction. Families with BD parents scored lower on balanced cohesion, family satisfaction, and communication, while higher on enmeshed (overly high, unbalanced cohesion) and chaotic (overly high, unbalanced flexibility) subscales compared to healthy controls. Differences on rigidity, disengagement, and balanced flexibility were not reported; the reader may assume that these other comparisons were non-significant. Within the BD offspring group, 55% were diagnosed with BD-NOS (n=11), MDD (n=19), or dysthymia (n=5).

Du Rocher Schudlich and colleagues (2008) recruited 272 youth aged 5-17 years, including 150 with BD, 31 with no psychiatric disorder, and the remainder with unipolar depression, dysthymia, or ADHD or disruptive behavior disorders without comorbid mood disorder. There were 76 families with at least one parent with BD, 91 families with at least one parent with unipolar depression but no parent with BD, and 105 families in which neither parent had a mood disorder (no BD or unipolar depression). They measured family transaction patterns using the Family Assessment Device (FAD; subscales on general functioning, problem solving, and communication) and perceived communication-conflict with the Conflict Behavior Questionnaire (CBQ), comparing offspring of BD parents to those with unipolar depression or no mood disorder. Parents not children reported on the

FAD and CBQ. The authors provided extensive consideration of confounders, mediation, and moderation in their modeling, and the interviewers received rigorous training.

Parent-reported conflict, as measured by the CBQ, was not significantly different across parent diagnostic groups. Families with one BD parent endorsed less adaptive family functioning on the FAD (total, general functioning, and problem solving scales, but not communication) compared to families without a parent with a mood disorder, but were not significantly different from families with one parent with unipolar depression. Families with two parents with a mood disorder (BD or unipolar depression) scored worse on all FAD scales compared to families with only one parent with a mood disorder or no mood disorders. Prevalence of BD among offspring was 84%, 54%, and 35% in the BD-, unipolar-, and no mood disorder-parented families respectively.

Ellenbogen and Hodgins (2009) compared a group of 28 offspring from 26 families with one parent with BD to a group of 26 offspring from 22 families with no current parental psychiatric disorders. At the time when parents completed the Parenting Dimension Inventory (PDI), the children were 6-13 years old (mean, 9 years). At the second time-point in the study, the children were 13-21 years (mean, 16.5 years; 92% of the sample aged 15-19 years). Parents were in a euthymic state when completing the PDI, which measures parenting attitudes and behaviors across the domains of supportiveness (nurturance, responsiveness, and non-restrictiveness), control (amount and type of discipline strategies, parents' maturity demands of their children), and structure (organization, consistency, and involvement). Mother, father, and stepparent scores were averaged for each child. Parents with BD endorsed lower levels of control than parents without psychiatric disorder. Differences on structure approached significance, being lower for BD parents, and were non-significant for supportiveness.

In an earlier paper reporting on the sample from which the 2009 sample was drawn, Ellenbogen and Hodgins (2004) found that parent neuroticism scores, not parent diagnostic status or a principle components analysis composite score of parenting from the PDI, predicted children's psychiatric symptoms on the Child Assessment Schedule. Nijjar, Ellenbogen, and Hodgins (2014) report on the lifetime psychiatric diagnoses of the offspring from the full longitudinal sample (n=128, after attrition of 18% of BD offspring and 17% of controls). Among BD offspring (mean age 20.5 years), approximately 66% (n=44) met criteria for at least one mental disorder, compared to 41% (n=28) of controls (mean age 19.2 years). While 33% (n=22) of BD offspring and 12% of controls (n=8) met criteria for a mood disorder, the majority of those were past diagnoses of MDD.

Doucette and colleagues (2013) studied the relationship of self-reported attachment during adolescence and psychiatric disorders measured longitudinally among offspring of a parent with BD compared to offspring of parents without any psychiatric history. The Inventory of Parent and Peer Attachment (IPPA), based on Bowlby's attachment theory, was developed to assess adolescents' perceptions of relationships with their parents and close friends, especially as sources of psychological security. It measures three dimensions: degree of mutual trust, quality of communication, and extent of anger and alienation, scored separately for mother, father, and peers. It was developed on an adolescent samples aged 16-20 years, but has been used with adolescents as young as 12 (Greenberg & Armsden, 2009). Mean age at completion of the IPPA in Doucette and colleagues' (2013) sample was 21.6 years among BD offspring and 16.5 years among Controls, with all offspring completing the IPPA aged 13 or older. This age cutoff may explain why the sample size for completed IPPA measures among BD offspring was 55 versus the 221 recruited, although some attrition may be loss to follow-up over time. They

do not report the number of families by parent diagnosis, only the number of offspring, which included siblings.

The IPPA provides a summary score, rather than subscales, and our focus is on the mother (IPPAm) and father (IPPAf) results. There were no significant differences between BD and control offspring on either IPPAm or IPPAf scores. Among BD offspring, approximately 41% (n=93) were diagnosed with a mood disorder; 13% (n=29) were diagnosed with BD. Almost no control offspring received a diagnosis of any mood disorder (n=2, or 3%) or BD (n=1, or 1.6%). As the authors note, offspring came from relatively intact families with medium to high SES, which may limit generalizability.

Weintraub (1987) reported on the Stony Brook High Risk Project, which was particularly concerned with schizophrenia but nonetheless met criteria for inclusion in this review (it is the only paper we review that has a group of parents with schizophrenia). In phase I of this comprehensive longitudinal study, the sample was comprised of 544 children aged 7–15 years in four groups according to parents' DSM-III diagnoses: 58 families and 134 offspring with a parent with BD, 31 families and 80 offspring with a parent with schizophrenia, 70 families and 154 offspring with a parent with unipolar depression, and 60 control families and 176 children with parents without psychiatric disorders. Two types of controls were recruited: a same-sex but otherwise random match from the classroom, and the other matched on sex, age, race, social class, and IQ. Attrition due to families moving or refusing to continue in the study from phase I to II (3 years after phase I) was 9.7% for families with a parent with schizophrenia, 21% for the families with a parent with a mood disorder (data combined), and 10% for controls. Those who refused were not different on sociodemographics compared to those who continued in the study, but were more severely disturbed and paranoid (the author did not compare across diagnostic groups).

Family environment was assessed using multiple measures for both parents and offspring at every phase of the study. The Family Evaluation Form (FEF) and Marital Adjustment Test (MAT) were administered to parents. The FEF is a semi-structured interview that assesses family solidarity, cohesion, conflict, finances and household resources, parenting behavior, marital adjustment, and relationships among children. Because the focus of the study is schizophrenia and the main objective of the paper was reporting risk factors for schizophrenia, BD-parented families were not compared against all other groups. Weintraub (1987) reported that marital discord (measured by the MAT) and family function (measured by the FEF) were not significantly different among the high-risk groups. Although offspring completed the Child's Report on Parental Behavior Inventory (CRPBI), which assesses perceptions of parents' child-rearing behaviors including acceptance, child-centeredness, control through guilt, instilling persistent anxiety, lax discipline, and nonenforcement of rules, results on this measure were not explicitly presented. Offspring also completed the Environmental Q-Sort and revised Minnesota-Briggs (M-B) History Scale to provide an evaluation of their parents and family environment "from their own phenomenological perspective" (p. 442), however results were not reported for BD families on the Q-Sort, or at all for the M-B History Scale.

Offspring aged 18 years and over were assessed for DSM-III diagnoses. Of the offspring of parents with BD, schizophrenia, unipolar depression, or no psychiatric disorder, 20% (n=21), 22.8% (n=17), 15.2% (n=20), and 9.6% (n=12), respectively, were themselves diagnosed with a psychiatric disorder. Among the BD offspring receiving a diagnosis, almost half had a mood disorder. Substance use disorders were common across all groups.

Petti and colleagues (2004) used a within-pedigree design to compare families with versus without a parent affected with BD. The authors refer to the non-BD group as

'unaffected' but do not clarify whether that means unaffected by BD specifically or by any psychiatric disorder. Fourteen pedigrees comprised of 30 nuclear families participated, split into two groups: 23 offspring of a parent with BD, and 27 offspring with unaffected parents (age range 6-17 years).

Both offspring and parents' perceptions of the home and social environment were assessed using the Home Environment Interview for Children (HEIC) a semi-structured interview designed to complement diagnostic interviews for children such as the Diagnostic Interview for Children and Adolescents, the instrument used to diagnose offspring psychiatric disorders in this study (Reich & Earls, 1987; Reich, Earls, & Powell, 1988. The authors did not identify which sections of the interview were selected or how they were quantified, although they present results on four dimensions. Scores on closeness of siblings, financial difficulties, closeness to relatives outside the nuclear family, and discipline were not significantly different between families with versus without a parent with BD, based on both parent- and child-report. Three times as many offspring of BD parents were diagnosed with a mood disorder: 39% (n=9) of offspring with a BD parent, compared to 11% (n=3) of offspring of a parent without BD.

Petti and colleagues (2004) assert that a within-pedigree design allows for better control for ethnic or cultural factors that are difficult to match (e.g., in typical case-control samples from the community). It may be more straightforward to delineate genetic versus environmental risk when studying family environment in siblings' families of origin, for example. However, as individuals move around different regions, experience socioeconomic changes, and partner with individuals from other families, it may become more difficult to delineate shared versus non-shared risk between offspring from subsequent generations.

Quantifying Offspring Psychiatric Diagnoses Across Studies

We computed prevalence ratios and 95% confidence intervals for as many comparisons of offspring psychiatric disorders by parent diagnosis as available data allowed (**Table 2.3**). When comparing offspring of parents with BD to offspring of parents with unipolar depression, schizophrenia, or chronic medical illness, we found no significant differences in their prevalence of a diagnosis of any psychiatric disorder (Hammen et al., 1990; Tarullo et al., 1994; Weintraub, 1987). Offspring in those comparisons ranged from mean ages of 9 and 13 years (Hammen et al., 1990; Tarullo et al., 1994) to above 18 (Weintraub, 1987).

We did, however, find a difference when comparing offspring of BD parents to offspring of parents without BD (a group that may, for example, include depressed parents aggregated with healthy parents) or to offspring of parents with no psychiatric disorder. A mood disorder was about 3.5 times more likely among offspring of parents with BD than without in a within-pedigree design with offspring 6–17 years of age (mean around 10 for girls and 12 for boys) (Petti et al., 2004). Another study covering a similar age range (mean age around 11.5 years) found that a diagnosis of BD was almost twice as likely among offspring with than without at least one parent with BD (Du Rocher Schudlich et al., 2008).

Offspring of parents with BD were diagnosed more frequently with psychiatric disorders than were offspring of parents without any psychiatric history. In examining any psychiatric diagnosis among the offspring, one study of preadolescent and adolescent siblings did not find a difference between offspring of BD parents compared to offspring of diagnosis-free parents (Tarullo et al., 1994), while three other studies with older, on average, samples, found a difference, with the offspring of BD parents being anywhere from 50% more likely (Nijar et al., 2014; mean ages approximately 19-20 years) to over twice as likely to

receive a psychiatric diagnosis compared to controls (Hammen et al., 1990, offspring around age 13; Weintraub, 1987, offspring ages 18 and older).

The estimated prevalence ratios are higher when focusing on mood disorders. Two studies presenting diagnoses on participants in or past peak onset age of BD found higher prevalence of mood disorders among offspring of BD parents compared to controls: Nijar and colleagues (2014) and Doucette and colleagues (2013; mean ages 20-25 years) found offspring of BD parents to be over two times and 13 times more likely, respectively, to receive a mood disorder diagnosis, with BD offspring in the Doucette sample to be over 8 times as likely as controls to receive a diagnosis of BD themselves. Vance and colleagues (2008) found an elevated prevalence of mood disorders among BD offspring but the difference was not significant, based on a large variance due to small sample size. Lastly, one study found that BD offspring were over 19 times more likely to receive a diagnosis of a mood disorder compared to offspring of parents with no psychiatric disorder, although ages of the children under study ranged from 8-12 years, so the magnitude of association could certainly change over time (Romero et al., 2005).

Comparisons were not possible for 3 of the 12 papers in the review because psychiatric disorders were only measured in the BD offspring and not in the offspring of the comparison groups (Chang et al., 2001; Ferreira et al., 2013; Park et al., 2015). Chang and colleagues (2001) used normative data on the FES as their comparator group, and psychiatric disorder was not measured in the normative sample (Moos, personal communication); however, 54% of the BD offspring were diagnosed with a psychiatric disorder, which is higher than the population average (Merikangas et al., 2010). Ferreira and colleagues (2013) found that 47% of the offspring of BD parents had psychiatric disorder, which is similar to Chang and colleagues (2001). In the control group, offspring with psychiatric disorder were

excluded, due to criteria in the larger study from which the sample was drawn (S. Caetano, personal communication). Park and colleagues (2015) had a similar exclusion criterion, and found a similar proportion of their offspring of BD parents to be diagnosed with a mood disorder, at 55%.

Differences in Family Environment by Offspring Psychiatric Diagnosis

Eight of the 12 studies tested for associations between *offspring* psychiatric diagnosis and family environment in addition to reporting differences on family environment between parent groups as described above. The main replicated finding was higher conflict or negativity in families with a child with BD (or mood disorder).

Although prevalence of offspring psychiatric disorders was not significantly different across groups in the behavioral observation studies (see Table 2.3), there were associations with family environment. Burge and Hammen (1991) found that maternal positivity but not task productivity predicted diagnoses of mood disorders in offspring. Neither maternal positivity nor task productivity were associated with non-mood psychiatric disorders in offspring. Tarullo and colleagues (1994) found that preadolescent offspring psychiatric disorders were positively associated with both maternal and child critical/irritable behavior, and inversely associated with engagement. Additionally, when preadolescent children had no past-year psychiatric disorder, severely ill mothers were significantly less engaged than well mothers. With adolescents with no past-year psychiatric disorder, BD mothers were least engaged, compared to unipolar depressed and well mothers. The adolescents with no past-year psychiatric disorder were also less comfortable/happy interacting with mothers with BD compared to unipolar depressed and well mothers. When adolescents did have a psychiatric problem in the past year, well mothers were more engaged with them than they were with offspring with no problems.

In the three studies employing the FES to measure parent-reported family environment (Chang et al., 2001; Ferreira et al., 2013; Romero et al., 2005), the authors tested within BD families for differences in family environment based on whether the high-risk offspring were themselves diagnosed. Both Chang and colleagues (2001)—comparing any Axis I disorder versus none and BD versus no BD—and Romero and colleagues (2005)—comparing BD versus no BD—with mean offspring ages around 10 and 8-12 years respectively, reported no significant differences in FES scores by offspring diagnosis. On the other hand, Ferreira and colleagues (2013), studying offspring with a mean age of 12, found that within families with a parent with BD, those with offspring diagnosed with a psychiatric disorder scored higher on parent-reported control than families with offspring without psychiatric disorder. Families with BD parents and affected offspring, compared to BD families with unaffected offspring and control offspring, scored lower on cohesion, intellectual-cultural orientation, and active-recreational orientation, and higher on conflict and control subscales of the FES.

Another study found higher scores on parent-reported conflict (on the CBQ rather than the FES; Du Rocher Schudlich et al., 2008) in families in which offspring were diagnosed with BD compared to no Axis I disorders, but family functioning was not significantly associated with offspring BD diagnosis. Impaired family functioning—especially communication and problem solving—was predictive of conflict levels. After adjusting for conflict, impaired family functioning was more strongly associated with child diagnoses other than BD. Testing paths among parental mood, family functioning, conflict, and youth BD, they tested a child effects model, which fit the data poorly, and a bidirectional model, which did not improve fit. When paths in both directions were included, the effect of youth BD on conflict was non-significant while the effect of conflict

on youth BD remained large (Du Rocher Schudlich et al., 2008, p. 858). This study found that BD was nearly twice as prevalent among the offspring of parents with BD than without, highlighting the relevance of conflict (and its pathway from impaired communication and problem solving) on offspring BD diagnosis.

Parents but not offspring reported higher levels of discipline in the home in families in which offspring were affected with BD, regardless of whether the parent was affected (Petti et al., 2004). Among BD offspring, perceived attachment to either parent was not associated with diagnosis of a psychiatric disorder, although offspring perceptions of attachment with their mother were associated with offspring mood disorder—a finding the authors dismissed as a spurious without explanation (Doucette et al. 2013).

Four of the 12 studies we reviewed did not report associations between family environment and offspring psychiatric diagnosis (Ellenbogen & Hodgins 2009; Park et al., 2015; Vance et al., 2008; Weintraub, 1987). However, Ellenbogen and Hodgins (2009) found that parenting support was inversely associated with children's externalizing behavior at time 1, as measured by the parent-report Child Behavior Checklist (CBCL), and with children's internalizing behavior at time 2, as measured by the Youth Self-Report CBCL. Additionally, Park and colleagues (2015) found that within the BD group, parent-reported enmeshment and poor family satisfaction and communication moderated the relationship of child BDNF genotype and child-reported social anxiety symptoms.

Risk of Bias Across Studies

Table 2.2 provides a summary of our risk of bias assessment using the RoBANS tool. We describe here the common findings across studies and how they address PICOS.

Publication bias. We followed up on conference abstracts and dissertations/theses initially excluded during our criteria review in an attempt to find unpublished studies,

searching the literature and contacting authors, as needed, to identify subsequent papers in peer-reviewed journals (Song et al., 2013). Attempts to follow up abstracts, dissertations, and unpublished outcomes in studies that otherwise met inclusion criteria yielded no additional papers.

Selection bias. The selection of participants in the RoBANS tool addresses the Participants and Comparators in PICOS. The possibility of selection bias is a concern in observational studies. When using convenience sampling, there is potential for differences between those who volunteer for studies and those who do not (Hernan, Hernandez-Diaz, & Robins, 2004). They may experience more severe forms of disorders and be more motivated, or, alternatively, they may be higher functioning if they are able to participate in research. There may be further differences when cases and controls are drawn from the clinic versus the community. In particular, participants drawn from clinic users are different from the general population of individuals with and without BD. The studies seldom reported participation rates or the characteristics of non-participants. Large-scale epidemiologic surveys and randomized controlled trials attempt to increase internal and external validity as well as generalizability of research studies, but even they are not immune to selection bias.

All studies used validated diagnostic interviews and trained interviewers, with varying levels of education (mostly post-graduate). Half of the studies we reviewed had a low risk of bias, in that the parent diagnoses were clearly measured with good diagnostic separation of groups, and we were reasonably certain that the groups came from comparable source populations. When the risk of bias was unclear (see Table 2.2), it was mostly because we could not be sure that cases and controls came from the same source population. For one study (Hammen et al., 1987) different diagnostic measures were used between groups (SADS

for psychiatric parental groups, MMPI for controls). The normative controls used by Chang and colleagues (2001) as the sole comparators were from a different time period and region as the BD parent group and were not assessed for psychiatric disorder, indicating potential for a high risk of bias.

Confounding. Confounding variables in the RoBANS tool partially addresses the Study Design in PICOS. Residual, or unmeasured confounding, is a potential concern in any observational study. It is not possible to know the full extent of unmeasured confounding in observational studies, but basic variables such as age, race, sex, and various measures of socioeconomic status that are often considered when attempting to adjust for possible confounding. The 12 studies described above were rated as having low risk of bias in this area, having presented consideration of sociodemographics in their modeling, with some studies presenting more thoughtful and complex models than others. However, parent comorbidities and age were rarely modeled.

Measurement of exposure. The measurement of exposure in the RoBANS tool addresses the Intervention/Exposure in PICOS. A criterion for high risk of bias in measurement of exposure, according to the RoBANS tool, is use of self-reported data. Whether self-report measures of an exposure such as family environment should be considered to have a high risk of bias is debatable. Nonetheless, from this perspective, the majority of the studies in this review were assigned high risk of bias in measurement of exposure. Two studies have unclear risk of bias in measurement of exposure because they employed interviews (Petti et al., 2004; Weintraub, 1987), which still rely on the participant to report information where the interviewer may also influence reporting. Of the studies of direct observation of behavior of parents, one used a standardized procedure for evaluating the observation (Burge & Hammen, 1991); it was assigned low risk of bias. The other

investigators developed their own structured coding system (Tarullo et al., 1994); the authors did not provide further information on the genesis of the system.

Blinding of outcome assessments. Blinding in the RoBANS tool partially addresses the Outcomes in PICOS by considering potential bias in detection due to inadequate blinding of outcome measures. The outcome measure was psychiatric diagnoses among offspring. Five studies demonstrated low risk of bias by either blinding raters to parent status (Burge & Hammen, 1991; Romero et al., 2005; Tarullo et al., 1994), completing diagnoses of the children first by treating the offspring as the probands (Du Rocher Schudlich et al., 2008), or blinding interviewers to study hypotheses and specific parental diagnoses even though, in the context of family genetics studies, the interviewers knew families came from BD pedigrees (Petti et al., 2004). Three studies had an unclear risk of bias because they did not mention blinding (Doucette et al., 2013; Ellenbogen & Hodgins, 2009; Weintraub, 1987). Three additional studies had an unclear risk of bias: although blinding to parent diagnostic status was not possible due to sampling decisions and study group composition, it was unclear whether lack of blinding affected prevalence of offspring diagnosis (Chang et al., 2001; Ferreira et al., 2013; Park et al., 2015). In the last study (Vance et al., 2008), two coauthors completed all diagnostic interviews, but it was unclear whether this approach was a source of bias.

Incomplete outcome data. Attrition in the RoBANS tool partially addresses the Outcomes in PICOS. In six studies, the same number of participants were screened and analyzed (Chang et al., 2001; Du Rocher Schudlich et al., 2008; Ferreira et al., 2013; Petti et al., 2004; Romero et al., 2005; Vance et al., 2008). In another study, there was minimal loss to follow-up, which was equal across study groups (Ellenbogen & Hodgins, 2009), leading us to assign low risk of bias due to attrition in these 7 studies. In contrast, one study had very

high attrition that was different between groups, which may indicate high risk of bias (of 100 BD and 60 controls screened, 22 and 28 had family environment data; Park et al., 2015). The other studies were unclear. Doucette and colleagues (2013) reported a relatively large difference between the full sample and the number with completed IPPA data, but the age cut-off may be the reason for this difference. Attrition was not high in the Stonybrook High Risk Project; refusers were not significantly different from consenters on sociodemographic characteristics, but they were "more severely disturbed and more paranoid" than the consenters (Weintraub, 1987, p. 441). There was 10-15% loss to follow-up in the papers from the UCLA Family Stress project and the NIMH Childrearing Study, which is modest for longitudinal studies, but the authors did not address whether there were significant between-group differences related to attrition or discuss sensitivity analyses; accordingly, we do not know whether attrition affected their outcomes (Burge & Hammen, 1991; Tarullo et al., 1994).

Selective outcome reporting. The handling of outcome reporting and whether it is biased in the RoBANS tool partially addresses the Outcomes in PICOS. The majority of the studies we reviewed had low risk of bias related to selective reporting, with findings reported for all key outcomes addressed in their objectives and methods (Chang et al., 2001; Doucette et al., 2013; Du Rocher Schudlich et al., 2008; Ferreira et al., 2013; Petti et al., 2004; Romero et al., 2005; Tarullo et al., 1994). For two of those studies, it was necessary to obtain prevalence of offspring diagnoses from other papers (Hammen et al., 1990 for Burge & Hammen, 1991; Nijar et al., 2014 for Ellenbogen & Hodgins, 2009). Three studies did not present all family environment scores, but, instead, only presented significant group differences (Park et al., 2015; Vance et al., 2008; Weintraub, 1987).

Discussion

We systematically reviewed the literature to identify 12 prospective, non-experimental studies of parental BD, family environment, and offspring psychiatric disorders. The 12 studies covered domains of family nurturance, communication, system maintenance, and values. The most consistent finding was lower parent-reported cohesion in families with a BD parent compared to families with no parental psychiatric disorders. Parents with BD, for the most part, endorsed family environments not significantly different than parents with other major psychiatric or physical illnesses. Children's perceptions were infrequently reported, and were mostly not different between groups. Prevalence of psychiatric disorders was higher among offspring of BD parents than parents without psychiatric disorders, but not compared to offspring of parents with other major disorders. Families in which a child was diagnosed with BD had higher conflict than families without a child with BD.

Summary of Differences in Family Environment by Parent Diagnosis

Family nurturance. In studies comparing families with parental BD versus no parental psychiatric disorder, a replicated finding is that BD parents report lower cohesion (Ferreira et al., 2013; Park et al. 2015; Romero et al., 2005). This finding is echoed in studies comparing BD parents to a U.S. normative sample (Chang et al., 2001, Romero et al., 2005). Even with the evidence for lower cohesion in families with a BD parent, there are still conflicting findings in which these high-risk families are not significantly different than controls on related constructs, including engagement (Tarullo et al. 1994, BD versus no parental psychiatric disorders and BD versus unipolar depression), offspring-perceived attachment (Doucette et al. 2013, BD versus no psychiatric disorders), and supportiveness (Ellenbogen & Hodgins, 2009, BD versus no psychiatric disorders).

Family communication. Findings from studies addressing communication and affect are mixed. Some parent reports suggest disrupted communication in BD high-risk families versus controls, with lower expressiveness (Romero et al., 2005, Vance et al., 2008) and communication (Park et al., 2015), and greater conflict (Ferreira et al. 2013) and negative inferential style (Vance et al. 2008) reported by parents. Greater conflict was reported in BD families compared to a U.S. normative sample (Chang et al. 2001, Romero et al. 2005). Other parents reported no differences on expressiveness (parental BD versus no psychiatric disorders, Ferreira et al., 2013; parental BD versus US normative controls, Chang et al., 2001 and Romero et al., 2005) and no differences on conflict (parental BD versus no psychiatric disorders, Romero et al. 2005 and Vance et al. 2008; parental BD versus unipolar depression, Du Rocher Schudlich et al. 2008 and Weintraub 1987; parental BD versus schizophrenia, Weintraub, 1987). Maternal critical/irritable behaviors were not significantly different between mothers with BD and well mothers, and BD versus depressed mothers (Tarullo et al. 1994). While one study (Du Rocher Schudlich et al., 2008) found that communication and problem solving were not different between parents with BD versus unipolar depression, the UCLA Family Stress project (Gordon et al., 1989) reported that BD mothers displayed less negative verbal behaviors and were more on-task than depressed mothers.

Offspring of BD parents reported no differences on expressiveness and negative inferential style compared to offspring of parents without psychiatric disorder (Vance et al., 2008), and were not different in observed critical/irritable behavior compared to offspring of mothers without psychiatric disorder and offspring of mothers with unipolar depression (Tarullo et al., 1994). Offspring of mothers with BD displayed more comfortable and happy interactions with their mothers than did the offspring of depressed mothers, but were not significantly different from offspring of well mothers (Tarullo et al., 1994).

Family system maintenance. Findings regarding components of system maintenance—such as organization, discipline, control, and flexibility—were mixed. Several studies have found BD parents score lower on structure and control (Ellenbogen & Hodgins 2009, BD versus no psychiatric disorder; Romero et al., 2005, BD versus US normative controls), lower on organization yet higher on control (Chang et al., 2001, BD versus US normative controls; Ferreira et al., 2013, BD versus no psychiatric disorder), and higher on chaos (too high/unbalanced flexibility) than parents without psychiatric disorders; Park et al., 2015). As in the literature on nurturance and communication, there were null findings on system maintenance, including: rigidity (too low/unbalanced flexibility) and balanced flexibility (Park et al., 2015, BD parents versus no psychiatric disorders); organization (Romero et al. 2005, BD parents versus no psychiatric disorders, BD parents versus US normative controls); general family functioning (Du Rocher Schudlich et al., 2008, BD versus depression; Weintraub, 1987, BD versus depression, BD versus schizophrenia); and discipline (Petti et al., 2004, BD parent versus no BD).

Family values and personal growth. Certain measures, such as the FES, capture family activities and preferences. When comparing families with parents with BD versus no psychiatric disorder, findings align regarding null differences on achievement orientation and independence (Ferreira et al., 2013; Romero et al. 2005). And while Romero and colleagues (2005) additionally found no significant between-group differences on intellectual-cultural orientation, moral-religious emphasis, and active recreation orientation, Ferreira and colleagues (2013) found BD parents scored lower than controls on all three of those components. Comparing contemporary families with a BD parent to a US normative sample from the 1970s, both Chang and colleagues (2001) and Romero and colleagues (2005) found BD families scored greater on intellectual-cultural orientation, lower on

independence, and not significantly different on active-recreational orientation. While the Chang et al. (2001) BD parents scored lower on achievement orientation, the Romero et al. (2005) BD parents were not significantly different from normative controls. And while the Romero et al. (2005) BD parents scored higher on moral-religious emphasis, the Chang et al. (2001) BD parents were not significantly different from normative controls.

Offspring Psychiatric Disorders and Associated Family Environment

All told, there was mostly-consistent evidence of elevated risk of developing psychiatric disorders—especially mood disorders—among offspring of parents with BD compared to offspring of parents with no psychiatric disorder. However, there was no evidence of elevated psychiatric disorders generally when comparing BD offspring to the offspring of parents with another chronic psychiatric or physical illness. Two studies comparing families with versus without BD parents (comparison groups including both mood disorder-free parents and those with depression) had significantly higher prevalence of mood disorders in offspring; in these two studies, there was higher parent-reported discipline (Petti et al., 2004) and higher parent-reported conflict (Du Rocher Schudlich et al., 2008).

In the studies reviewed herein, families in which offspring had a psychiatric disorder exhibited greater conflict than families in which the offspring did not have a psychiatric disorder. This is in line with other studies on youth with BD (i.e., irrespective of parent status). The Course and Outcome of Bipolar Youth study (Birmaher et al., 2014) identified different mood trajectories and associated predictors in a sample of 367 youths with BD-I, BD-II, or BD-NOS in the US. Family functioning was assessed using child and parent versions of the CBQ and FACES-II. Parent-reported conflict was lower among BD youth who spent greater proportion of time in euthymia, compared to the group of youth who

were ill with an improving course. The authors did not find any other significant differences on family functioning among trajectory classes, although scores on child-rated cohesion and adaptability were highest in the trajectory class with the highest proportion of time spent in euthymia. Families high on expressed emotion are characterized by high-conflict negative interactions that escalate, and these parents and partners are also more likely to attribute negative events involving their BD relative to personal, controllable factors; these negative family interactions are associated with relapse and social impairments in the BD individual (Miklowitz & Johnson, 2009). In samples of youth with BD, mother-child relationships have been reported to be higher in conflict and hostility, as well as lower in warmth, compared to healthy controls and children with ADHD (Geller et al., 2000; Schenkel, West, Harral, Patel, & Pavuluri, 2008); low maternal warmth, in turn, is associated with shorter time to illness recurrence (Geller, Tillman, Craney, & Bolhofner, 2004).

Most offspring of parents with BD do not develop the disorder. Therefore, aspects of the environment may protect against development of psychiatric disorder in those at risk due to family history. Alternatively, correlates of lower (or not significantly elevated) risk for psychiatric disorders may represent the absence of risk factors, rather than the presence of protective factors.

Related Literature

Use of the FES. We note some consistent findings on subscales of the FES. Comparing BD families to U.S. normative controls, both Chang and colleagues (2001) and Romero and colleagues (2005) found higher levels of conflict, control, and intellectual-cultural orientation; lower levels of cohesion and independence; and non-significant differences on expressiveness and active-recreational orientation. Their findings differed regarding organization, achievement orientation, and moral-religious emphasis. Comparing

BD families to families without psychiatric disorders in the parents, Romero and colleagues (2005) and Ferreira and colleagues (2013) were in accordance in finding lower levels of cohesion, and non-significant differences in achievement orientation and independence. However, their findings conflicted on all other subscales. These 3 studies offer 4 total comparisons (with Romero et al. providing both BD versus normative and BD versus healthy controls). In all 4 comparisons, BD families scored lower on cohesion. In 3 comparisons, BD families scored higher on conflict and control, and non-significantly different on achievement orientation, expressiveness, and active-recreational orientation. Findings were mixed on intellectual-cultural orientation, organization, independence, and moral-religious emphasis. In BD families in which both parents were diagnosed with BD (i.e., bilineal) compared to one parent (i.e., unilineal), Romero and colleagues found higher scores on cohesion and Ferreira and colleagues found higher scores on moral-religious emphasis.

These three studies (Chang et al. 2001, Ferreira et al. 2013, Romero et al. 2005) rely on parent reports of the family environment. Children may offer a different and important perspective on family environment, and the lack of significant findings relating offspring diagnosis to family environment may be related to this. Additionally, use of a normative sample as a comparison group may be problematic; comparing groups from different time periods and populations may obscure researchers' abilities to detect meaningful differences between groups. For example, there may be differences in parenting between the 1970s and 1990s and in different regions of the U.S., and the potential inclusion of parents with bipolar disorder in the normative sample prohibits a clean comparison of cases and controls. The FES is widely used but potential problems with reliability and validity have been noted (Boyd et al. 1997; Moos, 1990).

Divorce. Persons with BD are 80% more likely to be separated, divorced, or widowed than married or cohabitating (Grant et al., 2005). Divorce may be an indicator of or proxy for many different aspects of family dynamics, but is not necessarily negative unto itself. Research suggests that the conflict leading to and surrounding divorce, rather than the change in family structure, is associated with negative outcomes for children (Grych & Fincham, 1990; Cummings & Davies, 2010). Additionally, Hetherington (1989) found no differences under conditions of low stress and adequate social support between 'difficult' and 'easy' children in their adaptive abilities following divorce. Divorce was not explicitly modeled in the above studies. In many earlier studies, a majority of parents were married. It is possible that coming from a relatively intact family with financial resources may be a protective factor even in the face of family disruptions such as conflict, low cohesion, or insecure attachment.

Childhood maltreatment. Abuse and neglect in childhood (childhood maltreatment) are consistently associated with negative mental and physical health outcomes in both the short- and long-term (Chapman et al., 2004; Felitti et al., 1998; Johnson, Riley, Granger, & Riis, 2013; Repetti, Taylor, & Seeman, 2002). Individuals with BD retrospectively report a higher prevalence of exposure to childhood maltreatment than individuals without BD (Alloy et al., 2006), and exposure to childhood maltreatment is associated with early onset and a more pernicious course of BD, onset and recurrence of mania, suicidality, and substance abuse disorders in patients with BD (Daruy-Filho, Brietzke, Lafer, & Grassi-Oliveira, 2011; Gilman et al., 2015) and increased risk of mood disorders in offspring of BD parents (Doucette et al., 2016). We excluded studies on abuse because they represent extreme negative caregiving behaviors and we sought to capture the family environment more generally (e.g., climate) in the BD high-risk context. However, in

additional to carefully checking the papers picked up in our database searches, we hand searched for papers on abuse and neglect and none met our search criteria as they were all retrospective, and focused on BD patients not offspring of BD parents. It is possible that some of the above studies capture emotional abuse within their broader assessments of the family environment.

Family environment in BD adults' families of origin and among BD youth. Additional evidence about family environment in the BD high-risk context comes from retrospective reports of adult offspring of BD parents. In the Dutch Bipolar Offspring Study, a rejecting parenting style was significantly associated with first mood episode onset, and rejecting and overprotective parenting styles were significantly associated with the risk for recurrent episodes (Kemner et al. 2015). An earlier report from the Dutch Bipolar Offspring Study compared the BD offspring cohort to a population sample of 1122 young adults in the Netherlands (Reichart et al., 2007), and found the offspring of a BD parent perceived their mothers as less rejecting, less overprotecting, and more emotionally warm, and their fathers as less warm and less overprotecting. Additionally, compared to controls, BD offspring who were without DSM-IV diagnoses perceived both their fathers and mothers as less rejecting and less overprotecting, and their mothers as more emotionally warm, whereas the offspring with a BD diagnosis perceived their fathers as more rejecting. These differences may offer insight into potential protective factors among individuals at high risk for developing mood disorders, and underscore the importance of accounting for offspring mental health status when studying the family environment.

Limitations

Limitations at the review-level. Screening, criteria review, and data extraction were conducted by a single author (EKS). Comparisons are qualitative due to the wide variety of family environment measures spanning multiple domains.

Limitations at the study and outcome level (e.g., risk of bias). Subtype of BD was not always specified. Moreover, comparison of BD to no psychiatric history may reveal more about psychopathology in general than BD specifically. Weintraub (1987) noted that a psychiatric comparison group, not only diagnosis-free controls, in psychiatric research is essential to meaningfully interpret results about a specific diagnosis, not just general psychiatric morbidity. Also, psychiatric comorbidity is the norm, rather than exception, among persons with BD, but the papers reviewed here did not discuss the possible effects of comorbidities. There is heterogeneity in the family environments of families in which at least one parent has a BD diagnosis. Additionally, parental functioning and symptom level, rather than lifetime diagnostic status, may be relevant to understanding parent-child interactions and family climate.

Findings may not be generalizable to all families with BD parents. Many study samples were predominantly White and middle to high SES. There is robust literature indicating that warmth, firmness, and psychological autonomy granting are central domains of family environment—particularly the parent-child relationship—and the benefits of those characteristics transcend cultures (Steinberg, 2001). While some of the studies focused on the mother-child relationship, there were no studies focused on fathers only. Findings regarding BD mothers may not generalize to BD fathers. Convenience samples with volunteers at clinics may have external validity to other BD-affected families who access medical care, but the findings regarding family environment may not generalize to families who do not seek or have access to medical care.

Most studies relied on self-report measures of family environment, but these reports may be influenced by parents' characteristics, life experiences, and symptoms, in addition to the child's behavior. Children's perceptions of their family environments were rarely obtained. It is possible that offspring diagnosis could be significantly related to children's perceptions of family environment even when not related to parent-reported family environment. Children's reports of the family environment, however, were not significantly different based on case/control status of the parents.

Families with children developing psychiatric problems may seek out research studies more than families in which the offspring appear to be developing normally (regardless of parent diagnosis). The mean age of offspring in most studies was younger than the peak age of onset associated with BD and depression. Accordingly, these studies may underestimate the association between the exposure (family environment) and outcome (offspring mood disorders). Given that the prevalence of mood disorders among the high-risk offspring is already much higher than population estimates of peak onset, it possible that onset begins younger in high-risk samples than in the population. For example, Baldessarini and colleagues (2011) found that family history of BD was most prevalent in childhood compared to later onset of BD-I.

Conclusion

To our knowledge, this is the first systematic review linking prospective studies of family environment in the BD high-risk context and offspring psychiatric disorders. Family environment in BD-parented families is heterogeneous, although parents with BD report lower family cohesion than parents without psychiatric disorders or normative controls. Comparison to families without parental psychiatric disorders may identify problems with parental psychiatric illness generally, as opposed to parental BD in particular. Moreover,

current parental functioning or symptoms may offer insight to understanding parent-child interactions and family climate above and beyond parental lifetime psychiatric diagnoses. Recognizing the heterogeneity of individuals and family systems, it may be that it is less important to attempt to characterize all families with BD based on group means, than it is to characterize a particular sample under study in order to draw appropriate inferences. Finally, compared to parent-reports, there is a relative dearth of literature assessing children's prospective perceptions of the family environment in the BD high-risk context. Offspring-perceived family environment is a topic that merits further consideration, especially since higher family conflict is associated with offspring mood disorders.

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Table 2.1. Key characteristics of studies included in systematic review

Author (Year)	Sample, by Parent Group *N families (offspring)*	Study Design	Age of Offspring *range (mean) years*	Parent Diagnosis	Family Environment Assessment	Family Environment Findings by Parent Diagnosis	Offspring Psychiatric Diagnosis, Prevalence by Parent Group	Family Environment Findings by Offspring Diagnosis
Burge & Hammen, 1991	BD 12 (12) Unipolar 13 (13) Medical illness 11 (11) No psych 21 (21)	Longitudinal (6 mos)	8-16 (male 12.75; female 12.42)	*Parents:* SADS-L; MMPI short form for no-dx group *Offspring:* K-SADS	Direct behavioral observation, coding adapted from PIRS	*Maternal verbal behavior* BD vs. Depressed: > task productive; < off-task, negative/ disconfirming; n.s. positive/ confirming (Gordon et al., 1989)	BD: 72% Unipolar: 82% Medical illness: 43% No psych: 32% *any lifetime dx* (Hammen et al., 1990)	Offspring depressive dx predicted from positivity, n.s. task productivity. Offspring nonaffective dx n.s. related to maternal interaction characteristics.

						Child-report: n/a		
Chang et al., 2001	BD 36 (56) Normative sample of diverse families from US 1432	Cross-sectional	6-18 (10.4)	*Parents:* Semi-structured interview (DSM-IV criteria), and K-SADS-PL WASH-U-K-SADS and K-SADS-PL	FES	*Parent-report* BD compared to Normative: > CON, CTL, ICO; < AO, C, IND, ORG; n.s. ARO, EX, MRE *Child-report: n/a*	BD: 54% axis I; 14% BD I, II, or cyclothymia Normative: not measured	FES scores n.s. related to offspring dx (Axis I or BD) within-BD-parent group
Doucette et al., 2013	BD (221) Control (no psych) (63)	Cross-sectional (from longitudinal study)	7-20 at study entry Mean age for IPPA: BD offspring 21.6;	*Parents:* SADS-L *Offspring:* K-SADS-L	IPPA	*Child report* BD compared to Control: n.s., IPPA-mother, n.s. IPPA-father	BD: 41.2% mood disorder; 13.1% BD Control: 3.2% mood disorder;	Among BD offspring: IPPA n.s. associated with offspring psychopathology (any dx);

			Control 16.5			*Parent-report: n/a*	1.6% BD	IPPA-mother score positively associated with offspring mood disorder.
Du Rocher Schudlich et al., 2008	BD 76 (76) Unipolar 91 (91) Neither BD nor unipolar (no mood dx) 105 (105)	Cross-sectional	5-17 (11.57)	*Parents:* SADS-LB (primary caregiver), SADS-LB, FH-RDC (other parent) *Offspring:* K-SADS-PL or KSADS-E	FAD and CBQ	*Parent report* *FAD*: BD compared to Unipolar: n.s. all subscales; BD compared to no mood dx: > (i.e., worse) total score, general functioning, problem solving scales, n.s. communication	*BD in offspring* BD: 84% Unipolar: 54% No mood dx: 35%	Offspring with BD compared to no Axis I: > conflict (CBQ); n.s. family functioning (FAD total score, all subscales)

						CBQ: n.s. across groups *Child-report: n/a*		
Ellenbogen & Hodgins, 2009	BD 26 (28) No current psych hx, no lifetime mood dx 22 (26)	Longitudinal (8 yrs)	Time 1: 6-13 (9.1); Time 2: 13-21 (16.5)	*Parents:* SCID-I, medical records *Offspring:* DISC or SCID-I	PDI, when offspring were 6-13 yrs	*Parent report* BD compared to No psych hx: < Control (discipline strategies, maturity demands on children); n.s. Supportiveness (nurturance, responsiveness,	BD: 65.7% any lifetime dx, 32.8% mood dx Controls: 41.2% any lifetime dx, 11.8% mood dx (Nijjar et al., 2014)	Not reported by diagnosis.

						non-restrictiveness), Structure (organization, consistency, involvement) *Child-report: n/a*		
Ferreira et al., 2013	BD 47 (47) Control (No Axis I) 30 (30)	Cross-sectional	6-17 (BD 12, control 13)	*Parents:* SCID-I *Offspring:* K-SADS-PL	FES (validated to Portugese)	*Parent report* BD compared to Control: > CON, CTL; < ARO, C, ICO, MRE, ORG; n.s. AO, EX, IND *Child-report: n/a*	BD: 47% axis I; 12.8% BD, 10.6% unipolar Control: 0% (selected during recruitment to be free of DSM-IV diagnoses)	BD families with affected compared to unaffected offspring and Control offspring: > CON, CTL; < ARO, C, ICO; n.s. AO, EX, IND. Within BD families, those with affected offspring compared

						to unaffected offspring: > CTL, <C, n.s. all other subscales.		
Park et al., 2015	BD 64 (64; 22 complete FACES data analyzed) Healthy controls (HC) 51 (51; 28 complete FACES data analyzed)	Cross-sectional	9-18 (BD 13.73, HC 13.68)	*Parents:* SCID-I *Offspring:* WASH-U-K-SADS, K-SADS-PL	FACES-IV	*Parent report* BD compared to HC: < cohesion, family satisfaction, family communication; > enmeshment, chaos; n.s. rigidity, disengagement, balanced flexibility.	BD (% of n=64): 55% BD-NOS, MDD, or Dysthymia HC: 0% (selected during recruitment to be free of DSM-IV diagnoses)	Not reported by diagnosis.

						Child-report: n/a			
Petti et al., 2004	BD (23) Unaffected within-pedigree control group (27)	Cross-sectional	6-17 (males 12.1, females 10.2)	*Parents:* DIGS *Offspring:* DICA-R	HEIC	*Parent report and child report* BD compared to Unaffected: n.s. closeness of siblings, financial difficulties, closeness to relatives outside the nuclear family, discipline.	BD: 39% mood disorder Unaffected: 11% mood disorder *Mood disorders include bipolar I or II, major depressive episode, and dysthymia.*	Parent-reported discipline higher in families with bipolar-affected versus unaffected offspring.

Romero et al. 2005	BD 24 (24) 'Healthy' (No Axis I)27 (27) Normative 1432	Cross-sectional	8-12 (not reported)	*Parents:* SCID-P *Offspring:* WASH-U K-SADS	FES	*Parent-report* BD compared to Healthy: < C, EX; n.s. AO, ARO, CON. CTL, ICO, IND, MRE, ORG. BD compared to Normative: > CON, CTL, ICO, MRE; < C, IND; n.s. AO, ARO, EX, ORG. *Child-report: n/a*	BD: 71% mood disorder: 38% BD, 13% unipolar, 13% cyclothymia, 8% dysthymic disorder. Healthy: 3.7% (N=1) mood disorder (dysthymia)	BD families with vs w/o offspring with BD: n.s. all FES subscales

Tarullo et al. 1994	BD 22 (35) Unipolar 31 (58) 'Well' (No psych hx) 30 (54)	Cross-sectional (Time 3 from longitudinal study)	82 preadolescent children 8-11 (9.28), 65 adolescent children 12-16 (13.43)	*Parents:* SCID at Time 3 (SADS-L at Time 1) *Offspring:* DICA-R	Direct behavioral observation, Coding of behaviors factor analyzed	*Preadolescents:* Well *mothers* > engaged than BD mothers. Maternal critical/ irritable behavior n.s. *Children* of well and BD mothers > comfortable/ happy than children of unipolar. Child engagement, critical/ irritable n.s. *Adolescents:*	BD: 63% psychiatric disorder(s) in past year (59% preadolescents, 69% adolescents) Unipolar: 72% psychiatric disorder(s) in past year (71% preadolescents, 74% adolescents) Well: 46% psychiatric disorder(s) in past year (45%	*Preadolescents* : Children with and without past-year problem: mothers > critical/ irritable; children < engaged, > critical / irritable. *Adolescents*: BD mothers with children with No Problem < engaged than unipolar mothers of children with or without problems and well mothers of children with no problems.

Maternal engagement, critical/ irritable n.s. *Child* engagement, critical/ irritable, comfort/ happiness n.s.	preadolescents, 48% adolescents) Normative: Prevalence of psychiatric disorders not available for sample	Children with No Problems < comfortable/ happy with BD mothers than with unipolar or well mothers.

Vance et al., 2008	BD 20 (23) 'Control' 20 (24)	Cross-sectional	12-20 (not reported)	*Parents:* SCID-I *Offspring:* SADS-L	PACE and FRI	PACE: BD compared to Control: *Parent report* > negative consequences as result of hypothetical negative interpersonal events happening to their children; n.s.: *child report* FRI: BD compared to Control: *Parent report*: < expressiveness,	BD: 26% mood disorder 'Control': 4% mood disorder	Not reported by diagnosis.

						n.s. cohesion, conflict; n.s.: *child report*		
Weintraub, 1987	BD 58 (134) Schizophrenia 31 (80) Unipolar 70 (154) No psych hx 60 (176)	Longitudinal (~11 yrs)	Phase I: 7-15 (not reported); phase II follow-up 3 yrs later	*Parents:* CAPPS, hospital records, spouse's ratings of patient's psychiatric and social functioning *Offspring:*	FEF, MAT, CRPBI, Environmental Q-Sort, and Minnesota-Briggs History Scale revised	*Parent report* BD compared to schizophrenia and unipolar depression: n.s. marital discord (MAT), family function (FEF); *Child report* BD comparison not reported on	BD: 20% any DSM-III dx (of that, 47.6% mood) Schizophrenia: 22.8% any DSM-III dx Unipolar 15.2% any DSM-III dx No psych hx: 9.6% any DSM-III dx	Not reported by diagnosis.

	SADS or SCID	Environmental Q-Sort; CRPBI and MB-History Record results not explicitly presented.	*DSM-III diagnoses include any schizophrenic, mood, personality, adjustment-anxiety, or substance use disorders.*

Note: CAS=Child Assessment Schedule; CAPPS=Current and Past Psychopathology Scales; CRPBI=Children's Report of Parental Behavior Inventory; DIGS=Diagnostic Interview for Genetics Studies; DISC=Diagnostic Interview Schedule for Children; DSM=Diagnostic and Statistical Manual of Mental Disorders; Dx=diagnosis; FACES-IV=Family Adaptability and Cohesion Evaluation Scales, version IV; FAD=Family Assessment Device; FEF=Family Evaluation Form; FES=Family Environment Scale (subscales: AO= achievement orientation; ARO=active-recreational orientation; C=cohesion; CON=conflict; CTL=control; EX=expressiveness; ICO=intellectual-cultural orientation; IND=independence; MRE=moral religious emphasis; ORG=organization); FH-RDC=Family History Research Diagnostic Criteria; FRI=Family relationships inventory; HEIC=Home Environment Interview for Children; IPPA=Inventory of Parent and Peer Attachment; K-SADS= Schedule for Affective Disorders and Schizophrenia for School-Age Children; K-SADS-E=K-SADS-Epidemiological Version; K-SADS-PL=K-SADS-Present and Lifetime Version; WASH-U-K-SADS=Washington University in St Louis Kiddie Schedule for Affective Disorder and Schizophrenia; MAT=Marital Adjustment Test; MMPI=Minnesota Multiphasic Personality Inventory n.s.=not significant; PACE=Parental Attributions for Children's Events questionnaire; PDI=Parenting Dimension Inventory; PIRS=Peer Interaction Rating System; PPI=Parent Perception Inventory; SADS=Schedule for Affective

Disorders and Schizophrenia; SADS-L=SADS-Lifetime Version; SADS-LB=SADS-Lifetime Version, Bipolar; SCID=Structured Clinical Interview for DSM-III; SCID-I=Structured Clinical Interview for DSM-IV; SCID-P=SCID-Patient Edition; US=United States

Table 2.2. Assessment of risk of bias in analytic set using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS)

Author, Year	Selection of Participants	Confounding Variables	Measurement of Exposure	Blinding of Outcome Assessments	Incomplete Outcome Data	Selective Outcome Reporting
Burge & Hammen, 1991	Unclear	Low	Low	Low	Unclear	Low
Chang et al., 2001	High	Low	High	Unclear	Low	Low
Doucette et al., 2013	Unclear	Low	High	Unclear	Unclear	Low
Du Rocher Schudlich et al., 2008	Low	Low	High	Low	Low	Low
Ellenbogen & Hodgins, 2009	Low	Low	High	Unclear	Low	Low
Ferreira et al., 2013	Unclear	Low	High	Unclear	Low	Low
Park et al., 2015	Unclear	Low	High	Unclear	High	Unclear
Petti et al., 2004	Low	Low	Unclear	Low	Low	Low
Romero et al., 2005	Low	Low	High	Low	Low	Low
Tarullo et al., 1994	Low	Low	Unclear	Low	Unclear	Low
Vance et al., 2008	Unclear	Low	High	Unclear	Low	Unclear
Weintraub, 1987	Low	Low	Unclear	Unclear	Unclear	Unclear

Note: Low, Unclear, and High connote the risk of bias in that particular domain

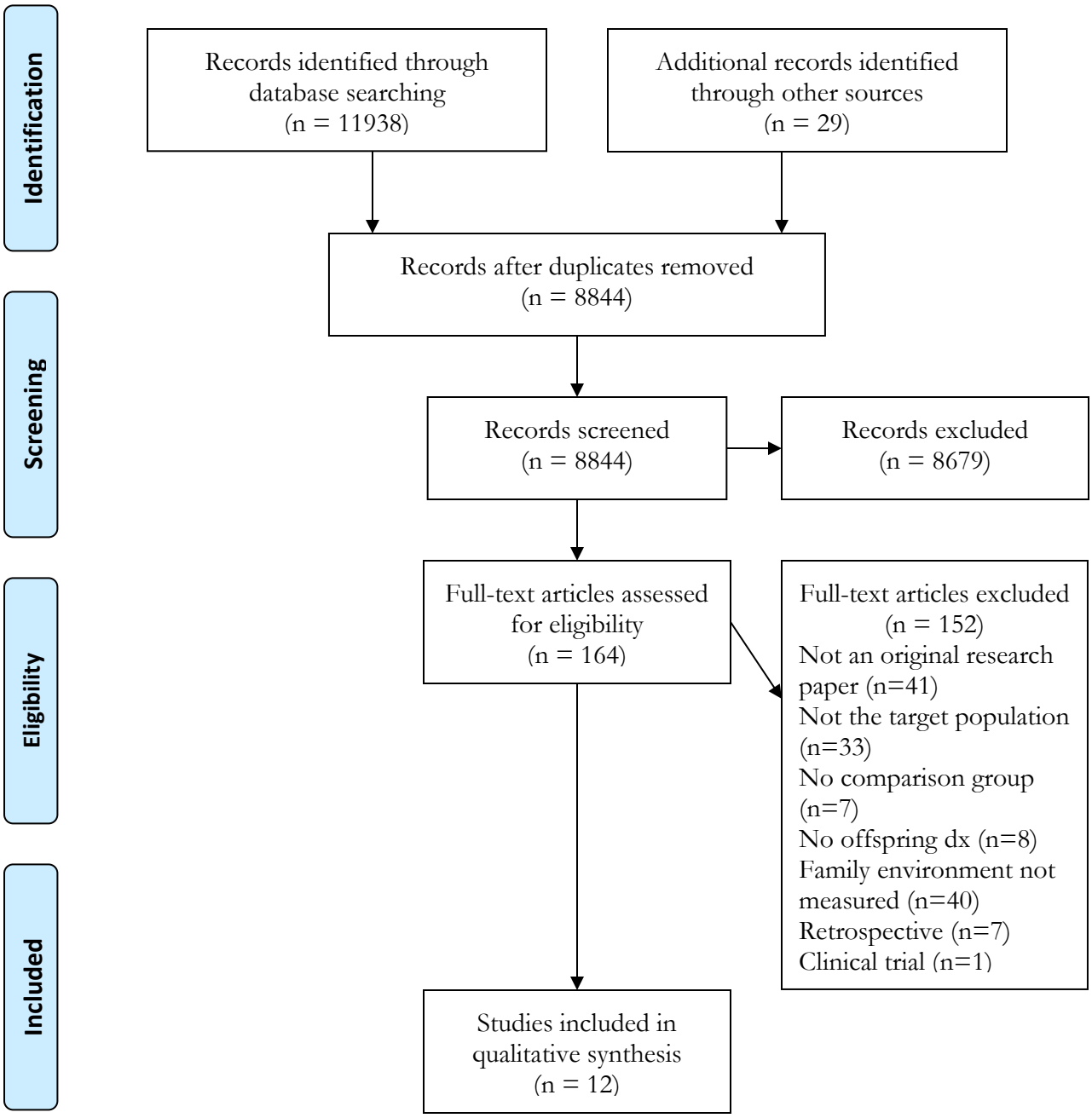
Table 2.3. Prevalence ratios of offspring psychiatric disorders by parent diagnostic group

		Offspring Psychiatric Diagnosis		
		Any Psychiatric Disorder	**Mood Disorder**	**Bipolar Disorder**
		Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI)
Parent Psychiatric Diagnosis	BD *versus* **No Psychiatric Disorder**	1.36 (0.92, 1.99); Tarullo et al., 1994 **1.59** (1.14, 2.22); Nijar et al., 2014 **2.08** (1.08, 4.03); Weintraub, 1987 **2.29** (1.32, 3.96); Hammen et al., 1990	**2.79** (1.34, 5.82); Nijar et al., 2014 6.26 (0.82, 48.07); Vance et al., 2008 **13.26** (3.36, 52.30); Doucette et al., 2013 **19.13** (2.75, 133.14); Romero et al., 2005	**8.27** (1.15, 59.50); Doucette et al., 2013
	BD *versus* **No BD**		**3.52** (1.08, 11.49); Petti et al., 2004	**1.92** (1.59, 2.31); Du Rocher Schudlich et al., 2008
	BD *versus* **Unipolar Depression**	0.88 (0.62, 1.25); Hammen et al., 1990 0.87 (0.64, 1.17); Tarullo et al., 1994 1.32 (0.76, 2.30); Weintraub, 1987		

BD *versus*	0.88 (0.50, 1.55); Weintraub, 1987
Schizophrenia	
BD *versus*	1.69 (0.86, 3.29); Hammen et al., 1990
Chronic	
Medical Illness	

Notes: BD, Bipolar Disorder; CI, Confidence Interval. Prevalence ratios in **bold** are significant at $p<0.05$ (95% CIs do not include 1).

Figure 2.1. PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Chapter 3: Patterns and predictors of offspring-perceived family environment among adolescents at high and low familial risk for bipolar disorder (Aim 2)

ABSTRACT

Children's perceptions of their family environment (FE) has been linked to their developmental outcomes. In the bipolar (BD) high-risk context, prospectively assessing the FE may provide insight into transmission of mood disorders in offspring, and highlight opportunities for intervention. We developed a person-centered model of FE based on offspring reports on the Conflict Behavior Questionnaire, Family Adaptability and Cohesion Evaluation Scales, and Home Environment Interview for Children. In a sample of 441 youth aged 12-22 years from the US and Australia (266 offspring of a parent with BD, 175 offspring of a parent with no psychiatric history), we found three pattern-classes of FE. Approximately two-thirds of the offspring perceived a well-functioning FE, characterized by nurturance, flexibility, and low conflict. The other groups of offspring, by comparison, perceived their families to be high conflict, low in warmth and cohesion, and low flexibility. Membership in the class with very high conflict and rigidity in the mother-child relationship was associated with parental BD when adjusted for demographic characteristics (OR 2.6, p=0.028), but not after adjusting for offspring BD. When adjusting for both parental BD and offspring BD, female (OR 2.6, p=0.012) and non-White (OR 3.5, p=0.023) offspring were associated with membership in the High Conflict with Mother class. Membership in the High Conflict with Father class was associated with offspring diagnosis of BD in unadjusted models only. There did not appear to be one homogenous 'signature' of the BD high-risk family environment. Parents and children presenting for research or clinical care related to mood disorders should have their family functioning assessed, with attention paid

to children's reports.

Key Words: high-risk, family environment, mood disorders, latent class analysis

Bipolar disorder (BD) is a persistent, severe, and impairing mood disorder that is associated with excess morbidity and mortality compared to the general population (Kessler, Merikangas, & Wang, 2007). Although the exact causes and mechanisms are unknown, both genetics and the environment are implicated in the development of BD, with offspring of parents with BD experiencing an 8–10-fold increased risk of developing BD (Cradock & Sklar, 2013) and increased risk of developing any mood disorder, and psychiatric disorders generally (DelBello & Geller, 2001; Rasic, Hajek, Alda, & Uher, 2014; Tsuang & Faraone, 1990). In a nationally representative sample, approximately 10% of BD cases report onset before age 13 and one-third before age 18 (Merikangas et al., 2007), with higher prevalence of early onset reported in clinical samples (Birmaher et al., 2009; Danner et al., 2009; Perlis et al., 2004). Index episodes are frequently depressive (Perlis et al., 2004), and onset in childhood or adolescence is associated with worse prognosis and significantly more clinical correlates compared to adult-onset BD (Holtzman et al., 2015; Perlis et al., 2004).

Bipolar disorder is also associated with role impairment (American Psychiatric Association [APA], 2000; Kessler et al., 2007). Role impairment may include difficulties in parenting, and associated challenges to the warmth and structure of the family environment. One less studied area is children's perceptions of their family environment in families with at least one parent with BD. The BD-high-risk literature has relied more on parent reports, but it is important to obtain children's reports, asthey may offer unique insights. Children's perspectives—their *experience* of what could be deemed an objective 'family environment', and how perception of their experienced family environment 'gets under the skin'—may be linked to their outcomes and wellbeing. The purpose of the present study was to take an offspring-centered approach to modeling the family environment, and test predictors of the environment.

Family environment has a central role in children's development. What constitutes 'family environment' ranges across theories and individual research studies, with different components of family dynamics assuming key positions. A positive family environment provides for children's emotional security, physical safety and wellbeing, and social integration, and facilitates children's self-regulation and independence (Bowlby, 1951; Repetti et al., 2002). In particular, caregiving behavior—including nurturance and acceptance, as well as structure and control—affects offspring physical and psychological development, and is the foundation for socialization (Basic Behavioral Science Task Force of the National Advisory Mental Health Council [NAMHC], 1996). Families characterized by conflict and aggression, and cold, unsupportive, neglectful relationships are considered especially risky to child development (Repetti et al., 2002). These characteristics may create or interact with preexisting vulnerabilities in offspring to confer risk for problems in emotional regulation, cognitive development, psychosocial functioning, and biological health (Johnson et al., 2013; Repetti et al., 2002).

A key source of knowledge on BD has been high-risk studies, which focus on subgroups with increased risk for a disorder (e.g., due to family history); these studies provide the opportunity to chart the emergence and trajectory of disorders. Psychosocial factors such as exposure to stressful life events, childhood maltreatment, and maladaptive parenting have been identified as possible risk factors for onset of mood episodes (Alloy et al., 2005, 2006; Miklowitz & Johnson, 2009); however, much of this work has been based on retrospective accounts of life experience among individuals with diagnosed illness. Evidence from prospective high-risk studies examining the environment in families with at least one parent with BD has centered on measures of nurturance; communication; and family system maintenance, including components such as organization, discipline, control, and flexibility.

Findings in these domains are contradictory, depending on the informant (parent or child) and comparison group (e.g., parents with no psychiatric disorder, parents with depression).

Offspring of BD parents often report no differences in cohesion, communication, and related domains in their families compared to controls. Based on behavioral observations of mothers and each of their two children in the NIMH Childrearing Study, Tarullo and colleagues (1994) found that preadolescent and adolescent engagement, critical/irritable behavior, and comfort/happiness were not significantly different between offspring of mothers with BD and offspring of well mothers. In a slightly older sample (ages 12–20 years), Vance and colleagues (2008) found that children's reports on parental inferential attribution/communication style and family relationships (cohesion, expressiveness, and conflict) were not significantly different between offspring of BD parents and offspring of parents without psychiatric disorders. Doucette and colleagues (2013) studied self-reported attachment—including degree of mutual trust, quality of communication, and extent of anger and alienation— among adolescent and emerging adult offspring of a parent with BD compared to offspring of parents without any psychiatric history. They found no significant differences on attachment with father or mother, although the high-risk offspring had significantly greater prevalence of psychiatric disorders compared to controls.

Although there is a trend in the literature toward lower parent-reported cohesion among BD parents compared to parents without psychiatric disorders (Ferreira et al. 2013, Park et al. 2015, Romero et al. 2005) and population controls (Chang et al., 2001), some studies show no significant differences in parent-reported cohesion and supportiveness between parents with BD or no psychiatric disorders (Ellenbogen & Hodgins, 2009; Vance et al., 2008). Findings on parent communication are mixed, with several showing no

significant differences in conflict and observed critical behavior between parents with BD and those with other psychiatric disorders (Du Rocher Schudlich et al., 2008; Tarullo et al., 1994; Weintraub, 1987) or no psychiatric disorders (Romero et al., 2005; Vance et al., 2008). Other studies show lower parent-reported expressiveness and communication (Park et al., 2015; Vance et al., 2008) and higher conflict and negative inferential style (Ferreira et al., 2013; Vance et al., 2008) comparing parents with BD versus no psychiatric disorders.

Several studies show that BD families are not significantly different from others in family system maintenance, including flexibility (Park et al., 2015), organization (Romero et al. 2005), general family functioning (Du Rocher Schudlich et al., 2008; Weintraub, 1987), and discipline (Petti et al., 2004). Other studies note that BD parents report lower control and structure (Ellenbogen & Hodgins 2009; Romero et al. 2005), or higher control yet lower organization (Chang et al. 2001; Ferreira et al. 2013) than parents without psychiatric history or normative controls.

Parent reports are ascertained much more frequently than child reports. Petti and colleagues (2004) found that scores on discipline, assessed via the Home Environment Interview for Children, were not significantly different between families with and without a parent with BD, based on both parent- and child-report, although parents reported higher discipline in families in which the offspring were diagnosed with BD. In sum, while these findings underscore the importance of measuring multiple constructs of family environment, there is a lack of consensus regarding an essential 'signature' of the BD-high-risk family, and suggest a need for a different approach.

There are several key reasons to obtain children's reports on their behavior and environment. Parents' reports may be influenced by their psychiatric symptoms and life history, leading to over-endorsement of problems or disagreement between informants

(Chilcoat & Breslau, 1997; Ringoot et al., 2015; Taber, 2010; Weissman et al., 1980). As shown in the BD high-risk literature, children's reports on the family environment are relatively understudied compared to parent reports, and at times offer a conflicting view from the parent reports. Yet, children as young as 4 years of age can describe the mood and behavior of their parents with BD, with children 7 years of age and older having additional insight into how parents' symptoms have affected them (Backer et al., 2016). Caregiver warmth and discipline influence children's perceptions of caregiver behavior, and those perceptions, in turn, influence the impact of caregiving (Basic Behavioral Science Task Force of the NAMHC, 1996), including psychological wellbeing. Children's perceptions of the family climate are related to but not necessarily direct reflections of their lived experiences in the family, and are largely influenced by the quality of the parent-child relationships, which may provide security for them and buffer them from stress (Grych & Fincham, 1990). For these reasons, the present study focuses on children's perceptions of the family environment.

Due to the heterogeneity of findings on family environment in the BD high-risk literature, a relative neglect of children's perspectives in these contexts, and the importance of addressing the multifaceted nature of family environment, we aimed to take a person-centered approach to modeling child-perceived family environment among a sample of adolescent and emerging adult offspring at high or low familial risk for bipolar disorder. We hypothesized that children's reports on three measures encompassing different constructs related to family environment reflect unobserved subpopulations of families, and provide a unique, sometimes overlooked, perspective (see **Figure 3.1** for conceptual framework). Specifically, our objectives were: 1) to identify latent pattern-classes of child-perceived family environment; and 2) test for predictors of membership in the pattern-classes of family

environment, including demographic and clinical characteristics.

Method

Participants and Procedures

The study sample consists of 441 participants aged 12–21 years at the time of their recruitment into a prospective study of adolescents at high or low familial risk for BD. The primary study took place from 2006–2013 at urban academic medical centers in the United States (US) and Australia. Institutional Review Boards and the Human Research Ethics Committee at the sites approved the study. Informed consent (or assent with parent consent for participants under age 18) was obtained from all participants. Additional details about study procedures are described elsewhere, by Nurnberger and colleagues (2011) and Perich and colleagues (2015).

Offspring at high-risk for familial BD ("high-risk [HR] offspring") were identified from probands with bipolar I disorder (BD-I), bipolar II disorder (BD-II), or schizoaffective disorder bipolar type (SAB) in the NIMH Genetics Initiative bipolar sample and other genetics studies, specialty clinics, and publicity. Control participants were recruited from general practitioners, motor vehicle records, and advertising. Individuals with a parent or sibling with BD-I, BD-II, recurrent Major Depressive Disorder, schizoaffective disorder, schizophrenia, recurrent substance abuse, or any psychiatric hospitalizations, or whose parent had a first-degree relative with a history of psychosis or hospitalization for a mood disorder, were excluded from the control group. Parent psychiatric diagnoses, or lack thereof, were confirmed using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). Although the primary study also included siblings and second-degree relatives of BD probands, the current analysis focuses specifically on *offspring* of parents with BD versus

offspring of parents with no psychiatric history. In some families, multiple offspring in the target age range participated.

Family Environment Measurement Model

We included three measures of family environment, as depicted in **Figure 3.1**.

Family Adaptability and Cohesion Evaluation Scales (FACES II). The FACES II is a 30-item self-report questionnaire designed for research that measures perceptions of family cohesion and adaptability. Sample items include, "*Each family member has input regarding major family decisions*" and "*Family members are supportive of each other during difficult times*," with a 5-point likert-type scale for responses ranging from "Almost Never" to "Almost Always." Higher scores represent healthy family functioning—FACES II does not tap into enmeshed (too high cohesion) or chaotic (too high adaptability) extremes of these dimensions (Kouneski, 2000). Cohesion has been defined as "the degree to which family members are helpful and supportive of each other" (Holahan & Moos, 1983, p.158) as well as family emotional bonding, closeness, and time together (Kouneski, 2000). Adaptability refers to flexibility of the family.

The FACES II has internal consistency of 0.87 for cohesion and 0.78 for adaptability, and test-retest reliability above 0.80 (Olson, Bell, & Portner, 1982). It also has good discrimination between clinical and nonclinical families; however, it is influenced by social desirability bias, and the two dimensions it measures (cohesion and adaptability) are correlated (r=0.65) (Kouneski, 2000). The FACES has been used to validate other measures including the Family Environment Scale and Family Assessment Device (Bloom, 1985). Parents and offspring in the Bipolar High-Risk Study completed the FACES II; we used child-reported family adaptability and cohesion subscales in the present study.

Conflict Behavior Questionnaire (CBQ). The CBQ is a 20-item true-false self-report questionnaire that measures perceived "communication-conflict behavior at home" (Robin & Foster, 1989, p. 78). It captures dissatisfaction with the other family member's behavior and conflicted interactions between family members, based on the assumption that family conflict is characterized by disapproval and complaints related to the behavior of others (Prinz, Foster, Kent, & O'Leary, 1979). Sample items include, "*My father screams a lot*" and "*When I state my own opinion, my mother gets upset.*" Parents in the Bipolar High-Risk Study reported on conflict with each participating child, and each child reported separately on conflict with their mother and father. We used child reports on mothers and fathers.

The full-length CBQ's internal consistency (coefficient / Cronbach's alpha) is high for adolescent offspring appraisal of mother (0.95) and the dyad (0.94), and for maternal appraisal of the adolescent offspring (0.88) and the dyad (0.90). On the original CBQ sample, CBQ scores had higher discriminant validity than observational data on the sample (Prinz et al. 1979). Scores on the CBQ-20, which is the version employed in this study, correlate 0.96 with the parent and child's scores on the long form, using items that best discriminated between distressed and non-distressed families in a sample including both mothers and fathers (Robin & Foster, 1989). Scores range from 0 to 20, with higher scores indicating higher conflict. Normative mean (standard deviation) scores for adolescents reporting on mothers are 8.4 (6.0) in distressed families and 2.0 (3.1) in nondistressed families, and for adolescents reporting on fathers they are 7.6 (5.4) for distressed families and 1.6 (1.6) for nondistressed families (Robin & Foster, 1989, p. 304). The normative scores were based on predominantly middle-class White families, but were comparable in a mostly female, Black sample of older adolescents (Robin & Foster, 1989).

Home Environment Interview for Children (HEIC). The HEIC is a semi-structured interview regarding the child's home and social environment, including relationships with parents and peers, home conflicts and stress, and dysfunctional behaviors, designed to complement diagnostic interviews for children (Reich & Earls, 1987; Reich, Earls, & Powell, 1988). Sample question stems ask, *"Do you feel very close to your [Mother/Father]?"* and "*Do you get into trouble with your [Mother/Father] more than, about the same as, or less than most kids?*". Mother-child agreement and test-retest reliability have been reported to be good, although exact psychometric properties are unpublished (data cited in Reich et al., 1988).

Because there were no established methods on interpreting or quantifying the HEIC, we conducted exploratory factor analysis on question stems of substantive importance to parent-child relationships (Appendix B). Due to inadequate solutions of the factor models using Father-focused questions, we focused on child responses regarding Mothers. We identified a best-fitting two-factor model based on 16 factor indicators. We extracted factor scores from that analysis for use in the measurement model described here. The two factors pertain to offspring-perceived maternal warm engagement and offspring-perceived maternal permissiveness.

Predictors

We tested BD high-risk group status (i.e., parental BD versus no parental psychiatric history) as a predictor of membership in family environment classes, adjusted for demographic characteristics including offspring age at interview, sex, race, and country of residence. We tested a further model adjusting those effects based on inclusion of offspring diagnosis of BD. Extensively trained clinicians interviewed offspring and parents separately using the *Schedule for Affective Disorders and Schizophrenia for School-Aged Children, bipolar disorder*

version (K-SADS; for details, see Nurnberger et al., 2011). Offspring lifetime DSM-IV psychiatric disorders were confirmed by best estimate consensus of two clinicians using direct interviews of offspring and parents and medical history records. A dichotomous variable for lifetime diagnosis of broad phenotype BD using all available information included the following diagnoses: BD-I, SAB, BD-II with recurrent depression, and BD not otherwise specified (BD-NOS).

Offspring age at interview, sex (binary Male or Female), and race (binary White or non-White) were each extracted from the K-SADS. Country of residence (Australian compared to US) was based on the study site location of the participants. As a proxy for family socioeconomic status (SES), we attempted to include highest number of years of education attained by either parent (using the parent with the highest number). This information was available for 120 of the 441 offspring, which prevented latent class regressions from running. Parent education was not significantly different between HR and control offspring (data not shown). Additionally, a previous analysis from this study (Nurnberger et al., 2011) examined occupation of the head of the household as a proxy for SES and did not find a significant difference between HR and control groups. Therefore, we did not include parental education.

Statistical Analysis

We used complex mixture modeling in Mplus version 7.4 (Muthén & Muthén, 1998-2012) to identify a person-centered model of child-perceived family environment and their correlates. Sample statistics were calculated using Stata Version 14 (StataCorp, 2015), based on unadjusted chi-square tests and univariate regressions.

Latent Class Analysis

Latent class analysis (LCA) is a special case of mixture modeling that is useful for

measuring patterns (e.g., types of family environment) using data from multiple observed variables called class indicators (e.g., scores on the CBQ, FACES II, and HEIC). The *classes* represent distinct subpopulations of people, and they are called *latent* because class membership is not known, but rather, it is inferred from the data using the class indicators (Muthén & Muthén, 1998-2012). The LCA classifies individuals, with the latent classes explaining the relation, or covariance, among class indicator variables (Muthén & Muthén, 1998-2012), and accounts for measurement error in constructs that are difficult to measure, such as family environment. Specifically, we performed latent profile analysis (LPA), which is another name for LCA with continuous, rather than categorical, class indicators. We accounted for clustering of siblings within families, which corrected standard errors and the chi-square test of model fit (Muthén & Muthén, 1998-2012).

Our sample size is adequate for both identifiability and estimability of the model. Regarding identifiability, we found that the parameters have unique interpretations by checking that the number of parameters is less than or equal to the number of pieces of data, using the equation (J*M)+(J-1)</= 2^M -1, where *J* represents the number of classes and *M* represents the number of indicators. Regarding estimability, we had enough data to estimate the parameters using a ratio of approximately 10-20 observations per parameter (Kline, 2005), regardless of whether we consider individuals (N=441) or family clusters (N=292) as the observations for 23 parameters.

Mplus makes use of all available data to estimate models using full information maximum likelihood (Schafer & Graham, 2002). On the HEIC, 79% of the sample had no missing responses, 20% of the sample was missing 1 to 3 responses, and 1% of the sample had greater than 5 responses missing. Data were complete on the FACES II for 88.4% of the sample, on the CBQ-mother for 85.7% of the sample, and on the CBQ-father for 81.9%

of the sample. We had 6 class indicators: family adaptability and family cohesion from the FACES; conflict with Mother and conflict with Father from the CBQ; and factor scores on offspring-perceived maternal warm engagement and permissiveness from the HEIC. To determine the number of classes, we examined goodness-of-fit indices including the Bayesian information criterion (BIC), entropy, Vuong-Lo-Mendell-Rubin likelihood ratio test, and Lo-Mendell-Rubin adjusted likelihood ratio test (LMR).

Latent Class Regression with Covariates

To identify predictors of membership in latent family environment classes, we tested the association of observed covariates (parental BD, offspring BD, and demographic characteristics) in the structural model with the categorical latent classes in the measurement model. This approach involved a series of regressions—linear for continuous observed variables (age) and logistic for binary categorical observed variables (high-risk group status, sex, race, country of residence) (Muthén & Muthén, 1998-2012). There were no missing data on high-risk group status (i.e., offspring of BD parents versus controls), age, sex, self-reported race, or country of residence. Best estimate consensus diagnoses were available for 91% of the offspring. Maximum likelihood estimation was used.

Results

Sample Characteristics

The study sample consisted of 441 participants, with 266 offspring of a parent with BD (HR) and 175 offspring of parents without psychiatric disorder (controls). Participants ranged in age from 12 to 22 years old at time of assessment, with a mean age of 16.7 years. Slightly over half of the sample was male (51.5%), and the majority of the sample (89.1%) self-reported White race. High-risk and control offspring did not differ significantly on age, sex, race, or country of residence. High-risk offspring were significantly more likely to be

diagnosed with BD than were control offspring ($p<0.001$): 34 HR and 1 control. Sample demographic characteristics are detailed in **Table 3.1**.

Pattern-Classes of Family Environment

For our first aim, we modeled patterns of offspring-perceived family environment. We compared goodness-of-fit indices for 1- through 5-class models (see **Table 3.2**), and found that a three-class model best fitted the data based on the BIC (see **Supplemental Figure 3.1**) and LMR (Nylund, Asparouhov, & Muthén, 2007). These classes represent 3 patterns of family environment, as perceived and reported by the offspring participants on the 6 class indicators. The three family environment pattern-classes are displayed using standardized scores (z-scores) in **Figure 3.2**. **Supplemental Table 3.1** contains raw mean scores and 95% confidence intervals for the 6 class indicators across each of the 3 classes.

Compared to two smaller classes, the largest class of youth (67.7% of sample) perceived their families to be higher on family cohesion, family adaptability, maternal warm engagement, and permissiveness; and, lower on conflict with father and conflict with mother. This larger class, which we labeled the 'reference class' or 'well-functioning' family environment, experienced their families as essentially nurturing, flexible, and low-conflict. The two smaller classes, in contrast, are characterized by low cohesion and adaptability and high conflict. We refer to the medium-sized class as the 'High Conflict with Father' class (20.8% of sample), and the smallest class as the 'High Conflict with Mother' class (11.5% of sample). Key differences on the class indicators are discussed below.

On the FACES II, the High Conflict with Father class and High Conflict with Mother class were not significantly different on cohesion and adaptability subscales, but were both significantly lower than the reference class. The two high-conflict classes did not significantly differ on mean CBQ-father scores, but the High Conflict with Father class

reported roughly 3 times higher conflict with their father than the reference class. The High Conflict with Mother class reported conflict with their mothers that was, on average, over 4 times higher than the High Conflict with Father class, and almost 8 times higher than the reference class, with significant differences in mean scores and associated 95% confidence intervals. The three classes were all significantly different from each other in levels of offspring-perceived maternal warm engagement derived from the HEIC, as well. The well-functioning class reported higher-than-average warm engagement, the High Conflict with Father class reported lower-than-average warm engagement, and the High Conflict with Mother class reported much lower-than-average warm engagement (a full standard deviation lower than the High Conflict with Father class). While the High Conflict with Father class and well-functioning reference class were not significantly different on offspring-perceived maternal permissiveness, youth in the High Conflict with Mother class reported significantly lower maternal permissiveness, indicating rigidity in the maternal-child relationship. A key distinguishing element in the classes is the quality of the relationship with the mother—levels of conflict (high) and warmth (low), also reflected in low permissiveness.

Predictors of Membership in Family Environment Pattern-Classes

Results of our second aim testing demographic characteristics (age, sex, race, and country of residence), parental BD, and offspring BD as potential predictors of membership in offspring-perceived pattern-classes of family environment are shown in **Table 3.3**. In unadjusted models, offspring BD was associated with membership in the High Conflict with Father class (OR 3.6, p=0.028), but the association did not remain after adjusting for demographic characteristics and parental BD. Membership in the High Conflict with Father class compared to the reference class was not associated with any clinical or demographic predictors in adjusted models. While parental BD was associated with membership in the

High Conflict with Mother class adjusted for demographic characteristic (OR=2.6, p=0.028; Adjusted Model 1), it was no longer significantly associated with class membership after adjusting for offspring BD (see Adjusted Model 2). In a model fully adjusted for both parental BD and offspring BD, only demographic characteristics predicted class membership (Adjusted Model 2). Females (daughters) were 2.6 times more likely to be in the High Conflict with Mother class than the well-functioning class (p=0.012), and offspring who identified as being non-White race were 3.5 times more likely to be in the High Conflict with Mother class than the well-functioning reference class (p=0.023).

Discussion

In a sample of 441 offspring of a parent with BD or parents with no psychiatric history, we found three patterns of child-perceived family environment. Specifically, we found one large class with essentially 'well-functioning' family environment, characterized by nurturance, flexibility, and low conflict, and two smaller classes characterized by high conflict and low warmth and cohesion, with substantial separation based on either high conflict with the father or very high conflict and rigidity with the mother. Membership in the High Conflict with Mother class versus reference was associated with parental BD initially, but not after adjusting for offspring BD. Only female sex and non-White race of offspring were significantly associated with membership in the High Conflict with Mother class when adjusting for both parental and offspring BD. Membership in the High Conflict with Father class was associated with offspring diagnosis of BD in the unadjusted model only, and was not associated with any other demographic or clinical predictors.

Girls and non-White offspring were more likely to be in the High Conflict with Mother class. Miklowitz and Johnson (2009) posit that while parents are critical of boys whose preadolescent onset of a mood disorder present as externalizing, they react critically

to older daughters whose adolescent onset occurs while seeking autonomy. Indeed, the mean age of our sample being nearly 17 may contribute to these findings. It is possible that the strong separation of classes based on maternal conflict and rigidity speaks to elements of authoritative versus authoritarian parenting, and perhaps conflict arises between mothers and their offspring due to or in concert with restricted psychological autonomy granting (Steinberg, 2001). Our findings of a strong association between female and non-White offspring and a lower-warmth family climate are similar to our earlier report exclusively focused on a variable-centered analysis of the HEIC (Appendix B). While Steinberg (2001) argues that the positive outcomes associated with authoritative parenting transcend culture, Henrich (2010) argues that samples drawn from "western, educated, industrialized, rich, and democratic" societies—such as ours—are not representative of the population/humanity at large. Although our sample may not be generalizable to all families affected by BD, it should have external validity to represent families affected by BD (and those without) who access health care services.

We found that offspring of a parent with BD were more likely to be in the class of youth who perceived High Conflict with Mother than the well-functioning family environment. Importantly, parental BD was no longer a significant predictor of class membership after adjusting for children's own BD, so there is a clear need to assess both the effect of child psychopathology and children's perceptions when studying the BD-high-risk environment. Other studies, typically using a variable-centered analytic framework, have reported null differences in offspring-reported family environment by parent diagnostic group (Doucette et al., 2013; Petti et al., 2004; Tarullo et al., 1994; Vance et al., 2008). It is possible that taking a person-centered approach that allows for clustering by unobserved child-perceived family types is more sensitive than testing means on family measures

according to parent-type. Children's perceptions of their family may serve as a conduit of familial risk, rather than risk being a direct corollary of parent diagnosis.

A curious finding was the lack of any significant association with membership in the High Conflict with Father class in adjusted models. Perhaps a degree of conflict with fathers among adolescents is normative, especially when paired with the lack of maternal rigidity seen in the High Conflict with Mother class. It is also possible that we failed to include relevant predictors of conflict with fathers. That being said, we did find that offspring BD was predictive of membership in the High Conflict with Father versus reference class in a model unadjusted for other predictors. It is possible that unless a child has disrupted mood, behaviors, and functioning sufficient to receive a psychiatric diagnosis, relationship with fathers are generally lower in conflict, and when that conflict does exists, they are more heterogeneous and less predictable than relationships with mothers. Additionally, it is possible that our group of BD-HR offspring would not be more likely to be in the high conflict classes than would, for example, a normative population sample.

Limitations

The number of offspring diagnosed with a BD was modest, and indeed, distributed across classes. It is also possible that our measurement model is incomplete or miss-specified, although the domains covered by our measures reflect those identified as important in the extant literature on family environment (see, e.g., Steinberg, 2001). Additionally, as Alloy and colleagues (2006) have pointed out, it may be that maladaptive parenting is associated with psychopathology generally in offspring, but not necessarily specific disorders. Our sample was mostly White; however, demographic characteristics were not significantly different between HR and control groups, and our overall sample was large and international. Finally, children's mental health is affected by and also affects the

family environment (Schermerhorn & Cummings, 2008; Sameroff & Fiese, 2000); our cross-sectional analysis means that we cannot deduce causality, although our interpretation is informed by theory and prior research to contextualize probable temporal relations among variables.

This study contributes to the literature on BD high-risk family environment in several ways. First, we focused on child reports, which is relatively understudied compared to parent reports, and may offer insight into the relationship between children's perceptions and to their developmental outcomes. The children and parents in this study were well-phenotyped, and a diverse array of current, rather than retrospective, perceptions of family functioning were captured. We included multiple covarying domains of family environment in our measurement model, taking a person-centered approach to capturing heterogeneity of experience without making a priori assumptions regarding environmental differences by splitting children into groups according to parent diagnosis. There is a robust literature on the importance of warmth, firmness, and psychological autonomy granting (Steinberg, 2001) in the parent-child relationship, the children's perceptions of which we capture, in addition to communication conflict. Finally, the adolescent offspring under study are old enough to provide information less susceptible to suggestion, confabulation, or response bias due to dichotomous thinking seen in younger children (Taber, 2010).

Conclusion and Implications

Although the association between maltreatment exposure and BD is well-established (Alloy et al., 2006; Daruy-Filho, Brietzke, Lafer, & Grassi-Oliveira, 2011; Gilman et al., 2015), the role of global family environment/climate is less-so, with conflicting evidence in BD high-risk studies. There does not appear to be one homogenous 'signature' of the BD high-risk family environment. We found that roughly one-tenth of the offspring in our

sample perceived their relationships with their mothers to be highly conflicted and rigid. The UCLA family stress study found that stress predicted levels of maternal positive affect, which predicted child depressive symptoms (Burge & Hammen, 1991). Indeed, we found that after accounting for offspring BD, parental BD was no longer associated with class membership.

Studying offspring of persons with BD may assist in detecting etiologic factors (such as the interaction of genetic and nongenetic risk processes); highlight timeframes most appropriate for interventions; and, identify children who are experiencing distress or impairment, pointing to a need for services for the child while identifying a potential source of stress for the parents (Hodgins, Faucher, Zarac, & Ellenbogen, 2002). Parent complaints about children may reflect their own health status or concerns, so it is important to assess the children's perceptions of their environment as well. Researchers and clinicians may be able to reach mothers (or other caregivers) and their families when they present for services for themselves or for their children, assess the family environment, and link them to psychosocial treatments with potential for improving family climate. By assessing and addressing family conflict, cohesion, and flexibility, we can improve offspring outcomes.

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Table 3.1. Demographic and clinical characteristics of offspring in the Bipolar High-Risk Study

	Total Sample (n=441)	High-Risk (n=266)	Controls (n=175)	p-value
Age, mean years ± SD	16.73 ± 2.85	16.59 ± 2.84	16.95 ± 2.87	0.115
Sex, n (%)				0.858
Male	227 (51.47)	136 (51.13)	91 (52.00)	
Female	214 (48.53)	130 (48.87)	84 (48.00)	
Race, n (%)				0.063
White	393 (89.12)	243 (91.35)	150 (85.71)	
Non-White	48 (10.88)	23 (8.65)	25 (14.29)	
Country, n (%)				0.830
U.S.	320 (72.56)	194 (72.93)	126 (72.00)	
Australia	121 (27.44)	72 (27.07)	49 (28.00)	
Bipolar Disorder, *follow-up*, n (%)	n=402 35 (8.71)	n=245 34 (13.88)	n=157 1 (0.64)	<0.001

Note: Percentages are within column.

Figure 3.1. Conceptual framework: Offspring-centered model of family environment

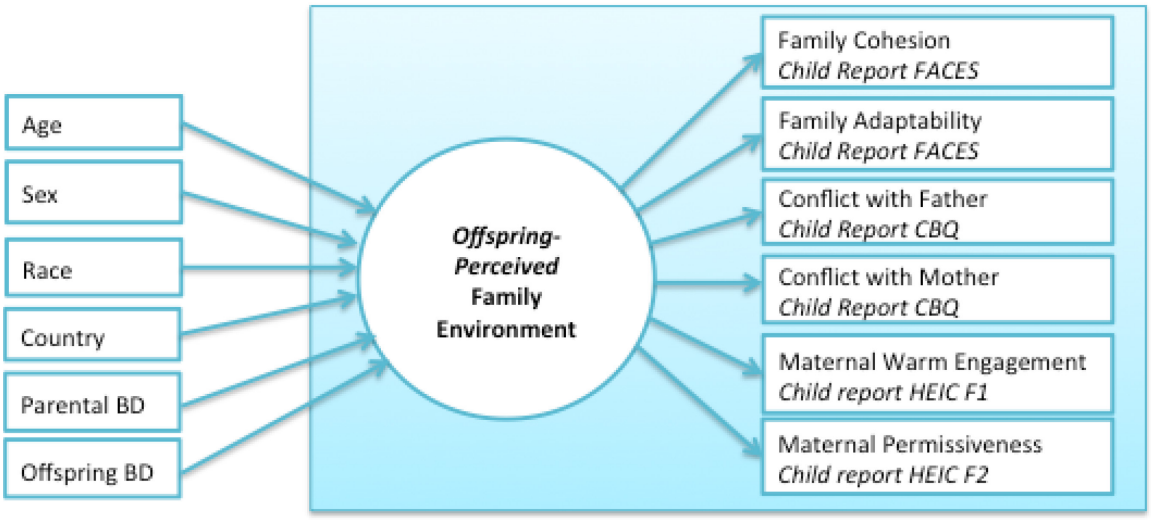


Table 3.2. Class enumeration: offspring-perceived family environment fit indices

J classes	# free parameters	Smallest Class *n (%)*	LL	BIC	Entropy	VLMR *p-value*	LMR adjusted *p-value*
1 class	12		-6096.988	12267.045			
2 class	19	66 (15)	-5843.097	11801.887	0.92	0.0000	0.0000
3 class	26	50 (11)	-5733.552	11625.42	0.828	0.0038	0.0043
4 class	33	37 (8)	-5679.846	11560.63	0.833	0.1516	0.1583
5 class	40	22 (5)	-5641.866	11527.293	0.839	0.0561	0.0595

Note: BIC, Bayesian Information Criterion; LL, log likelihood; LMR, Lo-Mendell-Rubin adjusted likelihood ratio test; VLMR, Vuong-Lo-Mendell-Rubin likelihood ratio test

Supplemental Figure 3.1. Bayesian Information Criterion across 3 classes

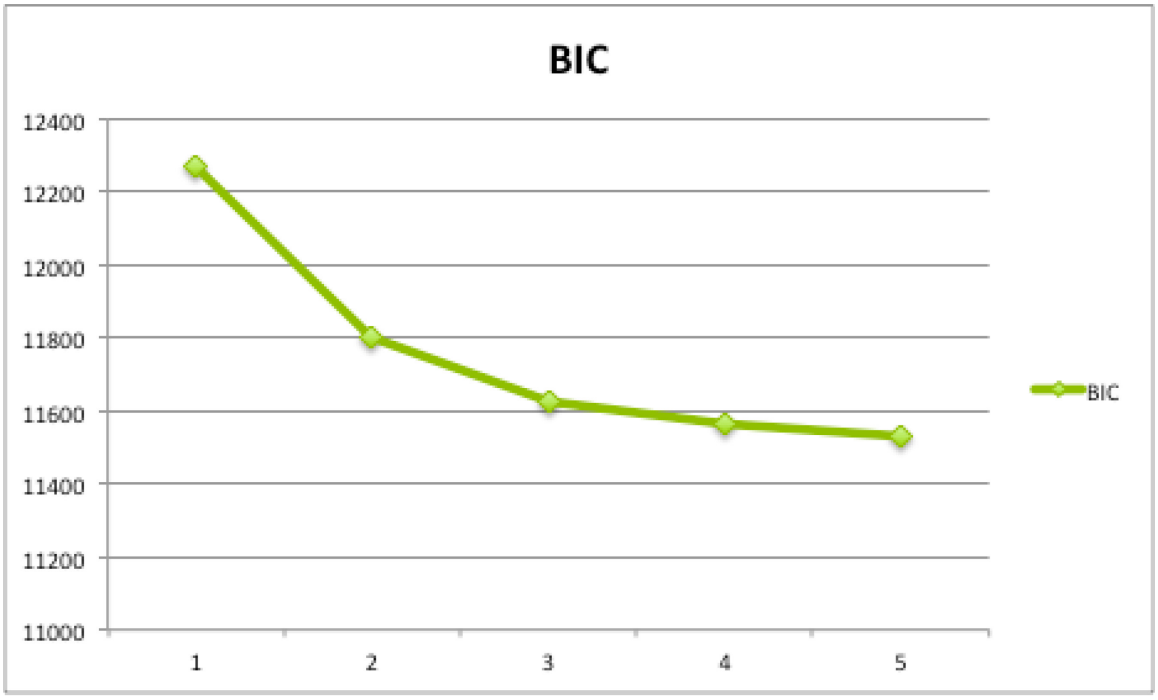
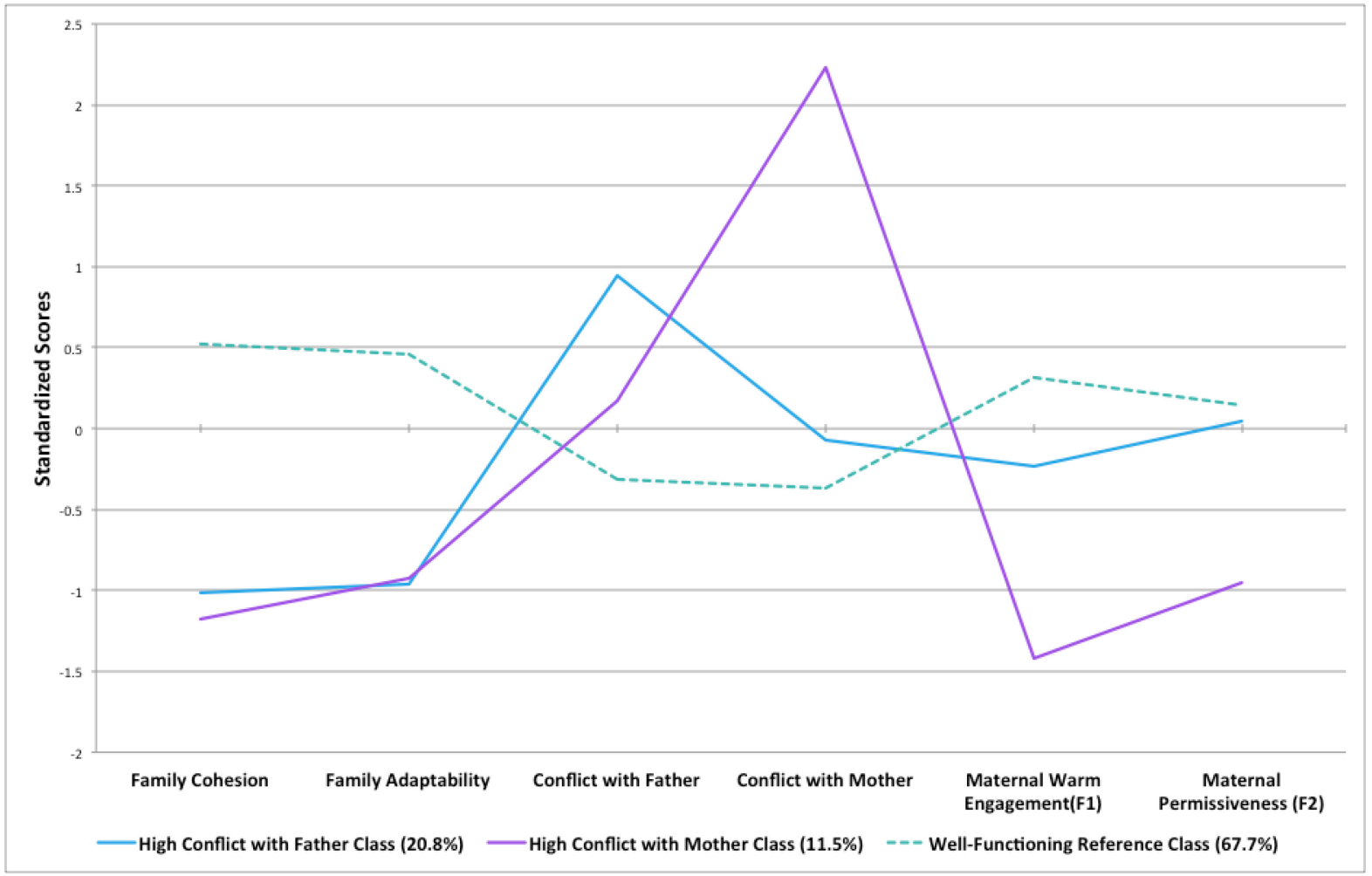


Figure 3.2. Three pattern-classes of offspring-perceived family environment



Supplemental Table 3.1. Raw scores for indicators across family environment classes

Class Indicator	Class Mean Score (95% Confidence Interval)		
	High Conflict with Father	*High Conflict with Mother*	*Well-Functioning*
Family Cohesion[a]	44.4 (40.7, 48.1)	42.7 (39.3, 46.0)	60.7 (59.4, 62.1)
Family Adaptability[a]	35.3 (32.8, 37.9)	35.7 (33.2, 38.1)	47.6 (46.4, 48.9)
Conflict with Father[b]	8.8 (6.1, 11.4)	5.0 (3.2, 6.7)	2.6 (1.9, 3.2)
Conflict with Mother[b]	3.1 (2.3, 3.9)	13.6 (12.2, 15.0)	1.8 (1.3, 2.2)
Maternal Warm Engagement[c]	-0.27 (-0.46, -0.08)	-1.20 (-1.44, -0.95)	0.16 (0.06, 0.25)
Maternal Permissiveness[c]	0.01 (-0.18, 0.21)	-0.78 (-1.10, -0.47)	0.09 (-0.001, 0.19)

Note:

[a] FACES-II subscale

[b] CBQ subscale

[c] HEIC factor score, see Appendix B

Table 3.3. Predictors of offspring-perceived family environment latent class membership

	High Conflict with Father versus Well-Functioning				High Conflict with Mother versus Well-Functioning			
	OR	Est.	SE	p	OR	Est.	SE	p
Unadjusted								
Age	1.06	0.058	0.052	0.261	1.05	0.049	0.052	0.348
Female	0.876	-0.132	0.302	0.66	**2.579**	0.947	0.353	**0.007**
Non-White Race	0.69	-0.371	0.514	0.471	2.259	0.815	0.47	0.083
Australia *(vs. US)*	0.673	-0.396	0.369	0.283	0.747	-0.292	0.421	0.488
Parental BD *(HR vs. Control)*	1.725	0.545	0.377	0.148	**2.303**	0.834	0.405	**0.039**
Offspring BD	**3.562**	1.27	0.578	**0.028**	3.327	1.202	0.642	0.061
Adjusted Model 1								
Age	1.065	0.063	0.054	0.242	1.067	0.064	0.061	0.292
Female	0.89	-0.116	0.318	0.714	**2.683**	0.987	0.368	**0.007**
Non-White Race	0.878	-0.13	0.517	0.802	**3.288**	1.19	0.52	**0.022**
Australian	0.687	-0.376	0.375	0.316	0.577	-0.55	0.467	0.24
Parental BD	1.691	0.525	0.383	0.171	**2.642**	0.971	0.443	**0.028**
Adjusted Model 2								
Age	1.04	0.039	0.091	0.667	1.074	0.07	0.062	0.255
Female	0.962	-0.039	0.365	0.914	**2.57**	0.944	0.375	**0.012**
Non-White Race	0.702	-0.354	0.685	0.605	**3.525**	1.26	0.553	**0.023**
Australian	0.795	-0.23	0.383	0.548	0.68	-0.386	0.628	0.538
Parental BD	1.207	0.188	0.386	0.626	2.094	0.739	0.45	0.1
Offspring BD	3.168	1.153	0.684	0.092	2.691	0.99	0.703	0.159

Notes: Est., effect estimate; OR, odds ratio; p, p-value; SE, standard error. Values in **bold** significant at $p<0.05$ level. Each covariate in unadjusted models is modeled independently on class; in adjusted models, each covariate in model is adjusted for all other covariates.

Chapter 4: Family environment and its interaction with polygenic risk in predicting bipolar disorder in youth (Aim 3)

ABSTRACT

Background: Bipolar disorder (BD) is a severe, impairing mood disorder with high heritability, approximately one-third of which is accounted for by common genetic variants. Individuals may have differential susceptibility to their family environment depending on their genetics. The objectives of this study were to test the main effects of offspring-perceived latent family environment and the interaction of polygenic risk with family environment on offspring mood diagnoses, in offspring at high or low familial risk for BD.

Methods: The sample is a subset from the Bipolar High-Risk Study: 266 offspring of a parent with BD and 175 control offspring of parents with no psychiatric disorders. Perceived latent family environment (FE) was modeled using offspring reports on the Conflict Behavior Questionnaire, Family Adaptability and Cohesion Evaluation Scales, and Home Environment Interview for Children. Offspring polygenic risk scores (BD-PRS) were derived from wave 1 Psychiatric Genomics Consortium data on BD using a $p<0.001$ threshold. Lifetime DSM-IV diagnosis of any major mood disorder (MMD) or broad phenotype BD was made using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children. We used a stepwise approach for latent class modeling with predictors and distal outcomes.

Results: Of 441 offspring aged 12-22 years, 61 were diagnosed with any MMD and 35 with BD. Youth who reported FE characterized by high father-child conflict and low family flexibility and cohesion were marginally more likely to be diagnosed with BD than were youth who reported warm, flexible, low conflict FE ($p=0.075$), adjusted for age, sex, genetic

ethnicity, and BD-PRS. Significant negative interaction between BD-PRS and membership in the High Conflict with Father class on likelihood of BD diagnosis was found (p=0.052); among youth in the High Conflict with Father class, lower polygenic risk was associated with higher liability of BD. Main and interaction effects on any MMD were not significant.

Conclusions: We detected modest association between FE and offspring BD. The significant negative interaction between BD-PRS and membership in the High Conflict with Father class indicates support for a liability threshold model. Taken together, these results support focusing on modifiable domains of family environment, such as communication and responsive caregiving, with the goal of preventing or reducing burden associated with BD.

Key Words: bipolar disorder, polygenic risk, gene-environment interaction, family environment, high-risk

Decades of genetics studies have demonstrated that bipolar disorder (BD) aggregates in families and that genetics play a substantial role in conferring risk (Bearden, Zandi, & Freimer, 2016; Craddock & Sklar, 2013). Because of global collaboration by the Psychiatric Genomics Consortium (PGC), genotyped BD cases and controls have increased greatly, and with them, the power to detect BD-associated genes—particularly common genetic variants (Lee et al. 2013; Purcell et al., 2009; Sklar et al., 2011). The single-nucleotide polymorphisms (SNPs) associated with BD are common genes of small effect individually, which additively increase risk (i.e., polygenic risk), and are estimated to account for 25% of the variance in risk for BD (Lee et al., 2013). In turn, these BD-associated SNPs may be used to create a summary polygenic risk score (PRS), which may be used as a measure of (common variant) genetic burden, particularly in high-risk samples (Fullerton et al., 2015; Smoller et al., 2013; Wray et al., 2014).

Having a family history of BD is the strongest known predictor of developing the disorder (Goodwin & Jamison, 2007), with offspring of BD parents at 8–10 fold increased risk of developing BD (Craddock & Sklar, 2013) and increased risk of developing mood and psychiatric disorders in general (Hodgins, Faucher, Zarac, & Ellenbogen, 2002; Rasic, Hajek, Alda, & Uher, 2014), compared to offspring of parents without psychiatric disorders. Monozygotic twin concordance for BD is estimated to be 40–70% and heritability estimates range from 63–93% (Bearden et al., 2016; Craddock & Sklar, 2013), which indicates that susceptibility to BD is likely due to a combination of genes and environment. The family environment—parent-child relationships, especially—is central to child development and may be a prime target for understanding risk processes in the BD high-risk context.

Considering a range of caregiving behavior, child abuse and neglect are on the severe negative end. It has been consistently demonstrated that these types of child maltreatment

are associated with negative mental and physical health outcomes in both the short- and long-term (Chapman et al., 2004; Felitti et al., 1998; Johnson, Riley, Granger, & Riis, 2013; Repetti, Taylor, & Seeman, 2002). Additionally, individuals with BD retrospectively report a higher prevalence of exposure to childhood maltreatment than do individuals without BD (Alloy et al., 2006; Gilman et al., 2015). However, there is less consensus regarding general family climate and functioning as prospectively assessed among BD high-risk offspring.

Warmth and firmness are two classic domains of parent-child relationships (Steinberg, 2001), with family communication being a major conduit of both. In a recent systematic review of prospective studies on family environment and offspring psychiatric disorders in the BD high-risk literature (Chapter 2), the authors found that parents with BD report lower cohesion compared to parents without psychiatric disorders, and high-risk families in which offspring are diagnosed with BD report higher conflict than families without offspring diagnosed with BD. Findings on family system maintenance (e.g., control, organization) and communication were mixed. Additionally, children's perceptions of the family environment were infrequently reported, and, when they were reported, differences between high-risk and control offspring were not significant.

Given the lack of consensus regarding the role of family environment as experienced by youth at familial risk for BD but the well-established importance of family environment on youth development generally, and the growing interest in polygenic risk for BD, we sought to clarify these relationships in the Bipolar High-Risk Study sample. Based on initial diagnostic and clinical characteristics of adolescent relatives of a BD proband and controls at four U.S. sites in the Bipolar High-Risk Study, Nurnberger and colleagues (2011) reported approximately 6-fold risk for lifetime major mood disorders in BD relatives versus controls; in particular, childhood anxiety and externalizing disorders predicted later mood disorders

among the relatives of a BD proband. Additionally, Wilcox and colleagues ([2017]) found that individuals with genetic risk for BD (family history of BD, and higher BD-PRS), especially those who experience traumatic events (exposure to bullying, sexual abuse, or domestic violence within the past year), had increased risk for suicide attempt, independent of having a mood or substance disorder. Severe problems in the home and social environment can have serious consequences, particularly among individuals at genetic risk for BD, even in the absence of diagnosable mood or substance problems. In the present study of offspring of parents with BD or no parental psychiatric disorder, we aimed to 1) assess the main effects of offspring-perceived family environment, as a latent construct, on prevalence of a) offspring mood disorders and b) offspring bipolar disorder, adjusted for offspring age, sex, genetic ancestry, and polygenic risk; and 2) test for an interaction between family environment and polygenic risk on offspring diagnoses, adjusted for offspring age, sex, and genetic ancestry (**Figure 4.1**).

Methods

Participants and Procedures

The study sample consists of participants aged 12–21 at time of recruitment into a prospective study of adolescents at high risk for familial BD. The study took place from 2006–2013 in the United States (US) at Indiana University, University of Michigan, Washington University in St. Louis, and Johns Hopkins University, and in Australia at the University of New South Wales. Institutional Review Boards approved the research at all US sites and the Human Research Ethics Committee approved the research at the University of New South Wales. Informed consent (or assent with parental consent for participants under age 18) was obtained for all participants. Additional details about study procedures

are described elsewhere, by Nurnberger and colleagues (2011) and Perich and colleagues (2015).

Offspring at high-risk for familial BD ("high-risk [HR] offspring") were identified from probands with bipolar I disorder (BD-I), bipolar II disorder (BD-II), or schizoaffective disorder bipolar type in the NIMH Genetics Initiative bipolar sample and other genetics studies, specialty clinics, and publicity. Control participants were recruited from general practitioners, motor vehicle records, and advertising, excluding individuals with a parent or sibling with BD-I, BD-II, recurrent Major Depressive Disorder, schizoaffective disorder, schizophrenia, recurrent substance abuse, or any psychiatric hospitalizations, or whose parent had a first-degree relative with a history of psychosis or hospitalization for a mood disorder. Parent diagnoses or lack thereof were confirmed using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). Although HR participants in the primary study also included siblings and second-degree relatives of BD probands, the current analysis focuses specifically on offspring only. In some families, multiple offspring participated.

Measures

Outcome Measures: Offspring Mood Diagnoses

Offspring were interviewed by extensively trained clinicians using the *Schedule for Affective Disorders and Schizophrenia for School-Aged Children, bipolar disorder version* (K-SADS; for details, see Nurnberger et al., 2011). Offspring lifetime DSM-IV psychiatric disorders were confirmed by best estimate consensus of two clinicians using direct interviews of offspring and parents and medical history records. A dichotomous variable for lifetime DSM-IV diagnosis of any 'Major Mood Disorder' (MMD) using all available information included the following diagnoses: recurrent Major Depression, BD-I, schizoaffective disorder bipolar type, BD-II with recurrent depression, and BD not otherwise specified (BD-NOS). A

dichotomous variable for lifetime DSM-IV diagnosis of BD using all available information was created based on a broad phenotype of BD including BD-I, schizoaffective disorder bipolar type, BD-II, and BD-NOS. This broad phenotype of BD captures lifetime history *at time of assessment*, which means individuals diagnosed with recurrent Major Depression were coded as 0 (*no BD)*, understanding that participants' diagnoses may evolve in the future. We modeled each distal outcome (Major Mood Disorder; BD) separately. Best estimate consensus diagnoses were available for 91% of the offspring.

Exposure of interest: Latent Family Environment

We previously used complex mixture modeling to identify three latent classes of offspring-perceived family environment based on children's reports on the *Conflict Behavior Questionnaire* (CBQ; Prinz, Foster, Kent, & O'Leary, 1979), *Family Adaptability and Cohesion Evaluation Scales, version II* (FACES II; Olson, Bell, & Portner, 1982), and the *Home Environment Interview for Children* (HEIC; Reich & Earls, 1984). Offspring reported on conflict with their mothers (CBQ-mother summary scores) and conflict with their fathers (CBQ-father summary scores); family adaptability and family cohesion subscales on the FACES II; and were interviewed on their perception of parent-child relationships at home, resulting in factors scores on offspring-perceived maternal warm engagement and offspring-perceived maternal permissiveness, derived from a factor analysis of responses to the HEIC (Appendix B). For the HEIC, youth were asked to report on the past year, if currently living with their biological parent(s), or the last year they lived together if currently living apart. For the CBQ and FACES, timeframe for 'describing family' or 'describing relationships' was current at assessment, without an exact period (e.g., past month) specified.

Exposure of interest: Genetic Risk

Genotyping and polygenic risk score creation for the Bipolar High-Risk Study have been described at length elsewhere (Fullerton et al., 2015; Wilcox et al., [2017]). Briefly, peripheral blood samples were collected from offspring for genetic analysis, with DNA extracted from whole blood by the Rutgers University Cell and DNA Repository for US participants and by Genetic Repositories Australia for Australian participants. Genome-wide SNP genotyping was conducted at Mt Sinai School of Medicine Genomics Core Facility using the Infinium PsychArray BeadChip (Illumina, Scoresby, Victoria, Australia) and standard PGC pipelines for genotype calling and quality control; successfully genotyped SNPs had a pass rate of at least 99.6% (Wilcox et al., 2017).

Bipolar Polygenic Risk Scores (BD-PRS) were created based on disease-associated SNPs from the PGC1-BD discovery sample (Sklar et al., 2011), using PLINK (Purcell et al., 2007) to create the additive score, then weighted by the disease-associated SNPs' log odds ratio. For this study, we tested a risk score based on a p-value thresholds (pT) of $p<0.001$, which represents 591 SNPs. The $pT<0.001$ was selected due to its salience in Wilcox and colleagues' (2017) gene-environment analysis of the Bipolar High-Risk Study. The BD-PRS was standardized for interpretability.

Demographic Characteristics

Offspring age at interview and sex (binary Male or Female) were extracted from the K-SADS; these data were complete. We controlled for offspring genetic ancestry rather than self-reported race in all models. In case of genetic differences between subpopulations, i.e., population stratification, it would be possible to obtain spurious significant associations due to that population stratification, which is why it is necessary to control for genetic ancestry. We modeled genetic ancestry based on two primary components (C1 and C2) from principal component analysis (PCA) of 164,680 SNPs, because they were the most

informative. Genetic ancestry was available for 90% of the sample. Occasionally, self-reported race differs from PCA ethnicity. Data on self-reported race (White versus non-White, based on reduction of US Census categories) were complete, shown in **Table 4.1**.

Statistical Analysis

We performed all latent variable modeling, including testing distal outcomes and gene-environment interactions, in Mplus version 8 (Muthén & Muthén, 1998-2017). Mplus makes use of all available data to estimate the measurement model using full information maximum likelihood, which is considered appropriate when data may be reasonably assumed to be missing at random (Muthén & Muthén, 1998-2017; Shafer & Graham, 2002). Sample statistics and logistic regression using generalized estimating equations (GEE) were calculated using Stata Version 14 (StataCorp, 2015).

Latent Profile Analysis

The process of class enumeration is described in detail elsewhere (Chapter 3), and is based on the assumption that individuals can be grouped into classes based on the indicators that reflect unobserved clustering of subpopulations. In conducting a complex latent profile analysis (LPA; a type of latent class analysis [LCA] using continuous indicators) to account for within-family clustering, we identified three patterns (classes) of offspring-perceived family environment (see **Figure 4.2**), based on the Bayesian Information Criterion and the Lo-Mendell-Rubin test, as well as class size and interpretability. The largest class of youth (67.7%) reported a family environment indicated by nurturance, flexibility, and low conflict, whereas the two smaller classes were characterized by low warmth and cohesion, rigidity, and high conflict. A medium-sized class of youth (20.8%) clustered together based on high conflict with father and low family flexibility, and the smallest-sized class (11.5%) of youth clustered together based on very high conflict and rigidity in the mother-child relationship.

The HR and control offspring were modeled together, such that HR and control offspring were in each of the three classes. In this analysis, females (daughters) were more likely to be in the High Conflict with Mother class than in the reference class (OR=2.87, p=0.005), adjusted for age, genetic ethnicity, and BD-PRS, and none of which significantly predicted class membership (data not shown). There were no significant predictors of membership in the High Conflict with Father class. Latent class predictors were modeled without distal outcomes.

Modeling Offspring Mood Disorders as Distal Outcomes

To test main and interaction effects of family environment and BD-PRS on offspring psychiatric disorders, we used a stepwise approach for latent class modeling with predictors and distal outcomes set forth by Masyn (2017). This approach builds on the manual BCH method for auxiliary outcomes in Mplus (Asparouhov & Muthen, 2015). In contrast to one-step approaches to modeling outcomes, this three-step approach adjusts for covariate effects (i.e., age, sex, genetic ancestry, and polygenic risk) on both the categorical latent classes and dichotomous outcomes. After the final unconditional LPA model is specified, individuals are classified into their most likely classes using posterior probabilities and classification errors are calculated (modal classification). Then, the modal latent classes with fixed classification errors are regressed on covariates and distal outcomes, also adjusting for effects of the covariates on the distal outcomes (Masyn, 2017). Specifically, we tested for risk of a) any MMD, and b) BD (broad phenotype) across the family environment classes (regardless of parent diagnosis), while adjusting for the influence of age, sex, genetic ancestry, and BD-PRS on both family environment and offspring diagnosis, conducting Wald and pairwise tests of model significance. In addition to obtaining the main effect of family environment, we tested for a statistical interaction of BD-PRS and family

environment on offspring diagnosis, again controlling for covariates. We assessed model significance using the Wald test, and pairwise comparison tests of the mean within-class BD-PRS for High Conflict with Father versus reference class and High Conflict with Mother versus reference class.

Results

Sample Characteristics

The study sample included 441 participants (representing 293 families) modeled together: 266 offspring of a parent with BD (HR) and 175 offspring of parents without psychiatric disorder (controls). Participants ranged in age from 12 to 22 years old at time of assessment, with a mean age of 16.7 years. Slightly over half of the sample was male (51.5%). High-risk and control offspring did not differ significantly on age, sex, or self-reported race. Although they differed significantly on the first two components of genetic ancestry ($p<0.001$), the components should not be taken individually, and are instead modeled together to adjust for ethnicity. A total of 61 offspring were diagnosed with a lifetime DSM-IV MMD. Nearly one-fourth of the HR offspring (n=56) were diagnosed with any MMD, compared to <3% of the controls (n=5). A total of 35 youth were diagnosed with BD, 34 of whom had a parent with BD, plus 1 control offspring. Sample statistics are in **Table 4.1**.

Main Effect of Family Environment on Offspring Mood Disorders

We present results for the main effect of family environment on offspring psychiatric disorders in **Table 4.2**, adjusted for offspring age, sex, genetic ethnicity, and BD-PRS.

Major mood disorders (any MMD). While 13.2% of offspring in the reference class were diagnosed with any MMD, 18% of the High Conflict with Father class and 23% of the High Conflict with Mother class were diagnosed with any MMD. Neither overall

family environment nor pairwise comparisons of High Conflict with Father (χ=0.378, p=0.408) and High Conflict with Mother (χ=0.538, p=0.264) versus reference class were significantly associated with offspring diagnosis of any MMD, adjusting for age, sex, genetic ethnicity, and BD-PRS (see **Table 4.2**).

Offspring female sex was associated with offspring diagnosis of any MMD (OR 1.78, 95% Confidence Interval [CI] 0.99–3.20, p=0.054), while offspring BD-PRS was negatively, though non-significantly, associated with any MMD (OR 0.85, CI 0.62–1.15, p=0.290) (data not shown).

Broad phenotype BD. As shown in **Table 4.2**, 6% of offspring in the reference class, 14.2% of the High Conflict with Father class, and 12.7% of the High Conflict with Mother class were diagnosed with BD. Although we did not find a significant overall effect for the family environment on offspring BD, or comparing risk of BD in the High Conflict with Mother versus reference class (χ=0.817, p=0.194) we found that offspring in the High Conflict with Father class were marginally more likely to have a BD diagnosis than were the offspring who perceived their family environment to be well-functioning (χ=1.045, p=0.075).

Demographic characteristics and BD-PRS were not significantly associated with offspring diagnosis of BD, although, as with any MMD, lower BD-PRS was non-significantly associated with BD (OR 0.72, CI 0.47–1.10, p=0.132) (data not shown).

Gene-Environment Interaction Effect on Offspring Mood Disorders

We present results for the interaction effect of latent family environment and BD-PRS on offspring psychiatric disorders in **Table 4.3**, adjusted for offspring age, sex, and genetic ethnicity. **Figure 4.3** displays the gene-environment interaction on offspring BD.

Any MMD. As shown in **Table 4.3**, 13% of offspring in the reference class, 18.6% of the High Conflict with Father class, and 23% of the High Conflict with Mother class were diagnosed with BD. Neither overall nor pairwise comparisons of the gene-environment interaction model on any MDD were significant (see Wald and z-tests in Table 4.3). We found that among offspring in Well-Functioning family environment (OR 0.92, CI 0.58–1.48, p=0.743) and High Conflict with Father family environment (OR 0.52, CI 0.14–1.91, p=0.322) there were negative, though non-significant, associations between BD-PRS and any MMD; and, among those in High Conflict with Mother family environment, increasing BD-PRS was associated with increasing risk of any MMD (OR 1.2, CI 0.55–2.48, p=0.693) (data not shown). Offspring female sex was marginally associated with offspring diagnosis of any MMD in the gene-environment interaction model (OR=1.76, CI 0.98–3.19, p=0.06; data not shown).

Broad phenotype BD. As shown in **Table 4.3**, 5.3% of offspring in the reference class, 15.9% of the High Conflict with Father class, and 13.2% of the High Conflict with Mother class were diagnosed with BD. Compared to the direct effect models, there was some minor (non-significant) class shifting in the gene-environment interaction effect models. We did not find a significant interaction overall between family environment and BD-PRS on offspring BD, or for gene-environment interaction for offspring in the High Conflict with Mother class. However, there was a significant gene-environment interaction conferring risk for BD in the High Conflict with Father class (z=2.889, p=0.052).

Interestingly, among those in High Conflict with Father family environment, increasing BD-PRS was associated with lower risk of BD (OR 0.09, CI 0.01–1.02, p=0.052) (data not shown). In contrast, we found that among offspring in well-functioning family environment, there was a positive, albeit non-significant, association between BD-PRS and

BD (OR 1.56, CI 0.57–4.25, p=0.382); likewise for offspring in High Conflict with Mother family environment (OR 1.13, CI 0.44–2.89, p=0.8) (data not shown). Liability for BD in the gene-environment interaction model is displayed in **Figure 4.3**, where the highest risk for BD in the High Conflict with Father class was seen among those with lower BD-PRS.

Discussion

In a sample of 441 offspring at high and low familial risk for BD, we found that offspring-perceived family environment, alone and in interaction with BD-PRS, was associated with offspring diagnosis of BD, but not any MMD. The significant effects were particular to offspring identifying high conflict in the father-child relationship and low family cohesion and flexibility. Membership in that 'High Conflict with Father' class compared to membership in the Well-Functioning (warm, flexible, low conflict) reference class was marginally predictive of increased risk for BD, adjusted for age, sex, genetic ancestry, and BD-PRS. Additionally, the *interaction* of membership in the High Conflict with Father class and BD-PRS was significantly associated with offspring BD. Interestingly, that gene-environment interaction was negative.

We found a negative statistical interaction between membership in the High Conflict with Father class and BD-PRS, which significantly associated with offspring BD. All but one of the youth diagnosed with BD had a parent with BD, and the youth who perceived a High Conflict with Father family environment had the highest risk of BD. Among youth in the High Conflict with Father class, lower polygenic risk was associated with higher liability of BD. High-risk offspring who were themselves affected with BD had lower mean BD-PRS than unaffected HR and affected control offspring (Supplemental Table 4.1). Mullins and colleagues (2016) recently reported a negative gene-environment interaction between polygenic risk for depression and history of childhood trauma on depression. They found

that individuals with depression and a history of moderate or severe childhood trauma tended to have lower PRS than other cases or controls, and suggested that the problematic environmental exposure (childhood trauma) may be more important in the development of depression among individuals with lower genetic risk than for those with higher genetic risk, consistent with the liability threshold model (Mullins et al., 2016, p. 766).

Membership in a 'High Conflict with Mother' class—characterized by high conflict and low warmth in the mother-child relationship and low overall family cohesion and flexibility—was not significantly associated with offspring diagnoses, either alone or in interaction with polygenic risk. Offspring female sex as a predictor of membership in the High Conflict with Mother class, and it was associated with offspring diagnosis of any MMD in main effect and interaction models. In contrast, sex was not associated with BD in main and gene-environment interaction models. This finding is not surprising given that female sex is associated with depression, whereas BD is equally prevalent among males and females (Bearden et al., 2016).

One limitation of our study is that our measure of genetic burden encompasses common genetic variation only, and it is a risk score based on BD-associated SNPs. It is possible that there is a different genetic mechanism at work in HR offspring; for example, perhaps early onset BD is due to rare variants or gene expression altered due to early life adversity, neither of which are measured by a summary score of disease-associated SNPs. As pointed out by Mullins and colleagues (2016), disease-associated SNPs used to create PRS are based on their main effect on a given diagnosis, but there could be different variants involved in gene-environment interactions. Further, it is possible that mania and depression are independently transmitted, rather than opposite poles of one disorder (Merikangas et al., 2014). When we used the BD-PRS as a measure of genetic burden on risk of any MMD,

which included depression, results were non-significant, which may speak to the specificity of the score to BD. Lastly, the ability to construct a useful score based on strong, valid disease associations may be limited by the ability to detect the disease-associated SNPs in the first place. With the next wave of PGC data, the power to construct predictive scores may increase. Nonetheless, we found a significant role for gene-environment interaction on youth BD using a well-phenotyped, international sample.

In general, the moderate associations we found may be due to the modest number of youth with mood diagnoses, although the fact that we found effects with only 35 BD cases is encouraging. Membership in the High Conflict with Mother class was not associated in main or interaction models with offspring mood diagnoses; however, this was the smallest class and had very few diagnosed youth. Indeed, there were a nontrivial number of youth diagnosed with a lifetime MMD in the Well-Functioning reference class, and we found that family environment did not predict MMD, whereas it did associate with diagnosis of BD (namely, the High Conflict with Father class). Additionally, although our full sample has not yet passed the peak age of onset for BD in the population, earlier age of onset is more prevalent in clinical samples (Birmaher et al., 2009; Danner et al., 2009; Perlis et al., 2004), and our high-risk study design allows for efficient case yield compared to epidemiologic samples. Onset in childhood or adolescence is associated with worse prognosis and significantly more clinical correlates compared to adult-onset BD (Holtzman et al. 2015) and this subset of youth may have a different, more severe, trajectory and different etiology than those who develop BD later. Diagnoses in this sample may evolve over time and future follow-up will provide insight into trajectories.

Family relationships and functioning are central to child development. When families experience heightened levels of conflict, with relationships lacking warmth and

support, this places children at risk for adverse psychological and physical outcomes across the life course (Repetti et al. 2002). Families with this type of difficulty create a stressful environment that may inhibit the cognitive development, emotion regulation, physical wellbeing, and neuroendocrine-immune function of youth (Johnson et al., 2013; Repetti et al. 2002). Stress—both as it is appraised psychologically and experienced physiologically—has been implicated in the onset, recurrence, severity, and excess morbidity associated with BD (Bender & Alloy, 2011; Brietzke, Mansur, Soczynska, Powell, & McIntyre, 2012; Miklowitz & Chang, 2008; Post & Leverich, 2006).

Our study design was cross-sectional, which prohibits causal attributions. Additionally, the family environment measurement model was based on self-report measures, which may be subject to biases due to recall or social desirability. However, offspring were reporting largely on contemporary family relationships and climate at the time of measurement. Our findings are consistent with the literature showing deleterious effects of a stressful family environment on children's psychological wellbeing, especially the literature linking low cohesion and high conflict to offspring BD in the BD high-risk context.

We developed a measurement model of offspring-perceived family environment in the BD high-risk context. Children's perspectives are less commonly ascertained than parents', but are important to understand because of the association between perceptions of their family environment and their own outcomes. Our assessments of risk for BD are based on offspring characteristics that do not necessarily require direct parent participation or assessment. Youth with BD (and controls) perceived three types of family environment. We found that youth reporting high conflict with their fathers and low family cohesion and flexibility were more likely to be diagnosed with BD compared to youth who report generally

well-functioning family dynamics and climate. Moreover, the perceived family environment interacted with BD-PRS in an inverse relation with BD, consistent with a liability threshold model. The HR offspring with BD had lower BD-PRS than unaffected HR offspring. It may be that high-conflict parent-child relationships are particularly problematic for offspring of a BD parent, and that a different genetic mechanism (not common variation) is at work for youth with family history of the disorder and early onset of their own disorder. BD is a complex mental disorder with genetic and environmental risk processes implicated in its etiology. Our findings support an emphasis on strengthening communication, warmth, and responsive caregiving to provide a health family environment in the BD high-risk context.

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Table 4.1. Sample statistics for offspring in the Bipolar High-Risk Study

	Total Sample (n=441)	High-Risk (n=266)	Controls (n=175)	p-value
Age, mean years ± SD	16.73 ± 2.85	16.59 ± 2.84	16.95 ± 2.87	0.202
Sex, n (%)				
Male	227 (51.47)	136 (51.13)	91 (52.00)	0.858
Female	214 (48.53)	130 (48.87)	84 (48.00)	
Race, n (%)				0.063
White	393 (89.12)	243 (91.35)	150 (85.71)	
Non-White	48 (10.88)	23 (8.65)	25 (14.29)	
Country, n (%)				0.830
United States	320 (72.56)	194 (72.93)	126 (72.00)	
Australia	121 (27.44)	72 (27.07)	49 (28.00)	
	n=399	. n=243	n=156	
BD-PRS, raw mean (SD)	.0009837	0011659	.0006998	0.001
	(.001415)	(.001433)	(.0013424)	
Offspring Mood Disorders				
	n=402	n=245	n=157	<0.001
Major Mood Disorder, n (%)	61 (15.17)	56 (22.86)	5 (3.18)	
Bipolar Disorder, n (%)	35 (8.71)	34 (13.88)	1 (0.64)	<0.001

Note: BD-PRS, Bipolar Polygenic Risk Score (based on disease associated SNPs from Psychiatric Genomics Consortium Wave 1, p-value threshold <0.001). Percentages are within column. Descriptive sample statistics not adjusted for family clustering.

Table 4.2. Main Effect of Latent Family Environment on Offspring Mood Disorders

Family Environment Class	Proportion with Diagnosis	Model Significance Tests Overall (*Wald*) and Pairwise (χ)
Major Mood Disorder		*Wald*=1.512, p=0.4695
Well-Functioning	0.132	–
High Conflict with Father	0.180	χ=0.378, p=0.408
High Conflict with Mother	0.230	χ=0.538, p=0.264
Bipolar Disorder		*Wald*=3.647, p=0.1615
Well-Functioning	0.060	–
High Conflict with Father	0.142	χ=1.045, **p=0.075**
High Conflict with Mother	0.127	χ=0.817, p=0.194

Note: All models adjusted for offspring age (continuous), sex (binary), genetic ancestry (continuous PCA ethnicity, first two components), and bipolar polygenic risk score (BD-PRS) at p-value threshold p<0.001.

Table 4.3. Bipolar Polygenic Risk Score by Latent Family Environment Interaction Effect on Offspring Mood Disorder Diagnoses

Family Environment Class	Proportion with Diagnosis	Model Significance Tests Overall (*Wald*) and Pairwise (z)
Major Mood Disorder		*Wald*=1.273, p=0.5292
Well-Functioning	0.130	–
High Conflict with Father	0.186	z=0.583, p=0.473 [a]
High Conflict with Mother	0.231	z=-0.231, p=0.613 [a]
Bipolar Disorder		*Wald*=4.002, p=0.1352
Well-Functioning	0.053	–
High Conflict with Father	0.159	z=2.889, **p=0.052** [a]
High Conflict with Mother	0.132	z=0.325, p=0.657 [a]

Note: All models adjusted for offspring age (continuous), sex (binary), and genetic ancestry (continuous PCA ethnicity, first two components). Bipolar polygenic risk score (BD-PRS) p-value threshold p<0.001.

[a] Statistical test of the significance of the interaction term of specific family environment class with mean BD-PRS

Figure 4.1. Conceptual model of gene-environment interaction on offspring mood

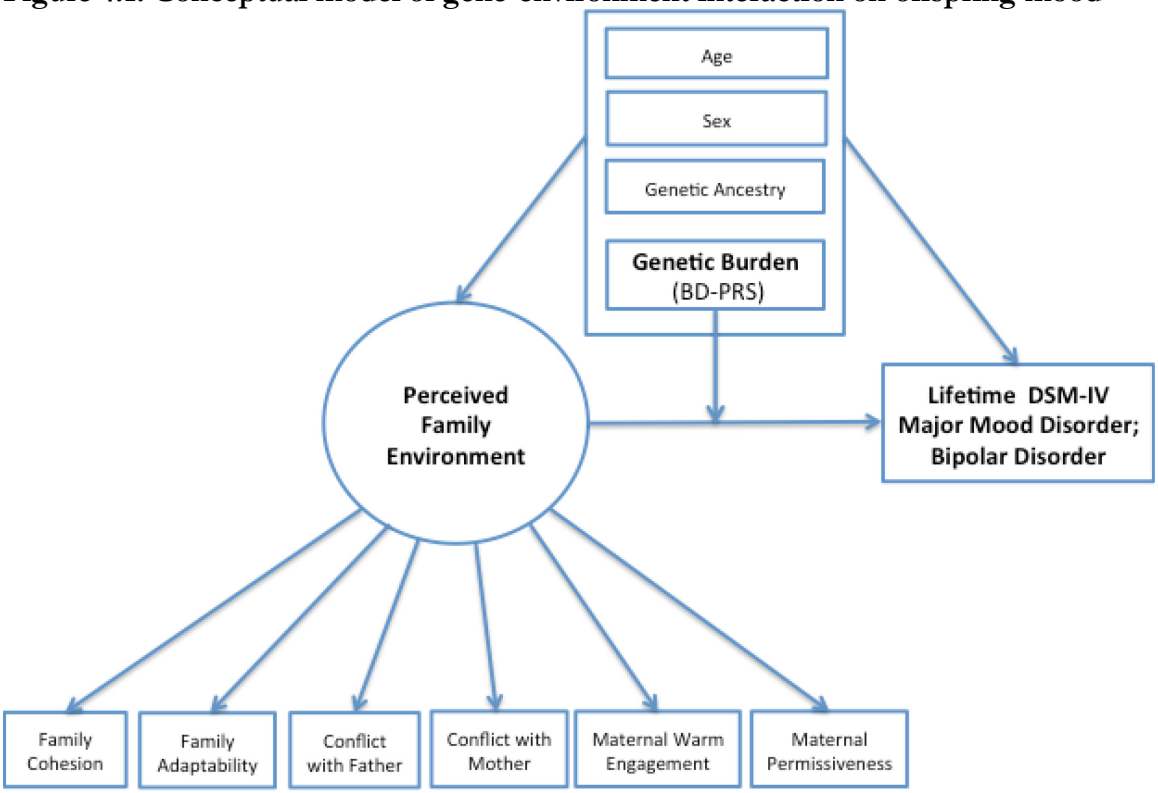


Figure 4.2. Latent classes of family environment based on scores on the CBQ, FACES, and HEIC

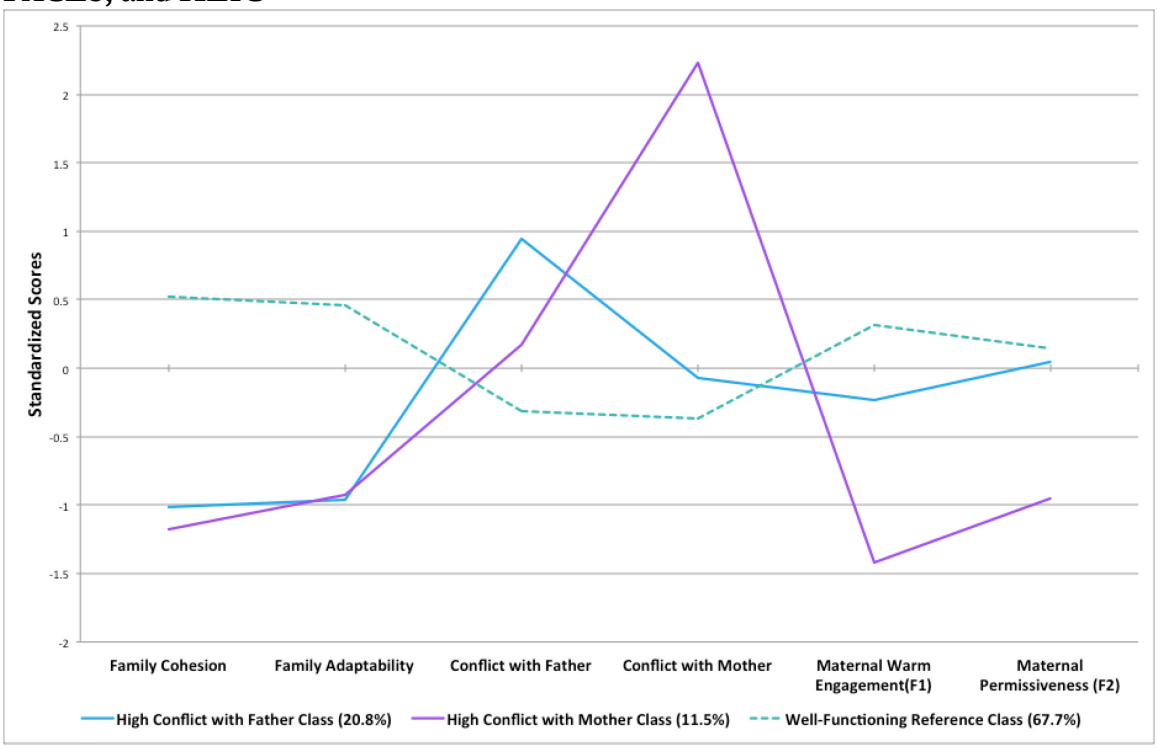
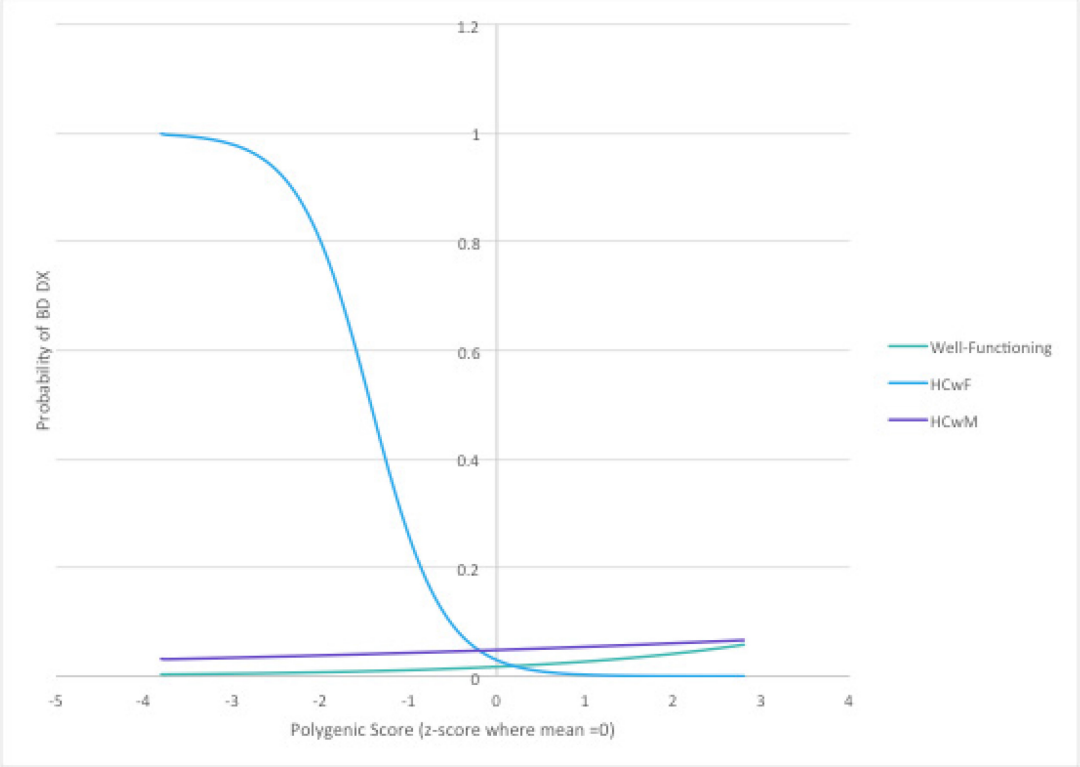


Figure 4.3. Interaction between offspring BD-PRS and three latent classes of offspring-perceived family environment on probability of BD diagnosis in offspring



Supplemental Table 4.1. Mean Standardized Bipolar Polygenic Risk Scores by Group and Affected Status

	High-Risk (n=266)			Controls (n=175)		
	BD	No BD		BD	No BD	
	n=34	n=211	*p*	n=1	n=156	*p*
BD-PRS	n=30	n=194	n=224	n=1	n=140	n=141
pT <0.0001	-0.46697	0.03490	0.010	0.30666	0.03309	0.790
pT <0.001	-0.20021	0.19606	0.051	0.51253	-0.20460	0.448

Note: BD, bipolar disorder; BD-PRS, bipolar polygenic risk scores; pT, p-value threshold. Mean standardized BD-PRS rounded to five digits.

CHAPTER 5: Discussion

Summary of Main Findings

The overarching goal of this project was to investigate the family environment in youth at high familial risk for bipolar disorder (BD): what about the family environment is particularly salient in this context, and does it confer risk for psychopathology in offspring, alone or in tandem with genetic burden? The specific aims were: 1) systematically review prospective, non-experimental studies of parental BD, family environment, and offspring psychiatric disorders, identifying characteristics of family environment associated with risk for psychiatric disorders among offspring of parents with and without BD (Chapter 2); 2) take a person-centered approach to modeling child-perceived family environment among a sample of adolescent and emerging adult offspring at high or low familial risk for bipolar disorder, a) identifying latent patterns (classes) of child-perceived family environment, and b) testing for predictors of family environment class membership, including demographic and clinical characteristics (Chapter 3); and 3) test the main effects of offspring-perceived latent family environment and the interaction of polygenic risk with family environment on offspring mood diagnoses in offspring at high or low familial risk for BD (Chapter 4).

In our systematic review of the prospective BD high-risk family environment literature, we found that family environment in BD-parented families is heterogeneous. The most consistent finding was lower parent-reported cohesion in families with a BD parent compared with families with no parental psychiatric disorders. Family environment was not different between BD parents and parents with other major psychiatric or physical illnesses. Children's perceptions were infrequently reported, and when they were reported, they often differed from parents' perceptions. Offspring of BD parents had higher prevalence of

psychiatric disorders than offspring of parents without psychiatric disorders, but not compared to offspring of parents with other major disorders. Families in which a child was diagnosed with BD had higher conflict than families without a child with BD.

For Aims 2 and 3, we used data from a multi-site prospective study of adolescents at high or low familial risk for BD in the US and Australia, the Bipolar High-Risk Study. We focused on a subset of offspring, 266 high-risk and 175 controls, who were, on average, just under 17 years of age and well balanced between boys and girls. We developed a person-centered model of latent family environment based on offspring reports on the Conflict Behavior Questionnaire, Family Adaptability and Cohesion Evaluation Scales, and Home Environment Interview for Children. As a preliminary step, we conducted a factor analysis of the Home Environment Interview for Children (Appendix B). Offspring perceived three patterns of family environment, including one large class with essentially 'well-functioning' family environment, characterized by nurturance, flexibility, and low conflict, and two smaller classes characterized by high conflict and low warmth and cohesion, with substantial separation based on either high conflict with the father or very high conflict and rigidity with the mother. Girls were more likely to be in the High Conflict with Mother class. Adjusting for offspring BD, parental BD was not significantly associated with family environment.

Next we tested liability for offspring mood disorders—depression and BD combined ('any MMD'), or broad phenotype BD—based on the main effects of latent family environment and interaction of family environment and polygenic risk. We found that membership in the High Conflict with Mother class was not significantly associated with diagnosis of MMD or BD. Indeed, family environment was not significantly related to offspring diagnosis of MMD as a main effect or in interaction with BD-PRS, although offspring in the conflict classes had higher proportionate risk of MMD than the reference

class. Offspring female sex was significantly associated with offspring diagnosis of any lifetime MMD. Additionally, youth in the high conflict classes were more likely to be diagnosed with BD, though the increased risk was only statistically significant for youth in the High Conflict with Father class. Specifically, membership in the High Conflict with Father class was marginally associated with offspring BD as a main effect, and significantly associated with BD in interaction with BD-PRS. Interestingly, the interaction was negative; among study participants in the High Conflict with Father family environment, increasing BD-PRS was associated with lower risk of BD, and, conversely, lower polygenic risk was associated with higher liability of BD.

Synthesis of Findings

Our review of the literature demonstrated that prospectively measured family conflict is higher in families with a BD parent who also have a BD child compared to those whose children do not have BD (Chang et al., 2001; Du Rocher Schudlich et al., 2008; Ferreira et al., 2013; Romero et al., 2005). Our findings from the Bipolar High-Risk Study are consistent with this literature. Specifically, youth in family environments characterized by low cohesion, low flexibility, and high conflict had higher liability for any MMD or BD, particularly in interaction with genetic risk, compared to youth who perceived their well-functioning family environments as warm, adaptable, and low in conflict. The findings in our review and own research are also consistent with research on youth with BD irrespective of parent diagnosis, which finds higher conflict and lower warmth in the families of youth ill with BD (Birmaher et al., 2014; Geller et al., 2000). High conflict and low warmth, in turn, has been associated with illness recurrence and social impairments in BD youth (Geller et al., 2004; Miklowitz and Johnson, 2009).

Our review further demonstrated support in the extant literature for lower parent-reported family cohesion in the context of parental BD versus no parental psychiatric disorders. In our sample, we found that membership in the High Conflict with Mother class—again, characterized by low warmth and high rigidity in the parent-child relationship and low overall family cohesion and flexibility—was initially associated with parental BD. However, the effect did not remain significant after adjusting for offspring BD. Taken together with the findings regarding higher conflict in families with parental and offspring BD, this result underscores the importance of assessing both children's psychiatric disorders and their perceptions of their family environment when assessing families affected by mood disorders. It also supports transactional models of child development, which emphasize the reflexive nature of parent's characteristics, children's characteristics, and their mutual influence on the parent-child relationship and family dynamics, with consequences for children's outcomes (Sameroff & Fiese, 2000; Schermerhorn & Cummings, 2008).

There were some differences by sex of the offspring and sex of the parent about whom the reporting child perceived high levels of conflict. Offspring female sex was significantly associated with membership in the High Conflict with Mother class and with offspring diagnosis of any lifetime MMD. However, membership in the High Conflict with Mother class was not significantly associated with diagnosis of any MMD or BD. Additionally, although parental BD predicted membership in the High Conflict with Father class in unadjusted models, it was not significantly associated after adjusting for demographic characteristics and offspring mood (none of which predicted membership in the class). Yet, membership in this High Conflict with Father class was significantly associated with offspring BD as a distal outcome accounting for and in interaction with BD-PRS. Regarding the mother-daughter relationship, Tarullo and colleagues (1994) found that adolescent

daughters and mothers were more critical-irritable when mothers met criteria for a major depressive episode in the past month, and noted that adolescent daughters may be more influenced by their mother's emotional state than boys are. It is possible that girls in our sample were more attuned to the mother-child relationship and this salience is reflected in strong class prediction.

Finally, we found a negative interaction between BD-PRS and latent family environment predicting offspring BD. Youth perceiving High Conflict with Father had the highest risk for BD with lower BD-PRS, and decreasing liability as the BD-PRS increases. All but one of the offspring diagnosed with BD had a parent with BD. We found that high-risk offspring affected with BD had lower mean BD-PRS than unaffected high-risk offspring, which was unexpected. Prior research on polygenic risk indicates that higher PRS may be associated with greater liability of developing the disorder. However, as noted by Visscher and Wray (2016), gene effects in a polygenic model do not have to be the same for all individuals, nor must the gene action be strictly additive. The lower BD-PRS among BD-affected high-risk offspring may also be an anomaly, or perhaps point to the role of rare variants not captured in a polygenic score based on GWAS. Recently, Mullins and colleagues (2016) also reported a negative gene-environment interaction conferring risk for mood disorders; specifically, they found that individuals with depression and a history of moderate or severe childhood trauma had lower mean PRS for depression compared to cases with less exposure or controls. With that mind, our findings may support a multifactorial liability threshold model for developing BD (Gottesman & Shelds, 1967; McGue, Gottesman, & Rao, 1983; Visscher & Wray, 2016).

Limitations and Offsetting Strengths

Our findings should be interpreted in the context of certain limitations, while also acknowledging the strengths and contributions to the literature from this project. These have been discussed in detail in preceding chapters.

Sample and design. Persons who volunteer to join a research study may not be representative of all persons experiencing the condition under study. Given our sample characteristics and findings, we believe that our sample represents the source population of families experiencing BD who access medical care, at least near the types of urban academic medical centers that recruited participants, and point to future directions that are relevant to this population. This also points to the need to assess and serve the general population of persons with BD who many be different from those in clinical samples. This analysis was cross-sectional, which prohibits conclusions regarding causality or prediction over time, but the associations are worthy of further inquiry. The Bipolar High-Risk Study offers a large high-risk sample and control group spanning two countries, with well-phenotyped and genotyped participants, and a rich array of psychosocial measures.

Diagnosis. Although the overall sample of offspring was large, international, and well balanced for age and sex, the number of youth diagnosed with mood disorders was relatively small. We used lifetime mood disorder diagnoses for our outcome, which may be subject to recall bias. Lifetime diagnosis may be less proximal to family environment than current symptoms. Additionally, youth may experience symptoms that do not meet criteria for a diagnosis that are nonetheless disruptive to the family, or, conversely, may have a lifetime diagnosis but are functioning harmoniously in the family; the same may be said of parents, although accurate measurement of parent status is not essential due to our analytic approach focusing on children's perceptions irrespective of parent affected status. That said, the youth experienced symptoms to the point of receiving a diagnosis, which indicates a

clinically significant severity worth studying. The diagnoses were made based on consensus of two psychiatrists reviewing child interviews, parent interviews, and medical records. With a mean age of 16.7 years, it is reasonable to assume that, although the diagnostic interviews may be subject to recall error or bias, both parents and children are likely to remember having a relatively recent mood disorder onset, and the circumstances surrounding these diagnoses may impact the family environment.

Family environment. Our measurement model was based on self-reported measures of several domains of family environment: communication/conflict, warmth/cohesion, and adaptability/permissiveness. The offspring reported their perceptions of the parent-child relationship and intrafamily dynamics. Our measurement model did not include offspring perceptions of the interparental relationship. To the extent that the interparental relationship affects both parent-child relationships and the intrafamily dynamics and climate, and children are not party to the full spectrum of the interparental relationship, we believe that our measurement model encompasses the key indicators of offspring-perceived family environment that were measurable (Steinberg, 2001).

Both the CBQ and FACES II were completed based on current environment. For most participants, responses to the HEIC were based on the past year leading up to assessment. Some participants—those who had not lived with their parents in the past year—reported on the last year that they had lived with their parents, which may introduce recall error. Nevertheless, the perceptions of high-risk offspring have been underreported, a gap in the literature that this study addresses by developing a model of child-perceived family environment. To the extent that there were missing data, full information maximum likelihood was used, comparable to use of multiple imputation, such that we were able to use

information from all participants in constructing our measurement model (Schafer & Graham, 2002).

By taking a latent variable approach to modeling family environment, we accounted for the covarying nature of the constructs, the importance of each being reflected in the extant literature. We identified unobserved subpopulations of youth experience based on their perceptions, while accounting for challenges with measurement error inherent in psychosocial constructs. Moreover, using person-centered models uncovered different types of perceived family environments, which were linked to offspring BD, and that were not apparent if comparing mean scores between high-risk and control offspring.

Genetic risk. Our measure of genetic burden for BD was a BD-PRS derived from wave 1 Psychiatric Genomics Consortium data on BD. Common variants have been estimated to explain one-quarter of the variance in liability for BD (Lee et al., 2013). Our score is based on a very small number of common genetic variants. By definition, it did not include rare variants or other genetic risk mechanisms that may be associated with BD. Nonetheless, we found that inclusion of the BD-PRS improved our model linking family environment to offspring BD, albeit in an interesting and unexpected way.

Implications and Future Directions

Family environment characterized by High Conflict with Father was significantly associated with offspring BD; it is important to study fathers, not just mothers. An additional benefit of assessing children's perceptions of their family environment is that it is not dependent on who brings them to the clinic. Additionally, because girls were more likely to be in the High Conflict with Mother family environment and were more likely to have MMD, and because of separation of the conflict classes based on parent sex, in the future we

will test whether sex of the parent with BD parent predicts family environment differently than parental BD generally.

Given that High Conflict with Father is associated with offspring BD, it will be important to longitudinally examine whether changes to key domains of offspring-perceived family environment (e.g., parent-child conflict, family flexibility and cohesion) predict changes in offspring psychiatric symptoms or functioning. For example, work by Miklowitz has shown reduction in expressed emotion was associated with reduced relapse (Miklowitz & Johnson, 2009). In youth at high familial risk for BD, we will test whether intervening on key family environment domains can prevent impaired psychosocial functioning. The health of parent-child relationships and family climate could be maximized to promote wellness in both BD parents and their children.

Lastly, in the context of complex disorders such as BD, it is ideal to include both environmental and genetic variables. The genetic etiology of BD is under study, and has been for decades. Collaboration of the Psychiatric Genomics Consortium should result in progress in this area.

Conclusion

Both in our own work and the extant literature, the family environment is heterogeneous among youth both at high and low familial risk for BD. There is not one 'signature' family environment associated with parental BD. However, high-risk youth experiencing a family environment that is high in conflict and low in warmth and flexibility are more likely to themselves have BD. Researchers and clinicians working with BD high-risk families may have the opportunity to reduce parental and child morbidity by attending to family cohesion and communication. To fully understand how family environment is linked to adolescent mental health in the BD high-risk context, it is important to assess the

adolescents directly. Using those assessments may offer insight into etiology or clinical implications not afforded by assessment of group means based on parental affected status alone. Understanding the genetics of intergenerational transmission of BD may be facilitated by taking into account environmental influences, such as the family environment, which impacts the full spectrum of child development including mental health.

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APPENDIX A. Search Strings and Number of Publications through September 2015, by Database

Database	Search Strings	Number of documents September 2, 2015
CINAHL	DE "Bipolar Disorder" or “bipolar disorder” or “bipolar” and "bipolar parents" or "parents with bipolar" or Predisposition or DE "Susceptibility (Disorders)" or DE "At Risk Populations" or offspring or DE "Biological Family" or DE "Predisposition" or DE "Offspring" or "high risk" or "at risk" or "at-risk" or "first-degree relative" or "biological family"	1494
Embase	'genetic predisposition'/exp OR 'genetic predisposition' OR bipolar NEAR/3 parents OR 'high risk population'/exp OR 'high risk population' OR 'genetic risk'/exp OR 'genetic risk' OR 'progeny'/exp OR progeny OR 'progeny'/syn AND ('bipolar disorder'/exp OR 'bipolar')	3434
PsycINFO	DE "Bipolar Disorder" or “bipolar disorder” or “bipolar” and "bipolar parents" or "parents with bipolar" or Predisposition or DE "Susceptibility (Disorders)" or DE "At Risk Populations" or offspring or DE "Biological Family" or DE "Predisposition" or DE "Offspring" or "high risk" or "at risk" or "at-risk" or "first-degree relative" or "biological family"	4915
PubMed	"Child of Impaired Parents"[Mesh] OR "Genetic Predisposition to Disease"[MeSH] OR "high risk offspring"[All Fields] OR "bipolar parents"[All Fields] OR "at risk"[All Fields] OR "at-risk"[All Fields] OR offspring[All Fields] OR "high risk"[All Fields] OR "high-risk"[All Fields] OR "familial risk"[All Fields] OR "first-degree relative"[All Fields] AND bipolar[All Fields] AND "bipolar disorder"[MeSH Terms]	2095

APPENDIX B: Offspring-perceived parental warmth and permissiveness in the bipolar high-risk context

Manuscript under revision with collaborators in the Bipolar High-Risk Study

ABSTRACT

The family environment is central to children's development. It has been hypothesized that family environment may be different in families with a parent with bipolar disorder (BD), which may influence risk processes in their offspring. This study identifies factors related to parent-child relationships and correlates of those factors, based on child reports on the Home Environment Interview for Children (HEIC) in a US and Australian sample of 441 offspring (mean age 16.7 years) of parents with BD (n=266) or no psychiatric disorder (n=175). Using complex exploratory factor analysis, a two-factor model fitted the data best, with factors we have designated as "offspring-perceived maternal warm engagement" and "offspring-perceived maternal permissiveness". For the full sample, after accounting for offspring lifetime diagnosis of a major mood disorder, parental BD was not independently associated with either offspring-perceived parent-child relationship factor. Female offspring, however, reported lower maternal warm engagement (p=0.050), adjusted for age, race, country of residence, parental BD, and offspring mood disorder diagnosis. Offspring major mood disorder was marginally associated with perceived maternal warm engagement and permissiveness in unadjusted analyses only. The findings from this study, using a large, international sample, offer research and clinical teams a set of brief questions regarding essential components of parent-child relationships, in the context of BD high-risk families, and point to the importance of children's own mood disorders in their perceptions of those relationships.

Key Words: High-risk, bipolar disorder, parent-child relations, factor analysis, mood disorders

Bipolar disorder (BD) is a severe, persistent, and impairing mood disorder affecting approximately 1–2% of the population (Kessler, Merikangas, & Wang, 2007; Merikangas et al., 2011). It is associated with psychiatric comorbidity, chronic physical disease, and premature mortality (Baldessarini, Pompili, & Tondo, 2006; Crump, Sundquist, Winkleby, & Sundquist, 2013; Merikangas et al., 2011; Walker, McGee, & Druss, 2015). Offspring of BD parents are at 8–10 fold increased risk of developing BD (Craddock & Sklar, 2013) and increased risk of developing mood and psychiatric disorders in general (Hodgins, Faucher, Zarac, & Ellenbogen, 2002; Rasic, Hajek, Alda, & Uher, 2014) compared to offspring of parents without psychiatric disorders. While heritability estimates range from 63–93%, non-genetic influences in the BD high-risk context remain an important area of study (Alloy et al., 2005; Craddock & Sklar, 2013). Among these influences, the family environment children experience is particularly critical to their development. It has been hypothesized that parental BD is associated with differences in family environment, with implications for offspring psychiatric risk.

A healthy family environment provides for children's emotional security, physical safety and wellbeing, and social integration, ultimately facilitating children's self-regulation and acquisition of behaviors that allow them to maintain wellbeing independent of caregivers (Bowlby, 1951; Repetti, Taylor, & Seeman, 2002). Key components of positive caregiving involve warmth, nurturance, and acceptance, as well as structure and effective discipline (Basic Behavioral Science Task Force of the National Advisory Mental Health Council [NAMHC], 1996; Steinberg, 2001). In contrast, families characterized by conflict and aggression, and cold, unsupportive, neglectful relationships are considered especially risky to child development (Repetti et al., 2002). These characteristics may create vulnerabilities in offspring, and interact with preexisting vulnerabilities (e.g., genetic risk), to put children at

risk in both the short- and long-term for problems in emotional regulation, cognitive development, psychosocial functioning, and biological health (Johnson, Riley, Granger, & Riis, 2013; Repetti et al., 2002).

Although there is a trend in the literature toward lower parent-reported cohesion among BD parents compared to parents without psychiatric disorders (Ferreira et al., 2013, Park et al., 2015, Romero, DelBello, Soutullo, Stanford, & Strakowski, 2005) and population controls (Chang, Blasey, Ketter, & Steiner, 2001; Romero et al., 2005), there have been studies in which parent-reported cohesion and supportiveness were not significantly different between parents with BD or no psychiatric disorders (Barron et al., 2014; Ellenbogen & Hodgins, 2009; Vance, Jones, Espie, Tai, & Bentall, 2008). Children's perspectives are less commonly reported, but when they are, frequently show no significant association between parent diagnostic status and family environment, including child-reported cohesion (Vance et al., 2008) and attachment (Doucette, Horrocks, Grof, Keown-Stoneman, & Duffy, 2013), and observed levels of child engagement, critical/irritable behavior, and comfortable/happy interaction with mothers (Tarullo, DeMulder, Martinez, & Radke-Yarrow, 1994). Several studies show that BD parents are not significantly different from parents without psychiatric disorders in areas of family system maintenance, including parent-reported flexibility (Park et al., 2015), structure (Ellenbogen & Hodgins, 2009), and organization and control (Romero et al. 2005). Other BD parents report lower control (Ellenbogen & Hodgins, 2009) or higher control and lower organization (Ferreira et al. 2013) compared to parents without psychiatric history. Children's perceptions of family system maintenance were not obtained in those studies.

Understanding the child's perspective is important. Caregiver warmth and discipline influence children's perceptions, which, in turn, influence the impact of caregiving (Basic

Behavioral Science Task Force of the NAMHC, 1996). For example, higher child-perceived parental neglect and rejection, retrospectively-reported, has been associated with increased risk of mood disorders in offspring of parents with BD (Doucette et al., 2016; Kemner, Mesman, Nolen, Eijckemans, & Hillegers, 2015). Correspondingly, children's positive views of maternal parenting behaviors and warmth have been found to be associated with better offspring diagnostic outcomes (Conrad & Hammen, 1993; Reichart et al., 2007). Additionally, children may report experiences, symptoms, or observations related to their home environment that may go unreported by parents (Reich & Earls, 1987). And, as shown in the BD high-risk literature, child reports are understudied relative to parent reports.

The Home Environment Interview for Children (HEIC) is a semi-structured interview for children regarding the child's home and social environment (Reich, Earls, & Powell, 1988). The HEIC has been used to study offspring of parents with versus without alcohol use disorder (Reich et al., 1988) and offspring of parents with versus without BD (Petti et al., 2004). Petti and colleagues (2004) found that scores on discipline were not significantly different between families with versus without a parent with BD, based on both parent- and child-report, although parents reported higher discipline in families with a child diagnosed with BD. However, there are no established methods on interpreting or quantifying the HEIC. A first step to using the information contained in the HEIC in quantitative analyses is theory-informed data reduction. Therefore, our preliminary aim was to identify the factor structure of items from the HEIC related to the parent-child relationship, in a sample of adolescent offspring of parents with BD and offspring of parents with no psychiatric history. Our primary aim was to test for associations between the offspring-perceived parent-child relationship factors and possible demographic and clinical

correlates of the factors, including age, sex, self-reported race, country of residence, parental BD, and offspring major mood disorder diagnosis.

Method

Participants and Procedure

This study sample consists of participants aged 12–21 years when recruited for a prospective study of adolescents at high risk for familial BD, which took place from 2006–2013 in the United States (US) and Australia. Institutional Review Boards approved the research at Indiana University, University of Michigan, Washington University in St. Louis, and Johns Hopkins University, and the Human Research Ethics Committee approved the research at the University of New South Wales. Informed consent (or assent with parental consent for participants under age 18 in the US and under 17 in Australia) was obtained for all participants. Additional details about study procedures are described by Nurnberger and colleagues (2011) and Perich and colleagues (2015).

Offspring at high-risk for familial BD ("high-risk [HR] offspring") were identified from probands with BD type I (BD-I), BD type II (BD-II), or schizoaffective disorder bipolar type in the NIMH Genetics Initiative bipolar sample and other genetics studies, specialty clinics, and publicity. Control participants were recruited from general practitioners, motor vehicle records, and advertising—excluding individuals with a parent or sibling with BD-I, BD-II, recurrent Major Depressive Disorder, schizoaffective disorder, schizophrenia, recurrent substance abuse, or any psychiatric hospitalizations, or whose parent had a first-degree relative with a history of psychosis or hospitalization for a mood disorder. Parent diagnoses or lack thereof were confirmed using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). The primary study included siblings and second-degree relatives of BD probands, however the current analysis focuses on offspring

of parents with BD versus offspring of parents with no psychiatric history. In some families, multiple offspring in the target age range participated.

Assessments

Offspring Demographic and Clinical Characteristics. Offspring were interviewed by extensively trained raters using the *Schedule for Affective Disorders and Schizophrenia for School-Aged Children, bipolar disorder version* (K-SADS; for details, see Nurnberger et al., 2011). Offspring lifetime DSM-IV psychiatric disorders were confirmed by best estimate consensus of two study psychiatrists who reviewed direct interviews of offspring, interviews with parents, and medical history records. Best estimate consensus diagnoses were available for 91% of the offspring. A dichotomous variable for lifetime diagnosis of a major mood disorder at study entry included: BD-I, schizoaffective disorder bipolar type, BD-II with recurrent depression, BD not otherwise specified (BD-NOS), or recurrent Major Depression. Interrater reliability (Kappa) for diagnosis of a major mood disorder was .82 (Nurnberger et al., 2011).

Demographics for the sample including offspring age, sex (binary Male or Female), and self-reported race (binary White or non-White, based on reduction of US census categories) were obtained during the K-SADS interview. Country of residence (Australian compared to US) was based on the study site location of the offspring. High-risk (HR) group status (having a parent with BD [HR offspring / 'parental BD'] versus parents with no psychiatric disorders [Control offspring]) was included as a key clinical correlate. There were no missing data on parental BD or demographics. Sample statistics and variance inflation factors (VIFs) were calculated using Stata Version 14 (StataCorp, 2015). We checked for multi-collinearity of covariates by calculating VIFs and found that all modeled covariates were close to 1, indicating no collinearity.

Family/Home Environment. The *HEIC* is modeled after Robins' Home Environment Interview (Reich et al., 1988, Robins et al., 1985). The HEIC captures information about the child's home and social environment, including relationships with parents and peers, home conflicts and stress, and dysfunctional behaviors (Reich et al., 1988), as reported by the child. Sample question stems ask *"Does your (M/F/O) ever go out of his/her way to say you did a good job when you do something well?"* and "*Do you have to let your family or someone else know where you are whenever you go somewhere?*" with many questions including sub-questions with separate responses regarding the child's biological mother and father. Mother-child agreement and test-retest reliability have been reported to be good, although the exact psychometrics are unpublished (data cited in Reich et al., 1988). For most participants, responses to the HEIC were based on the past year (i.e., the year leading up to assessment) relationship with biological parents(s). Some participants—those who had not lived with their parents in the past year—reported on the last year that they had lived with their parents.

Statistical Analysis

The goal of this study was to identify the factor structure of the HEIC and its correlates in a sample of offspring of parents with BD or no psychiatric disorder.

Preliminary aim: Identify factor structure of HEIC. We conducted complex exploratory factor analysis (EFA) using Mplus version 7.4 (Muthén & Muthén, 1998-2012) to identify the factor structure of the HEIC, accounting for clustering of siblings within families. We did not control for composition of the household (i.e., who was living in the home). Factor analysis is a variable-centered approach appropriate for research questions that assess differences in amount or frequency of latent factors, as opposed to person-

centered approaches that assess differences in patterns of co-occurring behaviors among people. All HEIC data are categorical.

Item selection. The HEIC includes 41 questions, some of which are multi-part. We sought to identify question stems of direct relevance to the parent-child relationship, excluding 19 questions for the following reasons: administrative (n=3; e.g., "Has the child had a relationship with his/her biological parents in the past year?"), sibling-focused (n=7), inter-parental relationship (n=1 [multipart]; e.g., "Do your parents fight when you are not around?"), parent social activities not directly related to child (n=3; e.g., "Does your [parent] have some friends s/he sees from time to time?"), peer socialization not directly involving parents (n=4; e.g., "Do you have any difficulty making friends?"), and redundancy (n=1). Despite the importance of the inter-parental relationship on child wellbeing, we did not include questions in the measurement model that were specific to households with both biological parents living together, in an effort to maximize internal validity and generalizability and minimize the extent of missing data. Half of all children under 18 in the U.S. live in a single-parent family at some point (Basic Behavioral Science Task Force of the NAMHC 1996), and persons with BD are 80% more likely to be separated, divorced, or widowed than married or cohabitating (Grant et al., 2005). That left a pool of 22 questions directly addressing parent-child relationship/home environment.

From the pool of 22 questions, we excluded 4 with very low variation in the distribution of responses. For example, 1% of the sample answered, no, they do not get to go to their friends' homes to visit; this item was excluded because such low variation in response is uninformative for factor identification. This left us with 18 out of the 22 question stems, comprised of 36 items to begin the EFA process. (Two had a part A and

part B, and 15 asked the question separately regarding the child's mother and father, which led to a total of 36 items for testing.)

Model fit. To identify which factor model best fitted the data, we examined the scree plot of eigenvalues and compared goodness-of-fit indices. Goodness-of-fit indices include the chi-square statistic, root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker-Lewis index (TLI), and standardized root mean square residual (SRMR) (Hu & Bentler, 1999). Mplus makes use of all available data to estimate the model using full information maximum likelihood (Schafer & Graham, 2002). Geomin, an oblique rotation used in Mplus that performs better than promax, allows for factors to be correlated, which is appropriate for psychosocial constructs and factor analysis (Asparouhov & Muthén, 2009; Muthén & Muthén, 1998-2012; Muthén & Muthén, 1999-2016).

Primary aim: Correlates of family environment. We tested possible correlates of the factors from the best-fitting factor model by conducting complex factor analysis with covariates in Mplus; this approach is an exploratory structural equation model (ESEM; Asparouhov & Muthén, 2009; Marsh, Morin, Parker, & Kaur, 2014) that accounts for clustering of siblings within families. The approach involves a series of linear regressions of continuous factors on independent variables. We tested age (both continuous and dichotomized into ages 12-19 and 20-22 based on the World Health Organization's definition of adolescence as ages 10-19 years [2017]), sex, self-reported race, country of residence, parental BD (i.e., HR versus control offspring), and offspring lifetime major mood disorder diagnosis as possible correlates of each of the factors in both unadjusted (Model 1) and adjusted (Model 2) models. For Model 2, we tested a fully adjusted model with all demographic and clinical characteristics, such that the effect estimate of any given

characteristic (e.g., sex) was adjusted for all other covariates (age, race, country of residence, parental BD, and offspring diagnosis of a lifetime major mood disorder).

Results

Sample Characteristics

The study sample consisted of 441 participants: 266 offspring of a parent with BD (HR) and 175 offspring of parents without psychiatric disorder (controls). Participants ranged from 12 to 22 years old at time of assessment, with a mean age of 16.7 years. High-risk and control offspring did not differ significantly on age, sex, self-reported race/ethnicity, or country of residence. Major mood disorders were approximately 7.5 times as likely in HR versus control offspring. Sample demographics are detailed in Table 1. **TABLE ONE HERE**

Preliminary aim: Factor structure of the HEIC.

Item selection and model fit. A well-identified factor should have at least 3 indicators. When conducting EFA on 36 items we sought a solution with no more than 12 factors. Comparing fit indices and observing the scree plot of eigenvalues, we found that the chi-square statistic was still highly significant ($p<0.001$) for models with greater than 12 factors (data not shown). Since many items were duplicative (separate responses for father and mother), we next conducted EFAs separately for child responses concerning Mother and Father.

For the EFA focused on Mothers, we started with 20 indicators and found that although a two-factor solution fitted the data, 4 items did not load significantly to either factor, so we removed them and fit models for 1 through 5 factors based on 16 indicators. Ultimately we found a two-factor model best fitted the data, based on RMSEA<0.05, CFI and TLI>0.95, and SRMR<0.08 (Hu & Bentler, 1999), with the chi-square test statistic

indicating that a three-factor solution did not fit better than two factors (see Table 2). Two factors were above the 'elbow' of the scree plot (DeVellis, 2012; figure not shown). **TABLE TWO HERE**

We followed the same procedure for an EFA with Father-focused questions. We started with the same 20 indicators used for the Mother-focused EFA. Although a four-factor solution best fitted the data, 2 items did not load to any factor, so we removed them and tested models for 1 through 5 factors based on 18 indicators. Again, a four-factor model best fitted the data, but only 2 indicators loaded to the fourth factor, which is not sufficient for a well-characterized factor. Thus, an identifiable model did not fit the data. Further scale development, outside the scope of this study, may enrich assessment of the Father-child relationship. Moreover, research has shown that the majority of childrearing is still performed by mothers (Basic Behavioral Science Task Force of the NAMHC, 1996; Parker & Wang, 2013). Therefore, the remainder of the analysis focused on 2 factors related to Mother-child relationships captured by 16 indicators from the HEIC (Table 3).

Characterizing the factor solution. Item loadings on each of the two mother-child relationship factors are shown in Table 3. Response distributions (including missing data) are available from the first author upon request. Each item has a loading for both factors, but gets assigned to the factor for which its loading is largest. A negative loading indicates that responses coded in the dataset to have lower numbers (e.g., 0 for "no" and 1 for "yes" in a dichotomous variable) 'load' onto the factor. For example, the item asking "*Would you say that your Mother spends time with you more than most parents, [the] same as most parents, or less than most parents?*" loaded to factor 1 with a value of -0.652. That means that a mother spending *more* time with her child than most parents do, as judged by the child, loads to factor 1.

Each factor is labeled and described based on the set of items that loaded to it, within the context of relevant research. Factor 1, which we have labeled "Warm Engagement," includes items related to cohesion (supportiveness, spending time together, affection, closeness) and positivity of maternal temperament (mother is happy, fair). Factor 2, which we have labeled "Permissiveness," captures elements of a laissez-faire approach to parenting, relatively low on irritability and discipline/firmness (mother does not criticize/correct child, and child gets into trouble less than most kids). A few items related to maternal warmth and closeness also loaded positively to Factor 2, but predominantly to Factor 1. **TABLE 3 HERE**

Primary aim: Correlates of family environment factors.

Results of our primary study objective testing relationships between the 3 HEIC factors and demographics (age, sex, self-reported race/ethnicity, country of residence), parental BD (high-risk group status), and offspring mood disorder diagnosis are shown in Table 4. First, we tested unadjusted relationships between factors and each individual covariate. Lower offspring-perceived maternal warm engagement was associated with female offspring sex (i.e., daughters; beta [b]=-0.360, Standard Error [S.E.]= 0.112, p=0.001) and parental BD (b=-0.298, S.E.=0.142, p=0.036), and marginally associated with offspring mood disorder diagnosis (b=-0.330, S.E.=0.179, p=0.065). Lower offspring-perceived maternal permissiveness was marginally associated with offspring mood disorder diagnosis (b=-0.298, S.E.=0.163, p=0.068).

Lastly, we tested a model with both clinical (parental BD, offspring mood disorder) and demographic (age, race, sex, country) characteristics as possible correlates of parent-child relationship factors, with each covariate's effect on the factor adjusted for the effect of all other covariates in the model (Model 2). Upon adjusting for both parental BD and

offspring mood disorder, only offspring female sex (b=-0.243, S.E.=0.124, p=0.050) was associated with lower offspring-perceived parental warm engagement. In other words, when accounting for the effect of offspring diagnosis of a major mood disorder, parental BD no longer associated with warm engagement (as it did in both crude models and a model adjusted for demographics only: b=-0.307, S.E.=0.141, p=0.030, not shown). Offspring-perceived maternal permissiveness was not associated with demographic or clinical characteristics in the fully adjusted model. Using dichotomized age rather than continuous, the association between offspring female sex and lower perceived warm engagement strengthened (b=-0.242, S.E.=0.122, p=0.047). Age (whether measured continuously or categorically), self-reported race, and country of residence did not associate with either factor in any models. **TABLE FOUR HERE**

Discussion

In a sample of adolescent and emerging adult offspring of parents with BD or no psychiatric disorders who completed the HEIC, we found that a two-factor model best fitted the data, representing offspring perceptions of maternal warmth/positive affect and cohesion/engagement ("warm engagement") and a laissez-faire approach to discipline and relationships ("permissiveness"). In a model fully adjusted for parental BD, offspring mood disorder diagnosis, age, race, sex, and country of residence, we found that girls perceived significantly lower maternal warm engagement. Parental BD was associated with lower offspring-perceived maternal warm engagement in crude models and adjusted for demographics, but after adjusting for offspring major mood disorder diagnoses, parental BD no longer associated with warm engagement. Although offspring mood disorder was marginally associated with lower perceived warm engagement and lower perceived permissiveness in unadjusted models, after adjusting for the effects of demographic

characteristics and parental BD, offspring mood disorder was not associated with either factor.

Children's own mental health conditions are an important component to understanding family environment, which is in line with transactional theories of child development and family systems (Sameroff & Fiese, 2000; Schermerhorn & Cummings, 2008). We found that offspring mood disorder was not independently associated with offspring-perceived maternal warm engagement or permissiveness after accounting for parental BD and demographic characteristics. Other BD high-risk studies have tested for an association between offspring psychiatric disorder and family environment. Doing within-group comparisons of offspring of BD parents—thus, holding 'parental BD' constant—offspring psychiatric disorders were not associated with any parent-reported subscales on the Family Environment Scale (Chang et al., 2001; Romero et al., 2005). In contrast, other studies have found that the families in which offspring were themselves affected with BD scored higher on parent-reported control (Ferreira et al., 2013), conflict (Du Rocher Schudlich et al., 2008), and parent-reported discipline (Petti et al., 2004) than the families in which the BD offspring did not themselves have a diagnosis of BD. We did not identify factors specific to control or conflict, and our variable for offspring diagnosis of major mood disorder included both BD and recurrent major depression, which may explain our findings that differ from those latter studies. Additionally, we focused on child-reported family environment, rather than parent reports.

In several BD high-risk studies, offspring perceptions of family environment did not differ significantly by parent diagnosis when measuring: behavioral observations of communication affect and engagement with mothers (Tarullo et al., 1994); offspring-reported expressiveness, conflict, cohesion, and judgments of parental negative

communication attribution style (Vance et al., 2008); and offspring-perceived attachment with mothers or fathers, a construct including the degree of mutual trust, quality of communication, and extent of alienation and anger (Doucette et al., 2013). Our finding of no association between parental BD and offspring-perceived family environment after adjusting for offspring mood disorders and demographics agrees with these studies. The parent-child relationship factors derived from the HEIC may have different correlates in different samples. It therefore remains important to measure constructs related to both nurturance and family system maintenance.

The temporal relationships of family environment and offspring psychiatric functioning are complex to disentangle, and not possible in a cross-sectional analysis such as this. However, offspring diagnoses are likely to be downstream in development compared to demographic characteristics and parental psychiatric disorder, which is why we tested correlates of offspring-perceived parent-child relationship factors in separate models with and without offspring mood disorders.

Two classic studies that focused on maternal-child family environment in high-risk families include the UCLA Family Stress Project and the NIMH Childrearing Study. Using a sample drawn from the UCLA Family Stress project, Gordon and colleagues (1989) studied 58 mother-child dyads in which the mother had BD, unipolar depression, a chronic medical illness, or no psychiatric history, and the offspring were aged 8–16 years. They assessed family environment using direct behavioral observation and coding of two core dimensions of family interaction—task productivity and affective quality. Mothers with BD scored higher than depressed mothers on task productive verbal behavior and lower on off-task and negative verbal behavior, but not differently from well mothers. Mothers with BD were not different from depressed mothers on positive statements. When comparing prevalence of

offspring psychiatric diagnoses, offspring of BD and depressed mothers and offspring of BD and chronically medically ill mothers were not significantly different, though offspring of BD parents were over twice as likely to receive a diagnosis compared to offspring of well mothers.

Tarullo and colleagues (1994) studied 83 mothers with BD, unipolar depression, or no psychiatric history, and each of their two children, who were participating in the longitudinal NIMH Childrearing Study. In contrast to the behavioral observation analysis in the UCLA Family Stress project (Burge & Hammen, 1991; Gordon et al., 1989), which coded maternal interaction, Tarullo and colleagues (1994) coded both maternal and child behaviors and factor analyzed them separately. In mothers' interactions with their adolescent children (aged 12–16 years) there were no main effects for maternal diagnosis on any of the mother or child factors. Additionally, maternal critical/irritable behavior with preadolescents (aged 8–11) was not significantly different by maternal diagnosis, and preadolescents' engagement and critical/irritable behavior were not significantly different by maternal diagnosis. However, maternal engagement with preadolescents was lower among BD mothers than among well mothers, and preadolescent children's comfort/happiness was greater with BD and well mothers than with unipolar depressed mothers. When they looked at the relationship of children's diagnosis on family environment, they observed that preadolescent children with no psychiatric problems in the past year were more engaged and less critical and irritable with mothers than were the preadolescents with a past-year psychiatric problem, and that adolescent children with no psychiatric problems in the past year were less comfortable and happy in their interactions with BD mothers versus depressed or well mothers (Tarullo et al. 1994).

We found a significant association between offspring female sex and lower offspring-perceived maternal warm engagement, although this relationship attenuated when accounting for offspring diagnosis of a mood disorder. Burge and Hammen (1991), reporting on an overlapping sample as Gordon and colleagues (1989), did not find any effect for the sex of the child on maternal family environment differences. However, Tarullo and colleagues (1994) did find that interactions between adolescent daughters and mothers were more critical when mothers met criteria for a major depressive episode in the past month, although the authors point to the need for cautious interpretation due to sample size. They also found that mother and child critical and irritable behavior was positively correlated for preadolescent and adolescent boys but not girls, and that mothers were more engaged with preadolescent boys than girls. Tarullo and colleagues (1994, p. 36) note that into adolescence daughters tend to identify with and maintain emotional involvement with their mothers, and may be more influenced by their mother's emotional state. With a mean age of just under 17 years in our sample, it is possible that the adolescent girls responding to our interview questions were more attuned to maternal affect than were the boys.

Limitations: The process of reporting on lifetime psychiatric symptoms may be subject to recall bias, however, a) this is a relatively young sample with onset in early adolescence; b) the version of the K-SADS developed for this study defined specific episodes in time and duration before assessing symptoms, and included questions targeting each DSM-IV criterion with anchor points; and c) the best estimate final diagnoses were made using all available information from multiple informants and medical records. Offspring were just under the age of peak onset for BD, although high-risk and clinical samples frequently have early onset of mood disorders. Participants who had not lived with their parents in the past year would have reported on the last year that they did live with

their parents, which may introduce recall bias. Finally, although the HEIC asks many of the questions individually for mothers, fathers, and other parent-like figures in a child's life, the responses to questions about fathers did not produce a well-identified model, so we analyzed offspring perceptions of the mother-child relationship.

Children's relationships with their parents and the home life surrounding those relationships have the potential to support or detract from healthy mental, physical, behavioral, and socioemotional development (Bretherton, 1992; Cummings & Davies, 2010; Grych & Fincham, 1990; Johnson et al., 2013; Repetti et al., 2002; Robin & Foster, 1989). It is important to measure children's perceptions of those relationship, for it is their perceptions of emotional climate and experiences, not just events themselves, that may be linked to their adjustment (Cummings & Davies, 2010; Grych & Fincham, 1990). For example, Grych and Fincham (1990) point to the potential of a warm, supportive family environment serving as a protective factor for children against stressors such as conflict by enhancing children's perception of emotional security. Accordingly, a contribution of this study is the focus on offspring perceptions, using a large international sample, while accounting for both child and parent psychopathology in our models.

Additionally, there was no established approach to the quantitative analysis of the HEIC, a semi-structured interview. We identified two key constructs pertaining to parent-child relations—essentially, warmth and firmness—from a set of 16 questions. Steinberg argues that the benefits of authoritative parenting during adolescence (warmth, firmness, psychological automony granting) cross culture and context (Steinberg, 2001). Items and factors drawn out by this study agree with decades of research supporting the central importance of parental warmth and firmness, and offer research and clinical teams a brief set

of questions that highlight children's perceptions of parent-child relationships, which may be especially important in this high-risk population.

We link offspring perceptions of lower parental warm engagement to female sex of the reporting offspring. An interesting finding is that while parental BD and offspring mood disorder were initially associated with lower perceived parental warm engagement when tested separately, their contributions were found to not independently associate with warm engagement in a model accounting for their joint effect. Indeed, after adjusting for offspring mood disorder, parental BD was not independently associated with either factor. Psychological functioning of children is both a contributor to family relationships and climate and an outcome of it, pointing to the importance of targeting upstream risk processes in research and preventive efforts. Families affected by mood disorders may experience differences in family environment compared to families in which the parents do not have psychiatric disorder, particularly if both parents and children are affected, and these differences must be interpreted through the lens of cultural sensitivity and developmental trajectories. Given the enduring effects of family relationships on child development, we emphasize the importance of assessing family context when studying or treating youth.

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Table B.1. Demographic and clinical characteristics of high-risk and control offspring

	Total Sample (n=441)	High-Risk (n=266)	Controls (n=175)	p-value[a]
Age, mean years ± SD	16.73 ± 2.85	16.59 ± 2.84	16.95 ± 2.87	0.202
Sex, n (%)				0.858
Male	227 (51.47)	136 (51.13)	91 (52.00)	
Female	214 (48.53)	130 (48.87)	84 (48.00)	
Race, n (%)				0.063
White	393 (89.12)	243 (91.35)	150 (85.71)	
Non-White	48 (10.88)	23 (8.65)	25 (14.29)	
Country, n (%)				0.830
U.S.	320 (72.56)	194 (72.93)	126 (72.00)	
Australia	121 (27.44)	72 (27.07)	49 (28.00)	
Major Mood Disorder, n (%)	(n=402) 54 (13.43)	(n=245) 50 (20.41)	(n=157) 4 (2.55)	<0.001

Notes: Percentages are within column. SD: Standard deviation.

[a] Unadjusted chi-square tests for categorical independent covariates and t-tests for continuous independent covariates

Table B.2. Fit statistics for factor analyses of Home Environment Interview for Children

J Factors	# Free Parameters	Chi-Square p-value	RMSEA	CFI	TLI	SRMR
1 Factor	16	0.0000	0.087	0.735	0.694	0.125
2 Factors	31	0.0018	0.034	0.966	0.955	0.062
3 Factors	45	0.0546	0.025	0.984	0.975	0.049
4 Factors	58	0.1462	0.021	0.991	0.983	0.041
5 Factors	70	0.3369	0.013	0.997	0.993	0.034

Notes: CFI: Comparative Fit Index; RMSEA: Root Mean Square Error Of Approximation; SRMR: Standardized Root Mean Square Residual; TLI: Tucker-Lewis Index

Table B.3. Factor Loadings for Exploratory Factor Analysis of the HEIC

Item	F1 Loading	F2 Loading
Y1B. Would you say that your mother spends time with you [more/same/less] than most parents?	**-0.652***	-0.143*
Y2A. Do you and your mother ever talk about the news or what's going on in the world?	**0.637***	-0.069
Y2B. Do you and your mother spend time talking about other things, like movies, your friends, or anything else?	**0.820***	-0.100
Y4A. Does your mother give you hugs or kisses to show that she cares about you?	**0.744***	-0.016
Y5A. Do you feel like your mother criticizes you or tells you that what you're doing is wrong?	-0.174*	**-0.497***
Y6A. Does your mother ever upset you by teasing you in a mean way or saying things that hurt your feelings?	**-0.406***	-0.317*
Y7A. Does your mother ever go out of her way to say you did a good job when you do something well? For example, when you get a good grade in school, does she tell you something nice about it or give you a reward?	**0.638***	0.040
Y8A. When you have problems or are worried about something, do you talk to mother?	**0.801***	-0.017
Z1A. When you do something that your mother thinks is wrong, does she yell or fuss at you [more/same/less] than most parents?	-0.046	**0.689***

Z2. Sometimes when kids do something wrong, their parents ground them – that is, not allow them to do something they want to do. Does your mother ground you [more/same/less] than most kids?	-0.057	**0.610***
Z3. Do you get into trouble with your mother [more/ same/less] than most kids?	0.003	**0.716***
Z4A. In your family, is your mother generally [yes, fair/no, too easy/no, too hard/does not scold or punish] in scolding or punishing (you/the kids)?	**-0.485***	0.081
AA4A. When you are in an activity like a game, a play, or a concert at school, does your mother usually attend?	**0.493***	0.034
AA6A. Would you say that your mother is a pretty happy person? (Interview instructs, "IF PARENTS OBVIOUSLY HAVE A TROUBLED LIFE, SAY "In spite of all their difficulties…"")	**0.595***	0.422*
AA7B. Do you feel very close to your mother?	**0.889***	0.210*
AA9. Everyone gets irritable and crabby some of the time, but some people seem to be irritable and crabby most of the time. Is your mother [more/same/less] fussy and crabby than most parents?	0.379*	**0.554***

Note: Loadings with an asterisk are significant at the $p<0.05$ level, and are bolded under their assigned factor (see column headings for loadings to F1 and F2).

Table B.4. Demographic and Clinical Correlates of HEIC Factors

	Factor 1 (Warm Engagement)			Factor 2 (Permissiveness)		
	Est.	SE	p-value	Est.	SE	p-value
Unadjusted (Model 1)						
Age (continuous)	-0.010	0.022	0.656	-0.016	0.021	0.440
Twenties (20-22 vs. 12-19 years)	0.030	0.142	0.831	0.028	0.149	0.853
Non-White Race (vs. White)	-0.338	0.287	0.239	-0.252	0.208	0.225
Female (vs. Male)	-0.360	0.112	**0.001**	0.050	0.119	0.672
Australian (vs. US)	0.010	0.173	0.953	0.104	0.139	0.454
Parental BD	-0.298	0.142	**0.036**	-0.213	0.134	0.112
Offspring Major Mood Disorder	-0.330	0.179	0.065	-0.298	0.163	0.068
Adjusted (Model 2)						
Age (continuous)	-0.014	0.023	0.537	-0.021	0.022	0.332
Non-White	-0.506	0.306	0.098	-0.402	0.232	0.082
Female	-0.243	0.124	**0.050**	-0.005	0.119	0.967
Australian	0.017	0.165	0.920	0.108	0.152	0.478
Parental BD	-0.149	0.157	0.342	-0.241	0.144	0.093
Offspring Major Mood Disorder	-0.257	0.186	0.168	-0.198	0.176	0.261

Notes: Est.=Estimate; SE=Standard Error. Covariates significant at the $p<0.05$ level are in **bold**. In Model 1, the associations between each individual covariate and the two factors are unadjusted for the effect of the other covariates. In Model 2, the association between the listed covariates and factors are adjusted for all other covariates in the model.

APPENDIX C: The Bipolar High-Risk Study (NIMH Genetics Initiative Study: Adolescents at High Risk for Familial Bipolar Disorder)

The National Institute of Mental Health Bipolar Disorder Genetics Initiative

In 1988, the National Institute of Mental Health (NIMH) began the Human Genetics Initiative. The NIMH Bipolar Disorder Genetics Initiative aims to establish a national resource of clinical data and biomaterials (cell lines and DNA samples) to facilitate psychiatric genetic research. Both extramural sites (including Indiana University, Johns Hopkins University, and Washington University of St. Louis) and the NIMH Intramural Research Program contributed to ascertainment of Bipolar pedigrees from 1991-1998, followed by collaborative research projects collecting pedigree samples and conducting molecular genetic analyses to augment the existing resources (National Institute of Mental Health [NIMH] Repository and Genomics Resource: NIMH Center for Collaborative Genomics Research on Mental Disorders, 2009-2017a).

The majority of probands for the initiative were ascertained systematically by screening consecutive admissions at local treatment facilities (The NIMH Genetics Initiative Bipolar Group, 1997). Rules for systematic ascertainment were described as follows: "1) the proband must have [BD-I] and be admitted to one of the treatment facilities [included in the initiative]; 2) a secondary affected first-degree relative must be available, with either [BD-I] or [schizoaffective disorder bipolar type]; and 3) either the proband or secondary affected relative must have at least 2 living siblings 18 or older. The family of origin of the proband must not be bilineal (both parents with [BD-I] or [schizoaffective disorder bipolar type])"

(The NIMH Genetics Initiative Bipolar Group, 1997). Non-systematically ascertained families were recruited via advertisement, advocacy groups, or through another source (not a clinical series), and were accepted if they passed a higher threshold for multiplex burden. By 1995, approximately 140 families with 1200 family members had been ascertained. Based on informativeness for linkage, 97 families and 540 family members were selected for genotyping and preliminary analysis (The NIMH Genetics Initiative Bipolar Group, 1997), with a second sample of 56 families and 353 family members.

In the next stage of the study, the consortium was expanded from 4 to 10 sites that included: Indiana University (with satellite sites at University of Louisville and Wayne State University in Detroit), Johns Hopkins University, the NIMH Intramural Research Program, Rush-Presbyterian Medical Center in Chicago, University of California at Irvine, University of California at San Diego, University of Chicago, University of Iowa, University of Pennsylvania, and Washington University in St. Louis (Dick et al., 2003). The first sample collected by the 10 sites consisted of 250 families and 1,152 family members independent of the previously collected families. The sample self-reported their race/ethnicity as 'Caucasian' (93%), African American (3.5%), or other (3.5%) (Dick et al., 2003).

Detailed descriptions of diagnostic procedures and genotyping are provided by the NIMH Genetics Initiative Bipolar Group (1997) and Dick and colleagues (2003). Information regarding numbers of people approached to participate in the NIMH Genetics Initiative, including characteristics of refusers/nonparticipants, is not available.

The Bipolar High-Risk Study

The study on which this dissertation was based came from the NIMH Bipolar Disorder Genetics Initiative: "Adolescents at High Risk for Familial Bipolar Disorder," funded through NIMH grant R01 MH068009 to principal investigator John Nurnberger

(NIMH Repository and Genomics Resource: NIMH Center for Collaborative Genomics Research on Mental Disorders, 2009-2017b). It was additionally funded through collaborative R01s MH073151 and MH068006. This study, discussed here as the Bipolar High-Risk Study, took place from 2005-2009 in the United States (US) and through 2013 in Australia. Recruitment of the Australian cohort was supported by the National Health and Medical Research Council (Program Grant number 1037196) and the Lansdowne Foundation. Institutional Review Boards at Indiana University School of Medicine, University of Michigan, The Johns Hopkins University School of Medicine, and Washington University at St. Louis approved all study procedures. Informed consent (or assent with parental consent for participants under age 18 years) was obtained from all participants after a thorough explanation of the study (Nurnberger et al., 2011). The Human Research Ethics Committee approved the research at the University of New South Wales, and informed consent (or assent with parental consent for participants under age 17 years) was obtained for all participants in Australia (Perich et al., 2015). Procedures for ascertaining high-risk and control participants in the US and Australia were the same.

Probands with bipolar disorder (BD) from the NIMH Genetics Initiative were characterized using the Diagnostic Interview for Genetics Studies (DIGS; Nurnberger et al., 1994) and Family Interview for Genetics Studies (FIGS; Maxwell, 1992); all had a lifetime DSM-IV diagnosis of BD-type I (BD-I), BD-type II with recurrent major depression (BD-II), or schizoaffective disorder, bipolar type (Nurnberger et al., 2011). The DIGS is a clinical interview featuring polydiagnostic capability, assessment of course and chronicity, and symptom description of major mood, psychotic, and related disorders. Diagnostic scoring is by algorithm and clinical judgment, with test-retest reliability as high as 0.95 (Nurnberger et al. 1994).

The FIGS is a complementary interview to the DIGS in which study participants provide information on their family members; this information, in addition to medical records, is used to facilitate psychiatric diagnoses (Maxwell, 1992). Approximately 40% of probands in the Bipolar High-Risk Study came from the NIMH Genetics Initiative (J. Nurnberger, personal communication). Probands with BD were additionally recruited from other genetics studies, specialty clinics, and advertising at the participating study sites. For some high-risk participants, the BD proband was a sibling, aunt, uncle, or grandparent; however, this dissertation used data only on offspring whose parent was the BD proband. Control parents were recruited from general medical practitioners, motor vehicle records, print and electronic media, and advertising at the universities and local communities surrounding the study sites. Parents were excluded from participating as controls if they had a diagnosis of BD-I, BD-II, recurrent major depression, schizoaffective disorder, or schizophrenia, or if they had a first-degree relative with a psychiatric hospitalization or history of psychosis.

Data were collected from 2006 through 2009 in the US and through 2013 in Australia. In high-risk and control families, all offspring aged 12 to 21 years were invited to participate. Offspring participation involved being interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, bipolar disorder version (K-SADS), providing a blood specimen for DNA analysis, and a battery of self-reported psychosocial measures. The study investigators adapted the K-SADS for the study by adding questions addressing time and duration of specific episodes, each DSM-IV criterion for affective disorders, phenomenologic detail, and screening for organic affective syndromes and psychosis, including anchor points, from the DIGS and Washington University K-SADS. Principal investigators, the clinical research manager, and study

coordinators of the Bipolar High-Risk Study extensively trained the interviewers, who had varying levels of post-secondary and post-graduate education in psychology-related fields (Nurnberger et al., 2011; Perich et al., 2015). At least one parent had to be living and available to complete the DIGS about themselves, the FIGS about their spouse and relatives, and the K-SADS-parent version about their child or children participating in the study.

Offspring diagnoses and age of onset were determined by consensus of two study psychiatrists with child specialty training, clinical psychologists, or clinical social workers, based on direct interview of offspring, parent interview, and medical records. The clinicians participating in the best-estimate final diagnosis procedures were blind to high-risk/control status of offspring, and followed DSM-IV criteria for making diagnoses. Inter-rater reliability was good for affective diagnoses (kappa=0.82) and other diagnoses (kappa from 0.70 to 0.85) (Nurnberger et al., 2011).

As of September 2009, fifteen offspring in the age range in the high-risk families did not participate at the US study sites, one of whom had autism, and four offspring in the age range in the control families did not participate, one of whom had cerebral palsy. Probands with substantial cognitive impairment were not included, and although IQ was not formally tested in offspring, the youth were required to be able to complete the interview and questionnaires in order to participate. One control offspring was diagnosed as having a learning disability and possible intellectual disability during the best-estimate process.

In all analyses for this dissertation, we adjusted for age and sex of offspring. For Aim 2 (Chapter 3), we further adjusted for race and country of residence (US or Australia). Self-reported race was based on US census categories and reduced to a binary variable of White (n=393) or non-White (n=48), the distribution of which was not significantly

different between high-risk and control offspring. For Aim 3 (Chapter 4), we adjusted for genetic ancestry based on principal components analysis of genetic data, rather than self-reported race.

When exploring the data and performing preliminary analyses, we initially tested a study site variable. Although some sites recruited proportionately more high-risk than control families, and vice versa, a 'site' variable did not change or significantly associate with any model, and thus we did not include a site variable going forward. As a proxy for family socioeconomic status (SES), we attempted to include highest number of years of education attained by either parent (using the parent with the highest number). This information was available for 120 of the 441 offspring, which prevented latent class regressions from running. Parent education was not significantly different between high-risk and control offspring. A previous analysis from this study (Nurnberger et al., 2011) examined occupation of the head of the household as a proxy for SES and did not find a significant difference between high-risk and control groups. Therefore, we did not include parental education.

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CURRICULUM VITAE

EMMA K. STAPP, M.H.S.

July 19, 2017

PERSONAL DATA

University Address:
Johns Hopkins Bloomberg School of Public Health
Department of Mental Health
624 N. Broadway, Rm. 798
Baltimore MD, 21205
Phone: 814-935-6807
Email: estokes9@jhu.edu

EDUCATION

2017	Ph.D., Mental Health Psychiatric Epidemiology Training Program Johns Hopkins Bloomberg School of Public Health, Baltimore, MD Thesis: *Family Environment and Polygenic Risk in the Bipolar High-Risk Context* Advisors: Peter P. Zandi, Ph.D. and Holly C. Wilcox, Ph.D.
2010	M.H.S., Mental Health Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
2004	B.A., Psychology The Pennsylvania State University, University Park, PA

HONORS AND AWARDS

2016	Honorarium, the Robert Wood Johnson Foundation
2001	Dean's List, The Pennsylvania State University

GRANTS AND FELLOWSHIPS

2013-2017	Predoctoral Fellow, Psychiatric Epidemiology Training Program National Institute of Mental Health and Johns Hopkins Bloomberg School of Public Health (T32MH014592); stipend and full tuition coverage for four years, Chief Fellow 2015-2016
2012-2013	Merit-Based Partial Tuition Scholarship

Department of Mental Health, Johns Hopkins Bloomberg School of Public Health

2000-2004 Academic Excellence Scholarship
Schreyer Honors College, The Pennsylvania State University

PUBLICATIONS

Manuscripts Under Review

1. Zandi, P. P., Ritchey, M., Maihofer, A., **Stapp, E. K.**, Alda, M., Alliey-Rodriguez, N., Anand, A., Andreassen, O., Balaraman, Y., Berrettini, W., Bertram, H., Bhattacharjee, A., Brennand, K., Burdick, K., Calabrese, J., Calkin, C., Claasen, A., Conroy, C., Coryell, W., Craig, D., DeModena, A., Feeder, S., Fisher, C., Frazier, N., Frye, M., Gage, F., Gao, K., Garnham, J., Gershon, E., Goes, F., Goto, T., Harrington, G., Jakobsen, P., Kamali, M., Kelly, M., Leckband, S., Lohoff, F., McCarthy, M., McInnis, M., Mertens, J., Mondimore, F., Morken, G., Nurnberger, J., O'Donovan, C., Oedegaard, K., Pham, S., Ryan, K., Schinagle, M., Schoeyen, H,. Schwebel, C., Shaw, M., Shekhtman, T., Shilling, P., Slaney, C., Szelinger, S., Tarwater, B., Yao, Nievergelt, C., & Kelsoe, J. (2017). Clinical predictors of response to lithium treatment in the Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder study. *American Journal of Psychiatry*.
2. Wilcox, H. C., Fullerton, J. M., Glowinski, A. L., Benke, K., Kamali, M., Hulvershorn, L. A., **Stapp, E. K.,** Edenberg, H. J., Roberts, G. M. P., Ghaziuddin, N., Fisher, C., Brucksch, C., Frankland, A., Kastelic, E., Miller, L., McInnis, M., Mitchell, P. B., & Nurnberger, J. N. Jr. (2017). The interaction of traumatic stress and bipolar polygenic risk score predicts suicide attempts among adolescents at familial risk for bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*.

Manuscripts in Preparation

1. **Stapp, E. K**., Musci, R. J., Fullerton, J. M., Glowinski, A. L., Mitchell, P. B., McInnis, M., Reich, W., Ghaziuddin, N., Hulvershorn, L. A., Roberts, G. M. P., Nurnberger Jr., J. I., & Wilcox, H. C. (2017). Offspring-perceived parental warmth and permissiveness in the bipolar high-risk context. Manuscript to be submitted to *Journal of Family Psychology*.
2. **Stapp, E. K.,** Musci, R. J., the Bipolar High-Risk Research Group, Nurnberger Jr., J. I., & Wilcox, H. C. (2017). Patterns and predictors of offspring-perceived family environment among adolescents at high and low familial risk for bipolar disorder. Manuscript to be submitted to *Journal of Research on Adolescence*.
3. **Stapp, E. K.,** Mendelson, T., Musci, R. J., & Wilcox, H. C. (2017). Parental bipolar disorder, family environment, and offspring psychiatric disorders: A systematic review. Manuscript to be submitted to *Journal of Affective Disorders*.
4. **Stapp, E. K**., Zandi, P. P., Fullerton, J. M., Musci, R. J., the Bipolar High-Risk Research Group, Nurnberger, J. I., & Wilcox, H. C. (2017). Family environment and its interaction with polygenic risk in predicting bipolar disorder in youth. Manuscript to be submitted to *Development and Psychopathology*.

5. Musci, R. J., **Stapp, E. K.,** Ballard, E. D., & Wilcox, H. C. (2017). Impulsive and aggressive phenotypes and suicide attempt in an urban adolescent sample: differences between males and females. Manuscript to be submitted to *JAMA Psychiatry*.
6. Kamali, M. K., Deng, R., **Stapp, E. K.,** & the Bipolar High-Risk Research Group. (2017). Stressful life events and clinical severity and diagnosis in a cohort of adolescents at familial risk for bipolar disorder.
7. **Stapp, E. K.**, Williams, S., & Gallo, J. J. (2017). The relationship between mental health, childhood maltreatment, and multimorbidity in a nationally representative sample of noninstitutionalized US adults.

PRESENTATIONS

Scientific Meetings

1. **Stapp, E. K.**, Zandi, P. P., Fullerton, J. M., Glowinski, A. L., McInnis, M., Mitchell, P. B., Wilcox, H. C., & Nurnberger Jr., J. I. (2017, May). *Mother-child conflict, bipolar polygenic risk, and their interaction in predicting offspring mood disorders*. Oral presentation at the 19th Annual Conference of the International Society of Bipolar Disorders, Washington DC.
2. **Stapp, E. K.**, Musci, R. J., & the Bipolar High-Risk Research Group. (2017, Accepted). *Patterns of perceived family environment among offspring at high or low familial risk for bipolar disorder*. Poster presentation at the 2017 biennial meeting of the Society for Research on Child Development, Austin, TX.
3. **Stapp, E. K.**, Musci, R. J., & the Bipolar High-Risk Research Group. (2016, September). *Child-perceived family environment in a cohort of adolescent and emerging adult offspring of parents with bipolar disorder or no psychiatric disorder [preliminary findings]*. Poster presented at the annual Interdisciplinary Population Health Research Conference, State College, PA.
4. **Stapp, E. K**., Mendelson, T., & Wilcox, H.W. (2015, March). *Characterizing family environment and offspring psychiatric outcomes in families with versus without bipolar parents: A systematic review*. Poster presented at the annual meeting of the American Psychopathological Association, New York, NY.
5. **Stokes, E. K.**, Buccino, D., Mondimore, F. M., Hackerman, F., Schweizer, B., Everett, A., & Zandi, P. (2011, December). *The Mood Disorders Clinic at The Johns Hopkins Bayview Medical Center: Successfully Integrating Research and Clinical Enterprises.* Poster presented at the annual Johns Hopkins Bayview Research Symposium, Baltimore, MD.
6. **Stokes, E. K**. & Buccino, D. (2011, November). *Development & Use of a Comprehensive Assessment Package: The NNDC Clinical Care Registry.* Oral presentation (plenary session) at the annual conference of the National Network of Depression Centers, Baltimore, MD.

Invited Talks

1. **Stapp, E.K.** (2017, March 1). *Family Environment and Polygenic Risk Interact to Predict Bipolar Disorder in Youth.* Annual pre-American Psychopathological Association Meeting of T32 NIDA and NIMH Training Programs, Columbia University Mailman School of Public Health, New York, NY.

2. **Stapp, E.K.** (2016, March 23). *Factor analysis of the Home Environment Interview for Children in a cohort at high risk for familial bipolar disorder.* Department of Mental Health Seminar Series, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

TEACHING

2016	Guest Lecturer: *Distal outcome modeling in latent class analysis.* Seminar on Statistical Methods for Mental Health, Profs. Rashelle Musci and Elizabeth Stuart, Johns Hopkins Bloomberg School of Public Health.
2016	Teaching Assistant: Suicide as a Public Health Problem, Profs. Holly Wilcox and Diana Clarke, Johns Hopkins Bloomberg School of Public Health
2015	Teaching Assistant: Prevention of Mental Disorders: Public Health Interventions, Profs. Nicholas Ialongo and George Rebok, Johns Hopkins Bloomberg School of Public Health

WORK EXPERIENCE

2015	Psychiatric Practice Guidelines Abstract Screener American Psychiatric Association, Arlington, VA
2012-2014	Graduate Research Assistant Johns Hopkins University School of Medicine, Baltimore, MD
2010-2012	Research Program Coordinator, Department of Psychiatry Johns Hopkins University School of Medicine, Baltimore, MD
2007-2009	Legal Assistant Saul Ewing LLP, Baltimore, MD
2005-2007	Legal Assistant Arnold & Porter LLP, Washington, DC
2001-2004	Research Assistant, Department of Psychology The Pennsylvania State University, University Park, PA

PROFESSIONAL SERVICE

2014	Conference abstract reviewer: Mental Health Section, American Public Health Association
2008-2009	Director of Membership: Women in eDiscovery, Baltimore Chapter

UNIVERSITY SERVICE

2016-2017	Departmental Representative: Doctoral Student Council, Johns Hopkins Bloomberg School of Public Health
2016-2017	Founder: Mental Health Manuscript Writing Student Group, Johns Hopkins Bloomberg School of Public Health
2013-2015	Vice President: Mental Health Student Group, Johns Hopkins Bloomberg School of Public Health

COMMUNITY SERVICE

2011	Volunteer: Help Beautify Baltimore City Schools, Johns Hopkins University
2008-2009	Mentor: Reginald F. Lewis High School, Community Law in Action Mentoring to Empower Program
2008-2009	Planning Committee Member and Volunteer: Baltimore City MLK Day of Service, Saul Ewing
2000-2002	Volunteer Outreach Worker and HIV Risk Reduction/Test Counselor: The AIDS Project, State College, PA

PROFESSIONAL ORGANIZATIONS

2016-	Society for Research on Child Development
2016-	Society for Research on Adolescence
2015-	Society for Epidemiologic Research
2012-	American Public Health Association
2008-2011	American Psychological Association of Graduate Students
2007-2009	Maryland Association of Paralegals *fka* Baltimore City Paralegal Association

LANGUAGES

English	Native
French	Limited working proficiency

RELATED PROFESSIONAL SKILLS

Data analysis in STATA, M*plus*, R

Certification in Phlebotomy for Research (2011)