Prevalence and Correlates of Childhood-onset Bipolar Disorder among Adolescents

Jessica S Barton (jessica.barton@camh.ca)
Centre for Addiction and Mental Health https://orcid.org/0000-0001-6666-6938
Megan Mio
Centre for Addiction and Mental Health
Vanessa Timmins
Centre for Addiction and Mental Health
Rachel H.B. Mitchell
U of T: University of Toronto
Benjamin I Goldstein
Centre for Addiction and Mental Health

Research

Keywords: Adolescent, Bipolar Disorder, Onset, Childhood, Familial loading

Posted Date: April 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-401900/v1

Abstract

Background

Early-onset Bipolar Disorder (BD) is associated with a more severe illness as well as a number of clinical factors amongst adults. Early-onset can be categorised as childhood- (age < 13) or adolescent- (age ≥ 13) onset, with the two displaying different clinical profiles. However, among adolescents, there is a paucity of research comparing the both prevalence and clinical profiles of childhood-onset to adolescent-onset BD. We set out to examine potential differences in demographic, clinical, and familial characteristics amongst adolescents with childhood- vs. adolescent-onset BD.

Methods

The study included 195 adolescents with BD, ages 14–18 years Age of onset was determined retrospectively by self-report. Participants completed the semi-structured K-SADS-PL diagnostic interviews along with self-reported dimensional scales. Analyses examined between-group differences in demographic, clinical, and familial variables, as well as individual manic and depressive symptom severity for most severe past episodes. Variables that were associated with age of onset at $p < 0.1$ in univariate analyses were evaluated in a logistic regression model.

Results

Approximately one-fifth of participants had childhood-onset BD (n = 35; 17.9%). A number of clinical and demographic factors were significantly associated with childhood-onset BD. However, there were no significant differences in individual depression and mania symptom severity. In multivariate analyses, the variables most strongly associated with childhood-onset were police contact, stimulant treatment, and family history of suicidal ideation (positively associated), as well as smoking and psychiatric hospitalization (negatively associated).

Conclusions

In this large clinical sample of adolescents with BD, one-fifth reported childhood-onset BD. Correlates of childhood-onset generally aligned with those observed in the literature, the majority of which were age-related. The lack of differences in individual manic and depressive symptom severity were particularly noteworthy. Future research is warranted to better understand the genetic and environmental implications of high familial loading of psychopathology associated with childhood-onset, and to integrate age-related treatment and prevention strategies.

Declarations

Ethics approval and consent to participate: Consent was obtained from all participants and their parent and/or guardian prior to participating. Ethical approval was granted by Sunnybrook Research Institute Research Ethics

Board. REB # 2295. All data was collected at Sunnybrook Research Institute. However all data was transferred with the Centre for Youth Bipolar Disorder's relocation to the Centre for Addiction and Mental Health. Thus, ethical approval was also granted by CAMH Research Ethics Board. REB 148/2020.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Competing Interests: The authors declare that they have no competing interests

Funding: No direct funding was received for this study. Dr. Goldstein acknowledges research grant support from Brain Canada, Canadian Institutes of Health Research, Heart and Stroke Foundation, National Institute of Mental Health, and the Departments of Psychiatry at the University of Toronto and Sunnybrook Health Sciences Centre.

Authors' contributions: Jessica Barton primarily wrote the manuscript and performed statistical analyses. Megan Mio assisted in manuscript preparation. Vanessa Rajamani assisted in quality control of data. Dr. Benjamin Goldstein contributed to study conception, design, and assisted with manuscript preparation. All authors contributed to revisions of the manuscript and have approved the final manuscript.

Acknowledgments: We would like to thank all staff, study participants and families for their time and contributions to this study.

Background

Numerous studies of adults with bipolar disorder (BD), including clinical and epidemiological samples, have found that earlier onset of BD is associated with a more severe illness (Goldstein and Levitt, 2006; Perlis et al., 2004). Childhood- and adolescent-onset has been associated with increased symptom severity and persistence, frequency of mood episodes, and comorbidities, as well as less responsiveness to treatment, and worse overall functioning (Holtzman et al., 2015; Lázaro et al., 2007; Perlis et al., 2009; Perlis et al., 2004; Post et al., 2010; Post et al., 2008; Wilens et al., 1999). Among adults with BD in the general population, 32% report childhood- or adolescent-onset, including 8% childhood-onset and 24% adolescent-onset (Goldstein and Levitt, 2006). In clinical samples, the prevalence of childhood- or adolescent-onset is 50-65% (Holtzman et al., 2015; Leverich et al., 2007; Perlis et al., 2004; Post et al., 2010). Similar to the general population, childhood-onset (14-27%) is less common than adolescent-onset (30-43%) in clinical samples (Holtzman et al., 2015; Leverich et al., 2007; Perlis et al., 2004). Among adults with BD, childhood-onset is associated with irritability (Lázaro et al., 2007); comorbid attention-deficit/hyperactivity disorder (ADHD) (Lázaro et al., 2007), conduct disorder (CD), and substance use disorder (SUD) (Holtzman et al., 2015); rapid cycling (Holtzman et al., 2015); and family history of mood disorders (Baldessarini et al., 2012; Holtzman et al., 2015) and substance abuse (Baldessarini et al., 2012). Whereas, compared to childhood-onset, adolescent-onset BD has been associated with greater prevalence of psychosis (Lázaro et al., 2007) and SUD (Perlis et al., 2004).

While well investigated within adult populations, fewer studies have investigated the clinical features of childhood-onset compared to adolescent-onset BD in adolescents. It is noteworthy that, as compared to adults with illness onset often decades prior, adolescents, with recent illness onset, could be less prone to recall bias. Some studies have found childhood-onset BD to be more common than adolescent-onset (58-75%) (Topor et al., 2013; Wilens et al., 1999). Other studies have reported that childhood-onset BD is associated with increased rates of ADHD or ODD (Masi et al., 2006) as well as a higher presence of any comorbid disorder, and a more insidious presentation of the illness (Song et al., 2010), as compared to adolescent-onset BD. The only characteristic thus far found to be more common in adolescent-onset vs. childhood-onset BD is comorbid SUD (Wilens et al., 1999).

Several studies have examined age of onset across three groups: children, adolescents with childhood-onset, and adolescents with adolescent-onset. These studies have found that children with BD have higher rates of ADHD (Faraone et al., 1997), and different manic symptoms (Topor et al., 2013) from the other groups. Children with BD and adolescents with childhood-onset BD have more family history of depression, anxiety, ADHD, CD, and suicidal behaviours (Rende et al., 2007). Other studies have reported no differences between groups (Findling et al., 2001; Geller et al., 2000a; Geller et al., 2000b; Kennedy et al., 2015a).

Despite extant studies, there remain a number of gaps in the literature on this subject. First, most studies have focused on BD-I subtype, with analysis of clinical characteristics restricted to mania symptoms. Second, several studies have relied on chart reviews, rather than direct interviews. Third, while there have been large studies on this topic in adults, most studies on this topic in adolescents have had modest sample size, which limits the comparative evaluation of clinical correlates. One exception to these limitations is the large Course and Outcome of Bipolar Youth (COBY) study (Birmaher and Axelson, 2006; Birmaher et al., 2009a) which found that: children experienced more irritability during depressive intervals compared to adolescents with either childhood- or adolescent-onset; both children and adolescents with childhood-onset BD experienced more mood lability and comorbid ADHD than adolescents with adolescent-onset BD; and adolescent-onset BD was associated with higher rates of comorbid CD, panic disorder and SUD as compared to the other groups (Birmaher and Axelson, 2006; Birmaher et al., 2009a).

Overall, there remains a paucity of research comparing childhood-onset to adolescent-onset BD in adolescents, with no studies on this topic, to our knowledge, since the aforementioned COBY paper in 2006. While most research has taken place within U.S. samples, studies have suggested lower rates of childhood- or adolescent-onset BD amongst non-U.S. samples (Post et al., 2017b; Post et al., 2008). We sought to replicate and expand previous studies by comparing the prevalence as well as the clinical and familial characteristics of childhood- vs. adolescent-onset BD in a large Canadian clinical sample. We hypothesized that adolescent-onset would be more common than childhood-onset BD, and that correlates of childhood-onset would align with those observed in the similarly designed COBY study.

Method

Subjects

Participants were 195 adolescents with BD-I, -II, or Not Otherwise Specified (NOS; akin to Other Specified Bipolar and Related Disorder), aged 14-18, who were recruited from a subspecialty clinic at a tertiary academic health

sciences centre in Toronto, Canada. The registry was approved by the institutional research ethics board, and written informed consent was provided by participants and at least one parent/guardian before study commencement. To evaluate the difference in clinical features of childhood-onset and adolescent-onset BD, the sample was divided into two subgroups according to the age of BD onset. Age of BD onset was defined as the age at which the individual first experienced an episode of mania or hypomania according to DSM-IV, or when study criteria for BD-NOS were met. Childhood-onset (n= 35) was defined as onset age of <13 years, while adolescent-onset (n=160) was defined as onset age of 13 years or older.

Procedure

All assessments were carried out by research staff who had a Bachelor's or Master's degree in a health sciences field and were trained under the supervision of the senior author (B. I. G., a licensed child-adolescent psychiatrist). The Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime (K-SADS-PL) version (Kaufman et al., 1997) was used to determine current and lifetime diagnoses, including BD and other psychiatric conditions. Diagnoses were based on information derived from interviews with the adolescent and their parents, and were based on DSM-IV criteria as this sample was recruited from 2012 through 2017, and the DSM-5 version of the K-SADS-PL was not available until December 2016. The mood sections of the K-SADS-PL were substituted with the extended K-SADS Depression Rating Scale (DRS) (Chambers et al., 1985) and K-SADS Mania Rating Scale (MRS) (Axelson et al., 2003). Criteria for BD-NOS were defined according to criteria used in the Course and Outcome of Bipolar Illness in Youth (COBY) study (Kennedy et al., 2015a). Diagnoses were determined using all available information, including adolescent and parent interviews and any available medical records. Clinical judgment was applied when conflicting information arose. Diagnoses were confirmed by a consensus meeting with a licensed child and adolescent psychiatrist following completion of the K-SADS-PL interview (B.I.G. or R.H.B.M.).

K-SADS-DRS and K-SADS-MRS were also used to score symptom severity for most severe lifetime episode, defined as the most severe period of experiencing depressive or manic symptoms, following the initial onset of symptoms. The severity of each core symptom within the K-SADS-DRS and K-SADS-MRS during this most severe period were rated.

The four factor Hollingshead Scale (Hollingshead, 1975) was used to determine socioeconomic status (SES). The Children's Global Assessment Scale (CGAS) was used to score the adolescent's global functioning over the current period, most severe past, and highest level in the past year (Shaffer et al., 1983). Information on comorbid diagnoses and clinical characteristics (e.g., psychosis, psychotropic and psychosocial treatment history) was obtained from the K-SADS-PL. Anxiety disorders were combined into one variable, "Any Anxiety Disorder(s)," which includes generalized anxiety disorder, social phobia, separation anxiety disorder, agoraphobia, panic disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and anxiety disorder not otherwise specified. SUD included alcohol or drug abuse or dependence. Lifetime cigarette smoking, was also ascertained via the K-SADS-PL, and computed as a "yes" or "no" variable. A Safety Form was used to record any lifetime police contact, lifetime involvement with child protective services, lifetime physical or sexual abuse, as well as any suicidality or non-suicidal self-injury that was not captured during the K-SADS-DRS interview (e.g., occurring outside the context of a depressive interval, such as while intoxicated or situationally dysregulated). The Children's Affective Lability Scale (CALS) was used to assess affect regulation

using an adolescent self-report and parent/guardian-report (Gerson et al., 1996). The Life Problems Inventory (LPI) self-report assessed dimensional traits of identity confusion, impulsivity, emotion dysregulation, and interpersonal problems (Rathus and Miller, 1995). Psychiatric history of first- and second-degree relatives was obtained from the adolescent and parent(s) through the Family History Screen (Weissman et al., 2000).

Data Analysis

Clinical and demographic variables were compared across the adolescent-onset BD and childhood-onset BD groups using t-tests or chi-squared tests. As BD subtype was an omnibus variable, it was dummy coded according to the three subtypes prior to analysis. False discovery rate (FDR) was used to correct for multiple comparisons (Benjamini and Hochberg, 1995). Variables associated with age of onset at $p<0.1$ after FDR correction were entered together in a backwards elimination logistic regression analyses. Square root transformation was carried out for any skewed variables prior to inclusion in multivariate analysis. All statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS), version 26.0.

Results

Socio-demographic and clinical characteristics

Socio-demographic characteristics of all participants can be seen in Table 1. Of the 195 participants enrolled, 17.9% had childhood-onset (n=35) and 82.1% had adolescent-onset (n=160). Participants in the childhood-onset group were significantly younger at the time of the study than those in the adolescent group. SES, sex, race, and living with both natural parents were not significantly different between the two groups.

le 1

ıographic characteristics of 195 adolescents with childhood-onset versus adolescent-onset bipolar ›rder

	Childhood-onset (n =35)	Adolescent-onset (n =160)	Statistics			
			t /χ^2	*p*	Cramer's V/ η^2	FDR-corrected *p*
›, years	15.8±1.54	16.9±1.39	-4.02	<.001	-0.58	<.001
io-economic status	4±0.95	4.1±1.01	-0.33	0.74	-0.05	0.74
(% female)	21 (60.0%)	106 (66.3%)	0.56	0.46	0.05	0.56
e (% Caucasian)	24 (68.6%)	99 (61.9%)	0.97	0.33	0.08	0.55
ng with both natural ents	11 (31.4%)	65 (40.6%)	1.22	0.27	0.09	0.68

In terms of clinical characteristics, as per Table 2, participants with childhood-onset were significantly more likely to have BD-NOS, and less likely to have BD-I. Participants with childhood-onset had significantly higher lifetime prevalence of ADHD, ODD, police contact, and

stimulant treatment, and higher parent-reported affective lability (CALS). Childhood-onset was also significantly associated with a lower lifetime prevalence of smoking. Lower lifetime prevalence of psychosis, second generation antipsychotics use, and psychiatric hospitalization were no longer significant after correction for multiple comparisons. In terms of family psychiatric history, per Table 3, childhood-onset participants had significantly more family history of depression, suicidal ideation, ADHD, SUD, alcohol use disorder (AUD), and CD.

le 3

t- and second-degree family history among 195 adolescents with childhood-onset versus adolescent-et bipolar disorder

	Childhood-onset (n =35)	Adolescent-onset (n =160)	Statistics			
			t / χ^2	*p*	Cramer's V/ η^2	FDR-corrected *p*
nia/hypomania	19 (54.3%)	66 (41.3%)	2.44	0.12	0.11	0.14
pression	31 (88.6%)	114 (71.2%)	5.90	0.02	0.17	0.03
cidal ideation	12 (34.3%)	26 (16.3%)	5.95	0.02	0.18	0.03
iety	24 (68.6%)	92 (57.5%)	1.46	0.23	0.09	0.23
HD	15 (42.9%)	38 (23.8%)	5.86	0.02	0.17	0.03
D	16 (45.7%)	41 (25.6%)	5.60	0.02	0.17	0.03
D	24 (68.6%)	49 (30.7%)	17.66	<.001	0.30	<.001
nduct Disorder	8 (22.9%)	12 (7.5%)	7.36	0.007	0.19	0.03
chosis	10 (28.6%)	27 (16.9%)	2.56	0.11	0.11	0.14

t Size = partial η2.

eviations: ADHD = attention-deficit hyperactivity disorder; SUD = substance use disorder; ODD; AUD = Alcohol Use Disorder

Multivariate analyses

All Table 1 - 3 variables with with $p \leq 0.1$ after FDR were examined. This included: BD-I, BD-NOS; lifetime ADHD, ODD, smoking, police contact, stimulant treatment, and psychiatric hospitalization; family history of depression, suicidal ideation, ADHD, SUD, AUD, and CD. Age, race, and sex were included as fixed covariates. Per Table 4, Childhood-onset was significantly positively associated with lifetime police contact (odds ratio (OR) = 0.11, 95% confidence interval (CI) = 0.02 – 0.52 p = 0.005), lifetime stimulant treatment (OR = 0.25, 95% CI = 0.07 - 0.96, p = 0.040) and family history of suicidal ideation (OR = 0.24, 95% CI = 0.06 – 0.95, p = 0.040), and significantly negatively associated with lifetime smoking (OR = 6.17, 95% CI = 1.38 – 27.52, p = 0.020) and psychiatric hospitalization (OR = 6.68, 95% CI = 1.43 – 31.18, p = 0.020). The regression model explained 54.4% of variance, and yielded an overall classification accuracy of 87.6%.

le 4

tivariate logistic regression results

	OR	Wald χ^2	p	95% CI of OR	
				Lower	Upper
ice contact	0.11	7.82	0.005	0.02	0.52
oking	6.17	5.68	0.02	1.38	27.52
nulant treatment	0.25	4.07	0.04	0.07	0.96
chiatric hospitalization	6.68	5.83	0.02	1.43	31.18
nily history of suicidal ideation	0.24	4.16	0.04	0.06	0.95
nily history of AUD	0.28	3.43	0.06	0.08	1.08

eviations: AUD = Alcohol Use Disorder

Individual depression and mania symptom severity

For lifetime depression and mania ratings, there were no significant between group differences for overall and/or any individual symptom severity.

Discussion

This study of 195 adolescents with BD found that approximately 1 in 5 reported illness onset in childhood. In univariate analyses, childhood-onset was positively associated with BD-NOS, comorbid ADHD and ODD, lifetime police contact, lifetime stimulant treatment, and higher scores on parent-reported emotional lability, as well as family history of depression, suicidal ideation, ADHD, SUD, AUD, and CD. Childhood-onset was negatively associated with lifetime smoking. In multivariate analyses, childhood-onset was positively associated with lifetime police contact, lifetime stimulant treatment, and family history of suicidal ideation, whereas smoking and psychiatric hospitalization were negatively associated with childhood-onset. Present findings expand upon prior literature, as few studies have examined this topic within an entirely adolescent sample.

Prior studies have found a higher prevalence of adolescent-onset compared to childhood-onset amongst adults with BD, although the differences are less pronounced than in the current study (Holtzman et al., 2015; Leverich et al., 2007; Perlis et al., 2004; Post et al., 2010). In contrast, prior studies in adolescents have found that childhood-onset is at least as common as adolescent-onset among adolescents with BD (Rende et al., 2007; Topor et al., 2013; Wilens et al., 1999). This difference could be in part due to differences in sample size, age, and/or factors related to nationality. Regarding nationality, there is evidence of earlier onset of BD in U.S. samples compared to European samples, which occurs in the context of higher familial loading, more medical comorbidity, and more adversity in U.S. samples (Post et al., 2017a). Another factor that likely contributes to differences in prevalence of adolescent-onset compared to childhood-onset is the definition of BD onset. Whereas the current study defined age of BD onset as the age at which the individual first experienced an episode of mania or hypomania, or when study criteria for BD-NOS were met, other studies use different definitions. For example, the COBY study defines BD onset as age at first mood episode (including depression). Together with the younger age of participants in COBY, this likely contributes to the higher rate of childhood-onset in COBY.

Analysis of the clinical characteristics associated with childhood-onset largely aligned with prior studies in adolescents with BD. As expected, adolescents with childhood-onset were younger. The finding that those with childhood-onset were significantly more likely to have BD-NOS, and less likely to have BD-I, as compared to those with adolescent-onset BD aligns with another COBY study (Birmaher et al., 2006). Higher prevalence of BD-NOS amongst those with childhood-onset could be due to their younger age, and the nature of subtype progression of the illness. That is, in contrast to adults, there are relatively high rates of diagnostic progression, with 25-45% of adolescents with BD-NOS later manifesting BD-I or BD-II (Axelson et al., 2011; Birmaher et al., 2006).

The finding that childhood-onset was associated with a comorbid ADHD (and with stimulant treatment) and comorbid ODD aligns with the younger age of these conditions in the general population, and is consistent with both the adult (Lázaro et al., 2007), and adolescent BD literature (Faraone et al., 1997; Masi et al., 2006). Those with childhood-onset were more likely to have experienced police contact. While this has not been investigated in relation to childhood- vs. adolescent-onset specifically, an earlier age of BD onset has been associated with police contact within both adult populations (Fazel et al., 2010; Fovet et al., 2015) and described in a prior publication based on the current sample (Barton et al., 2021). Childhood-onset was also negatively associated with lifetime smoking, which aligns with the epidemiology of smoking in adolescents in the general population and in BD specifically (Goldstein et al., 2008; Vermeulen et al., 2019; Wilens et al., 2008).

There was a consistent pattern of higher loading of familial psychiatric history in the childhood-onset group. In univariate analyses, childhood-onset was significantly associated with increased family history of depression, suicidal ideation, ADHD, SUD, AUD, and CD, and the same non-significant trend was observed for mania/hypomania, anxiety, and psychosis. Studies amongst adults have found childhood-onset to be associated with increased family history of mood disorders and SUD compared to adolescent-onset (Baldessarini et al., 2012; Holtzman et al., 2015). In line with our findings, in the COBY cohort, both children and adolescents with childhood-onset had higher rates of familial depression, suicidal behaviour, ADHD, SUD, CD, and anxiety, compared to adolescents with adolescent-onset (Rende et al., 2007). In general, across the BD populations, early-onset BD has been associated with higher familial loading compared to later-onset BD (Benazzi, 2004; Birmaher et al., 2009a; Strober et al., 2006). The mechanism underlying earlier BD onset in adolescents with higher loading of familial psychopathology is thought to comprise a combination of genetic and environmental factors (Alloy et al., 2006; Kennedy et al., 2015b).

Lastly, in terms of mood symptoms, there were no between-group differences in severity of lifetime most severe hypo/manic or depressive episodes, nor were there any between-group differences in individual manic or depressive symptoms within these episodes. Within adult populations, early onset, whether childhood- or adolescent-, is associated with greater symptom severity for depressive and manic episodes (Leverich et al., 2007; Perlis et al., 2004). Akin to our study, COBY did not find any difference in lifetime most severe manic or depressive intervals (Birmaher et al., 2009b). However, COBY did find between-group differences in specific mood symptom severity: in terms of depression symptoms, adolescents with childhood-onset had more guilt, negative self-image, terminal insomnia, and non-suicidal self-injury as compared to adolescents with adolescent-onset. In terms of manic symptoms, elation, decreased need for sleep, racing thoughts, increased goal-directed activity, and increased energy were all more severe in adolescents with adolescent-onset vs. adolescents with childhood-onset (Birmaher et al., 2009b). Relatedly, a recent long-term follow-up study of the

COBY cohort found equally high rates of hypo/manic episodes well into young adulthood among those with childhood- and adolescent-onset BD (Hafeman et al., 2020).

The current study has three primary limitations which should be considered. Firstly, while less of a concern than in adult studies, the current study was cross-sectional and retrospective. Secondly, in contrast to the COBY study, our study did not include a third group of children with BD, and had a small sample size for the childhood-onset group. Third, the sample was recruited from a tertiary outpatient setting, limiting generalizability of present findings to primary care or community samples.

Conclusions

Despite the acknowledged limitations, our study addresses a gap in the literature by investigating a large number of clinical and demographic factors associated with childhood-onset BD, in a sample that includes multiple BD subtypes. The pattern of findings overall converges with the prior literature. In addition, of particular note was the lack of difference in symptom severity between the two groups, and the very high familial loading of psychopathology in the childhood-onset group. Future longitudinal research is warranted to compare the overall and specific mood symptom manifestations of BD in childhood- vs. adolescent-onset. Gaining a better understanding of how the observed differences manifest, and change with age, can help better understand the trajectory of early-onset BD. Finally, future research is warranted to unpack the genetic and environmental impact of high familial psychopathology in relation to the emergence, treatment, and perhaps prevention or delay of childhood-onset BD.

References

Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Keyser, J., & Gerstein, R. K. (2006). A cognitive vulnerability–stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. *Development and psychopathology, 18*(4), 1055-1103. doi:10.1017/S0954579406060524

Axelson, D., Birmaher, B. J., Brent, D., Wassick, S., Hoover, C., Bridge, J., & Ryan, N. (2003). A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. *Journal of Child and Adolescent Psychopharmacology, 13*(4), 463–470. doi:https://doi.org/10.1089/104454603322724850

Axelson, D. A., Birmaher, B., Strober, M. A., Goldstein, B. I., Ha, W., Gill, M. K., . . . Keller, M. B. (2011). Course of Subthreshold Bipolar Disorder in Youth: Diagnostic Progression From Bipolar Disorder Not Otherwise Specified. *Journal of the American Academy of Child & Adolescent Psychiatry, 50*(10), 1001-1016.e1003. doi:https://doi.org/10.1016/j.jaac.2011.07.005

Baldessarini, R. J., Tondo, L., Vazquez, G. H., Undurraga, J., Bolzani, L., Yildiz, A., . . . Tohen, M. (2012). Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World psychiatry : official journal of the World Psychiatric Association (WPA), 11*(1), 40-46. doi:10.1016/j.wpsyc.2012.01.006

Barton, J., Khoubaeva, D., Mio, M., Timmins, V., Fiksenbaum, L. M., Mitchell, R. H. B., & Goldstein, B. I. (2021). Prevalence and correlates of police contact amongst youth with bipolar disorder. *J Affect Disord, 283*, 243-248. doi:10.1016/j.jad.2021.01.078

Benazzi, F. (2004). Bipolar II disorder family history using the family history screen: findings and clinical implications. *Compr Psychiatry, 45*(2), 77-82. doi:10.1016/j.comppsych.2003.12.003

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological), 57*(1), 289-300. Retrieved from http://www.jstor.org/stable/2346101

Birmaher, B., & Axelson, D. (2006). Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Development and psychopathology, 18*(4), 1023-1035.

Birmaher, B., Axelson, D., & Goldstein, B., Strober, M., Gill, M. K., Hunt, J., ... & Yen, S. (2009a). Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *American Journal of Psychiatry, 166*(7), 795-804.

Birmaher, B., Axelson, D., Strober, M., Gill, M. K., Valeri, S., Chiappetta, L., . . . Keller, M. (2006). Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry, 63*(2), 175-183. doi:10.1001/archpsyc.63.2.175

Birmaher, B., Axelson, D., & Strober, M., Gill, M. K., Yang, M., Ryan, N., ... & Goldstein, T. (2009b). Comparison of manic and depressive symptoms between children and adolescents with bipolar spectrum disorders. *Bipolar Disorders, 11*(1), 52-62.

Chambers, W. J., Puig-Antich, J., & Hirsch, M., Paez, P., Ambrosini, P. J., Tabrizi, M. A., & Davies, M. (1985). The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Archives of general psychiatry, 42*(7), 696–702. doi:https://doi.org/10.1001/archpsyc.1985.01790300064008

Faraone, S. V., Biederman, J., & Wozniak, J., Mundy, E., Mennin, D., & O'DONNELL, D. (1997). Is comorbidity with ADHD a marker for juvenile-onset mania? *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(8), 1045-1055.

Fazel, S., Lichtenstein, P., Grann, M., Goodwin, G. M., & Långström, N. (2010). Bipolar disorder and violent crime: new evidence from population-based longitudinal studies and systematic review. *Arch Gen Psychiatry, 67*(9), 931-938. doi:10.1001/archgenpsychiatry.2010.97

Findling, R. L., Gracious, B. L., & McNamara, N. K., Youngstrom, E. A., Demeter, C. A., Branicky, L. A., & Calabrese, J. R. (2001). Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disorders, 3*(4), 202-210.

Fovet, T., Geoffroy, P. A., Vaiva, G., Adins, C., Thomas, P., & Amad, A. (2015). Individuals with bipolar disorder and their relationship with the criminal justice system: a critical review. *Psychiatr Serv, 66*(4), 348-353. doi:10.1176/appi.ps.201400104

Geller, B., Zimerman, B., & Williams, M., Bolhofner, K., Craney, J. L., DelBello, M. P., & Soutullo, C. A. (2000a). Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology, 10*(3), 157-164.

Geller, B., Zimerman, B., & Williams, M., Bolhofner, K., Craney, J. L., DelBello, M. P., & Soutullo, C. A. (2000b). Six-month stability and outcome of a prepubertal and early adolescent bipolar disorder phenotype. *Journal of Child and Adolescent Psychopharmacology, 10*(3), 165-173.

Gerson, A. C., Gerring, J. P., & Freund, L., Joshi, P. T., Capozzoli, J., Brady, K., & Denckla, M. B. (1996). The Children's Affective Lability Scale: a psychometric evaluation of reliability. *Psychiatry research, 65*(3), 189-198. doi:https://doi.org/10.1016/s0165-1781(96)02851-x

Goldstein, B. I., Birmaher, B., Axelson, D. A., Goldstein, T. R., Esposito-Smythers, C., Strober, M. A., . . . Iyengar, S. (2008). Significance of cigarette smoking among youths with bipolar disorder. *American journal on addictions, 17*(5), 364-371.

Goldstein, B. I., & Levitt, A. J. (2006). Further evidence for a developmental subtype of bipolar disorder defined by age at onset: results from the national epidemiologic survey on alcohol and related conditions. *American Journal of Psychiatry, 163*(9), 1633-1636. doi:10.1176/ajp.2006.163.9.1633

Hafeman, D. M., Goldstein, T. R., Strober, J. M., Merranko, J., Gill, M. K., Liao, F., . . . Birmaher, B. (2020). Prospectively Ascertained Mania and Hypomania Among Young Adults with Child- and Adolescent-Onset Bipolar Disorder. *Bipolar Disord*. doi:10.1111/bdi.13034

Hollingshead, A. (1975). *Four Factor Index of Social Status.* Yale University unpublished manuscript. New Haven, CT.

Holtzman, J. N., Miller, S., Hooshmand, F., Wang, P. W., Chang, K. D., Hill, S. J., . . . Ketter, T. A. (2015). Childhood-compared to adolescent-onset bipolar disorder has more statistically significant clinical correlates. *Journal of affective disorders, 179*, 114-120.

Kaufman, J., Birmaher, B., & Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980-988. doi:https://doi.org/10.1097/00004583-199707000-00021

Kennedy, K. P., Cullen, K. R., & DeYoung, C. G., & Klimes-Dougan, B. (2015a). The genetics of early-onset bipolar disorder: A systematic review. *Journal of affective disorders, 184*, 1-12.

Kennedy, K. P., Cullen, K. R., DeYoung, C. G., & Klimes-Dougan, B. (2015b). The genetics of early-onset bipolar disorder: A systematic review. *Journal of affective disorders, 184*, 1-12.

Lázaro, L., Castro-Fornieles, J., De la Fuente, J. E., Baeza, I., Morer, A., & Pàmias, M. (2007). Differences between prepubertal-versus adolescent-onset bipolar disorder in a Spanish clinical sample. *European child & adolescent psychiatry, 16*(8), 510-516.

Leverich, G. S., Post, R. M., & Keck Jr, P. E., Altshuler, L. L., Frye, M. A., Kupka, R. W., ... & Denicoff, K. (2007). The poor prognosis of childhood-onset bipolar disorder. *The Journal of pediatrics, 150*(5), 485-490.

Masi, G., Perugi, G., & Millepiedi, S., Mucci, M., Toni, C., Bertini, N., ... & Pari, C. (2006). Developmental differences according to age at onset in juvenile bipolar disorder. *Journal of Child and Adolescent Psychopharmacology, 16*(6), 679-685.

Perlis, R. H., Dennehy, E. B., Miklowitz, D. J., DelBello, M. P., Ostacher, M., & Calabrese, J. R., ... & Nierenberg, A. A. (2009). Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: results from the STEP-BD study. *Bipolar Disorders, 11*(4), 391-400.

Perlis, R. H., Miyahara, S., Marangell, L. B., Wisniewski, S. R. , Ostacher, M., DelBello, M. P., Bowden, C. L., . . . Nierenberg, A. N. S.-B. I. (2004). Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). . *Biological Psychiatry, 55*(9), 875-881.

Post, R. M., Altshuler, L. L., Kupka, R., McElroy, S. L., Frye, M. A., Rowe, M., . . . Leverich, G. S. (2017a). More childhood onset bipolar disorder in the United States than Canada or Europe: Implications for treatment and prevention. *Neuroscience & Biobehavioral Reviews, 74*, 204-213.

Post, R. M., Altshuler, L. L., & Kupka, R., McElroy, S. L., Frye, M. A., Rowe, M., ... & Nolen, W. A. (2017b). More childhood onset bipolar disorder in the United States than Canada or Europe: Implications for treatment and prevention. *Neuroscience & Biobehavioral Reviews, 74*, 204-213.

Post, R. M., Leverich, G. S., & Kupka, R. W., Keck Jr, P. E., McElroy, S. L., Altshuler, L. L., ... & Grunze, H. (2010). Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. *The journal of clinical psychiatry, 71*(7), 864-872.

Post, R. M., Luckenbaugh, D. A., & Leverich, G. S., Altshuler, L. L., Frye, M. A., Suppes, T., ... & Grunze, H. (2008). Incidence of childhood-onset bipolar illness in the USA and Europe. *The British Journal of Psychiatry, 192*(2), 150-151.

Rathus, J., & Miller, A. (1995). *Life problems inventory*. Montefiore Medical Center/Einstein College of Medicine. New York, NY.

Rende, R., Birmaher, B., & Axelson, D., Strober, M., Gill, M. K., Valeri, S., ... & Iyengar, S. (2007). Childhood-onset bipolar disorder: Evidence for increased familial loading of psychiatric illness. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(2), 197-204.

Shaffer, D., Gould, M. S., & Brasic, J., et al. (1983). A Children's Global Assessment Scale (CGAS). *Archives of general psychiatry, 40*(11), 1228-1231. doi:10.1001/archpsyc.1983.01790100074010

Song, M., Yoon, H., & Choi, I., Hong, S. D., & Joung, Y. S. (2010). Differences of clinical characteristics and phenotypes between prepubertal-and adolescent-onset bipolar disorders. *Journal of Korean medical science, 25*(6), 912-917.

Strober, M., Birmaher, B., Ryan, N., Axelson, D., Valeri, S., Leonard, H., . . . Keller, M. (2006). Pediatric bipolar disease: current and future perspectives for study of its long-term course and treatment. *Bipolar Disord, 8*(4), 311-321. doi:10.1111/j.1399-5618.2006.00313.x

Topor, D. R., Swenson, L., & Hunt, J. I., Birmaher, B., Strober, M., Yen, S., ... & Ryan, N. (2013). Manic symptoms in youth with bipolar disorder: factor analysis by age of symptom onset and current age. *Journal of affective disorders, 145*(3), 409-412.

Vermeulen, J. M., Wootton, R. E., Treur, J. L., Sallis, H. M., Jones, H. J., Zammit, S., . . . Munafò, M. R. (2019). Smoking and the risk for bipolar disorder: evidence from a bidirectional Mendelian randomisation study. *Br J Psychiatry*, 1-7. doi:10.1192/bjp.2019.202

Weissman, M. M., Wickramaratne, P., Adams, P., Wolk, S., Verdeli, H., & Olfson, M. (2000). Brief screening for family psychiatric history: the family history screen. *Arch Gen Psychiatry, 57*(7), 675-682. doi:10.1001/archpsyc.57.7.675

Wilens, T. E., Biederman, J., Adamson, J. J., Henin, A., Sgambati, S., Gignac, M., . . . Monuteaux, M. C. (2008). Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: a controlled study. *Drug Alcohol Depend, 95*(3), 188-198. doi:10.1016/j.drugalcdep.2007.12.016

Wilens, T. E., Biederman, J., & Millstein, R. B., Wozniak, J., Hahesy, A. L., & Spencer, T. J. (1999). Risk for Substance Use Disorders in Youths With Child-and Adolescent-Onset Bipolar Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 38*(6), 680-685.

Table 2

le 2

ical characteristics, treatment history, and dimensional traits among adolescents with childhood-
et versus adolescent-onset bipolar disorder

	Childhood-onset (n =35)	Adolescent-onset (n =160)	Statistics			
			t /χ^2	*p*	Cramer's V/ η^2	FDR-corrected *p*
olar Subtype						
·I	3 (8.6%)	50 (31.3%)	7.46	0.006	0.20	0.046
·II	12 (34.3%)	59 (36.9%)	0.08	0.77	0.02	0.82
not otherwise specified	20 (57.1%)	51 (31.9%)	7.92	0.005	0.20	0.046
od Symptom Severity and Functioning						
nia – most severe past	28.52±10.23	28.80±9.39	-0.16	0.88	-0.02	0.90
nia – past month [a]	20.30±10.20	17.24±12.79	1.50	0.14	0.40	0.35
pression – most severe past [a]	31.26±7.10	30.81±10.92	0.31	0.76	0.07	0.82
pression – past month [a]	18.24±10.41	20.05±13.14	-0.88	0.38	-0.23	0.59
AS – most severe past	44.44±7.92	41.40±8.48	1.92	0.06	0.28	0.18
AS – past year	56.29±11.15	60.36±11.45	-1.89	0.06	-0.27	0.18
AS – current	53.74±9.65	52.21±10.61	0.77	0.44	0.11	0.66
etime Comorbid Diagnoses						
HD	23 (65.8%)	61 (38.1%)	11.34	<.001	0.25	<.001
iety disorders	27 (77.1%)	122 (76.3%)	0.53	0.47	0.05	0.68
nber of anxiety disorders	1.56±1.33	1.42±1.22	0.60	0.55	0.09	0.76
SD	5 (14.3%)	13 (8.1%)	1.6	0.21	0.21	0.46
D	7 (20.0%)	56 (35.0%)	2.34	0.13	0.11	0.34
D	18 (51.4%)	41 (25.6%)	10.91	<.001	0.24	<.001
nduct Disorder[b]	3 (8.6%)	8 (5.0%)	0.85	0.36	0.07	0.59
ing Disorder	9 (25.7%)	47 (29.4%)	0.19	0.67	0.03	0.77
er Characteristics						
cide attempt	7 (20.0%)	38 (23.8%)	0.24	0.63	0.04	0.77
cidal ideation	22 (62.9%)	96 (60%)	0.09	0.76	0.02	0.82
f-injurious behaviour	20 (57.1%)	85 (53.1%)	0.18	0.67	0.03	0.77
oking (yes)	9 (25.7%)	78 (48.8%)	6.23	0.01	0.18	0.049
etime sexual abuse[b]	2 (5.7%)	19 (11.9%)	1.05	0.31	0.08	0.56
etime physical abuse[b]	4 (11.4%)	8 (5%)	2.17	0.14	0.11	0.34
etime psychosis[b]	1 (2.9%)	25 (15.6%)	3.89	0.049	0.14	0.17
etime police contact	19 (54.3%)	49 (30.6%)	6.84	0.009	0.19	0.048
etime child protective vices[b]	6 (17.1%)	14 (8.8%)	3.52	0.17	0.20	0.40
etime Treatment History						
A[c]	12 (34.3%)	92 (57.5%)	4.95	0.03	0.16	0.11
ium	4 (11.4%)	32 (20.0%)	1.10	0.29	0.08	0.55
RI Antidepressants[d]	13 (37.1%)	57 (35.6%)	0.19	0.66	0.03	0.77
n-SSRI Antidepressants[e]	4 (11.4%)	20 (12.5%)	0.002	0.96	0.004	0.96
nulants[f]	13 (37.1%)	27 (16.9%)	8.62	0.003	0.21	0.04
chiatric hospitalization	10 (28.6%)	83 (51.9%)	5.28	0.02	0.17	0.09
ensional Traits						
LS						
olescent report	34.06±16.19	29.97±17.69	1.22	0.23	0.18	0.47
ent report	30.03±15.70	22.41±15.32	2.54	0.01	0.38	0.049
ulsivity	35.41±16.05	32.63±14.56	0.98	0.33	0.15	0.56
otional dysregulation	40.94±16.31	37.73±16.84	1.01	0.32	0.15	0.56
ntity confusion	41.79±17.02	43.21±16.88	-0.44	0.66	-0.06	0.77
erpersonal problems	38.29±16.53	36.77±15.58	0.51	0.61	0.08	0.77

es for all continuous variables are written as mean ± SD, categorical variables are written as n (% within group). Effect Size = partial η2 or

er's V. [a] Homogeneity of Variance not met, Welch's test used. [b] Fisher's exact [c]SGA = risperidone, olanzipine, aripiprazole, ziprasidone,

[uel. [d] SSRI antidepressants = zoloft, paroxetine, prozac, fluvoxamine, citalopram, lexapro. [e] Non-SSRI antidepressants = wellbutrin, ron, effexor, cymbalta. [f]Stimulants = ritalin, concerta, adderall, dexedrine.

eviations: BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; CGAS, Children's Global Assessment Scale; ADHD ention-deficit hyperactivity disorder; PTSD = post-traumatic stress disorder; SUD = substance use disorder; ODD = oppositional defiant der; SGA = Second generation antipsychotics; SSRI = selective serotonin reuptake inhibitor; CALS = Children Affective Liability Scale; Life Problems Inventory