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Psychopathological Outcomes of Adolescent Borderline Personality Disorder Symptoms

Running title: Outcomes of Adolescent BPD

Catherine Winsper, Ph.D., Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick (catherine.winsper@warwick.ac.uk)

AND R & I Department, Caludon Centre, Coventry and Warwickshire Partnership Trust, Clifford Bridge, Coventry, CV2 2TE;

Dieter Wolke, Ph.D., Dr rer nat h.c., Department of Psychology and Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick (D.Wolke@warwick.ac.uk);

Jan Scott, PhD., Academic Psychiatry, Institute of Neuroscience, Newcastle, University, Newcastle NE6 4BE, England (jan.scott@newcastle.ac.uk);

Carla Sharp, Ph.D., Department of Psychology, University of Houston, Texas (csharp2@uh.edu);

Andrew Thompson, MD, FRCPsych. Department of Psychology and Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick
AND Orygen, The Centre of Excellence in Youth Mental Health, Melbourne, Australia
(Andrew.Thompson@orygen.org.au);

***Steven Marwaha, Ph.D., MRCPsych.** Institute for Mental Health, School of Psychology, University of Birmingham, 52 Pritchatts Road, Edgbaston, B15 2TT, UK, email:
s.marwaha@bham.ac.uk ; Tel: 0121 414 3665 AND Birmingham and Solihull Mental Health Foundation Trust, UK

***Corresponding author**

Abstract

Objective: Despite considerable morbidity and functional losses associated with adolescent Borderline Personality Disorder (BPD), little is known about psychopathological outcomes. This study examined associations between adolescent BPD symptoms and subsequent depressive, psychotic, and hypomanic symptoms. **Methods:** We used data from the Avon Longitudinal Study of Parents and Children. Participants were adolescents living in the community who had data for all longitudinal outcomes (N=1758). We used logistic regression and path analysis to investigate associations between BPD (5 or more probable/definite symptoms) reported at age 11-12 years and depressive and psychotic symptoms reported at age 12 and 18, and lifetime hypomanic symptoms reported at age 22-23 years. **Results:** Adolescent BPD symptoms were associated with psychotic symptoms (OR: 2.36, CI: 1.82-3.06) and diagnosis of depression at age 18 years (OR: 1.30, CI: 1.03-1.64), and hypomanic symptoms (OR: 2.89, CI: 2.40-3.48) at 22-23 years. Path analysis controlling for associations between all outcomes, indicated that BPD symptoms were independently associated with depressive symptoms ($\beta=0.97, p<.001$) at 12 years and hypomanic ($\beta=0.58, p<.01$) symptoms at 22-23 years. BPD symptoms were also associated with psychotic symptoms at age 12 years ($\beta=0.58, p<.01$), which were linked ($\beta=0.34, p<0.01$) to psychotic symptoms at age 18 years. **Conclusion:** Adolescents with BPD symptoms are at future risk of psychotic and hypomanic symptoms, and a diagnosis of depression. Future risk is independent of associations between psychopathological outcomes, indicating that adolescent BPD symptoms have multifinal outcomes. Increasing awareness of BPD in early adolescence could facilitate timely secondary prevention of these symptoms subsequently helping to prevent future psychopathology.

Key words: borderline personality disorder, outcome, depression, hypomania, psychotic, path analysis, adolescents, ALSPAC.

Introduction

Borderline Personality Disorder (BPD) is a common and serious mental disorder with community prevalence ranging from 0.7% to 1.8% (Lieb et al., 2004; Winsper et al., 2019). The validity and clinical importance of adolescent BPD is increasingly recognized (Sharp and Fonagy, 2015; Winsper et al., 2016a). Indeed, BPD may be better conceptualized as a youth disorder, arising in early adolescence and then slowly declining from young adulthood onwards (Chanen et al., 2014). Adolescents with BPD are common among help seeking populations. Adolescent BPD is reported in up to 11% of psychiatric outpatients (Chanen et al., 2004) and 33-49% of psychiatric inpatients (Chanen et al., 2014; Grilo et al., 1998). These individuals often experience long-term social, educational, work and financial impairment, and have a substantial need for healthcare (Winsper et al., 2015a). Nevertheless, our understanding of the outcomes of adolescent BPD remains rudimentary.

Our previous systematic review indicated a limited number of prospective studies investigating links between adolescent BPD and subsequent psychopathology (Winsper et al., 2015a). Existing studies are limited by methodological problems. Clinical studies are confounded by treatment effects, and the sampling of individuals with severe psychopathology. Community studies are restricted by the lack of validated, structured assessment tools specifically designed to screen for adolescent BPD, and moderate sample sizes limiting power for detecting specific diagnostic or sub-syndromal level associations (Cohen et al., 2007). Some community studies tend to focus on high risk populations, e.g., oversampling for conduct

disorder (Stepp et al., 2012), or are focused on twin populations (Belsky et al., 2012). Further, few studies have controlled for earlier life experiences (e.g., abuse), which have been found to link to later psychopathology (Jaffee, 2017). Another major issue is that the extant literature primarily focuses on associations between adolescent BPD and future personality disorders (Lofgren et al., 1991; Chanen et al., 2004), anxiety and depression symptoms (Wenning, 1990; Johnson et al., 1999), substance misuse (Cohen et al., 2007) and self-harming behaviors (Johnson et al., 1999). There is very limited evidence examining associations with subthreshold or threshold psychotic (Thompson et al., 2012) or bipolar-spectrum disorders. These omissions needs to be addressed as psychotic symptoms are relatively common in adult BPD (Kaess et al., 2014) and concurrent comorbidity between BPD and bipolar disorder is approximately 25-30% (George et al., 2003). Finally, previous studies have not simultaneously modelled pathways between BPD and multiple psychopathological outcomes, despite the known high levels of comorbidity between psychopathologies (Winsper et al., 2016a). Such an approach is now needed to determine whether associations represent independent links between adolescent BPD symptoms and subsequent psychopathologies, or whether such associations are an artefact of symptom overlap.

Aims

We bridge these gaps in the literature by addressing the following questions:

1) Are BPD (5 or more probable/definite) symptoms in early adolescence associated with subsequent depressive (reported at 12 and 18 years), psychotic (reported at 12 and 18 years), and lifetime hypomanic (reported at 22-23 years) psychopathology following adjustment for early environmental risks?

2) Are the associations between BPD symptoms and psychopathology reported in late adolescence/early adulthood (i.e., 18 and 22-23 years) significantly mediated by psychopathological symptoms in early adolescence (i.e., 12 years)?

Methods

Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a UK birth cohort study examining the determinants of development, health, and disease during childhood and beyond.

The study is described in detail elsewhere (Boyd et al., 2013). ALSPAC recruited pregnant women in Avon with expected dates of delivery between the 1st April 1991 and 31st December 1992. Fourteen thousand, five hundred and forty-one pregnant women were initially enrolled in the study and had returned at least one questionnaire or attended a “Children in Focus” clinic by the 19th July 1999. Out of the initial 14, 541 pregnancies, all but 69 had known birth outcome.

These 14, 472 pregnancies yielded 14,676 fetuses in the initial sample. Of these, 14, 477 were singleton, 195 were twin, three were triplet and one was quadruplet. There were 14,062 live births of which 13, 988 children were alive at 1 year of age (see Figure 1 flowchart for sample numbers at each stage of the study). When the oldest children were approximately 7 years old, the sample was bolstered with eligible cases who had failed to join the study originally.

Consequently, when considering variables collected from the age of seven onwards there are data available on 14,701 children (an additional 713 children). The study website contains details of the data available through a fully searchable data dictionary

(<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>). From the first trimester of pregnancy, parents completed postal questionnaires about the study child’s health and development. The child attended annual assessment clinics, including face-to face interviews,

psychological and physical tests. Ethical approval for the study was obtained from the ALSPAC Law and Ethics committee and the local research ethics committees.

Assessments

BPD symptoms at 11-12 years

Adolescents were interviewed to assess BPD symptoms over the past 2 years. Trained psychologists used a face-to-face semi-structured interview: the UK Childhood Interview for DSM-IV Borderline Personality Disorder [UK-CI-BPD] (Zanarini et al., 2004). The UK-CI-BPD was adapted from the US version of the CI-BPD and both are based on the module for BPD in the Diagnostic Interview for DSM-IV Personality Disorders. The inter-rater and test-retest reliability of the DSM-III, DSM-III-R and DSM-IV versions of this measure are good to excellent (Zanarini and Frankenburg, 2001). In a test of convergent validity, the CI-BPD diagnosis was significantly associated with clinician diagnosis ($\kappa=0.34$, $p<0.001$), and other measures of BPD (i.e., Borderline Personality Features Scale, Personality Assessment Inventory - Borderline subscale) reported by patients and parents (Sharp et al., 2012). The inter-rater reliability of the UK-CI-BPD within the current sample ranged from 0.36 to 1.0 (median: 0.88); 86% of the κ values were within the excellent range of > 0.75 (Zanarini et al., 2011).

Consistent with the DSM-IV and DSM-5 Section II conceptualisations of BPD, the UK-CI-BPD covers nine symptoms: intense inappropriate anger; affective instability; emptiness; identity disturbance; paranoid ideation; abandonment; suicidal or self-mutilating behaviours; impulsivity, and intense unstable relationships. Each symptom was rated as: absent (score=0), probably present (score=1), or definitely present (score=2). Definitely present refers to very

frequent occurrence (daily or at least 25% of the time), and probably present refers to repeated but not very frequent occurrence. As in previous studies (Winsper et al., 2012; Winsper et al., 2015b), we constructed a dichotomous BPD symptom variable. Participants were assigned a positive status if they scored 1 or 2 on five or more of the DSM-IV diagnostic criteria. This symptom threshold (i.e., 5 or more symptoms) is consistent with the current DSM-5 diagnosis of BPD (American Psychiatric Association, 2013). However, we lowered the frequency threshold to include the repeated (score of 1) and very frequent (score of 2) occurrence of each symptom to ensure that sufficient positive cases were identified in our community sample. Therefore, our BPD assessment is more sensitive than current clinical diagnosis.

Depressive symptoms at 12 years

Child reported depressive symptoms over the past two weeks were assessed using the Short Mood and Feelings Questionnaire (SMFQ) (Angold et al., 1995). The SMFQ is a 13-item scale (items on 3-point scale) with high validity and reliability (Zwierzynska et al., 2013). Responses to items (no =0; sometimes = 1; true =2) were summed yielding a maximum score of 26 points. The total score for each participant was collapsed into a dichotomous variable (threshold score \geq 11), with higher scores consistent with clinically relevant levels of depressive symptoms (Zwierzynska et al., 2013).

Psychotic symptoms at 12 years

Psychotic symptoms were assessed with the semi-structured Psychosis-Like Symptom Interview, which contains 12 core questions. These are: hallucinations (visual and auditory); delusions (spied on, persecution, thoughts read, reference, control, and grandiosity); and experiences of thought interference (broadcasting, insertion, and withdrawal). Unspecified delusions were also

rated. Items are derived from the Diagnostic Interview Schedule for Children version IV (DISC-IV) and the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN). Trained interviewers rated each item as absent, suspected or definitely- present. The average kappa was 0.72 indicating good inter-rater reliability (Horwood et al., 2008). Consistent with previous research, we used at least one definite psychotic symptom (Singh et al., 2014), to demarcate the presence of relevant experiences.

International Classification of Diseases-10 (ICD-10) depression at 18 years

Depression was assessed with the Revised Clinical Interview Schedule (CIS-R) (Lewis et al., 1992). The CIS-R has been validated in community populations (Lewis et al., 1992) and is widely used in the Adult Psychiatric Morbidity Surveys of Great Britain. The CIS-R was self-administered via computerised interview during a research clinic. This scale establishes the severity of symptoms of depressive disorders in the past month and uses diagnostic cut-off points based on ICD-10 criteria. We used a categorical depression variable representing an ICD-10 diagnosis of mild, moderate or severe depression at the age of 18 years.

Psychotic symptoms at 18 years

Psychotic symptom since age 12 were assessed with the semi-structured Psychosis-Like Symptom Interview when participants were age 18 (Winsper et al., 2016b)(described above). The average kappa value was 0.83. Test-retest reliability was assessed with 162 adolescents re-interviewed after approximately 47 days (kappa=0.76, SE=0.078), 46 of whom were re-interviewed by the same interviewer (kappa=0.86, SE=0.136) (Zammit et al., 2013). Consistent

with previous research, the psychotic symptom outcome represented at least one definite psychotic symptom (Winsper et al., 2016b).

Hypomanic symptoms at 22 years

Participants completed the “*Your Life Now (at age 21+)*” postal questionnaire at age 22-23 years, including the Hypomania Checklist Questionnaire (HCL-32). Hypomanic symptoms were not assessed before this point. The HCL-32 is a self-report questionnaire pertaining to the lifetime experience of manic symptoms (Angst et al., 2005) Respondents are asked to consider a time when they were in a “high or hyper” condition and endorse various statements about their emotions, thoughts and behaviours during this time. There are 32 symptom statements, e.g., “I think faster,” and “I need less sleep.” The HCL-32 was developed to screen for possible subthreshold hypomanic syndromes in people with depressive disorders and has been used previously in non-clinical populations of youth.

Consistent with this previous work (Marwaha et al., 2017), we constructed a lifetime history of hypomania variable, with a threshold of 14+ out of 32 hypomanic features. Additionally, participants had to report: at least one occurrence of either “negative consequences” or “negative plus positive consequences,” due to hypomanic symptoms; *and* that mood changes caused a response (neutral, negative, or negative and positive) in close others; *and* that hypomanic symptoms lasted for a duration of at least “2-3 days.” A duration of 2-3 days or more was originally chosen because it was deemed important that the screening tool was sensitive to experiences of brief hypomania (i.e. syndromes lasting 2-3 days rather than the usual diagnostic threshold of 4 days). This duration increases the detection of individuals at risk of

bipolar disorder that meets diagnostic criteria and previous research had demonstrated that individuals who experience brief hypomania have similar clinical and family histories to individuals with BD-I and BD-II (Angst et al., 2005). We choose this conservative threshold (i.e., severity, duration, and impairment) to identify clinically relevant symptoms.

Psychosocial confounders

We controlled for gender, family adversity, and physical and sexual abuse, given they are associated with depression, psychotic symptoms and hypomania (Marwaha and Bebbington, 2015; Marwaha et al., 2016). Multiple family risk factors were assessed using the Family Adversity Index (FAI) during pregnancy ('long index'), 2 years ('long index'), and 4 years ('short index'). The FAI 'long index' comprises 18 items.(Wolke et al., 2012) The short index has 15 of the same items (e.g., financial status, housing). Each item was given one point (if yes). Points were summed at each time-point for a total FAI score.

Physical and sexual abuse were mother reported (postal questionnaire) when children were 1.5, 3.5, 4.8, 5.8, and 6.8 years old. We constructed two variables representing physical and sexual abuse respectively at any time-point.

Statistical Analysis

Missing data

Whilst 6091 completed the BPD interview at age 11 years, inclusion in the final sample depended on the child also having completed the depression computerised interview at 18 years, the psychotic symptoms interview at 18 years, and the hypomania questionnaire at 22-23 years.

This meant the sample for the final path model was 1758 (see **Figure 1**). We conducted logistic regressions to determine the predictors of missing data. These were male sex, low birthweight, and family adversity (**Table S1**). We therefore constructed weights for based on these predictors, to account for missing data within our analysis.

Logistic regression analysis

We chose to take an approach that used dichotomous variables so that measures of effect were odd ratios, which are generally more easily understood amongst clinicians than coefficients. Where possible the dichotomous variables are also linked with relevant clinical diagnoses, aiding the extent to which results are clinically interpretable. We conducted logistic regressions with *SPSS version 25*. BPD was the independent variable and depressive, psychotic, and hypomania symptoms were the dependent variables.

We developed our model in four stages, iteratively adjusting for confounders: 1) Unadjusted associations; 2) Adjusted for gender, family adversity, and physical/sexual abuse; 3) Plus depressive and psychotic symptoms at 12 years; 4) Plus depressive and psychotic symptoms at age 18 for the hypomanic outcome; depression at 18 years for the psychotic outcome; and psychotic symptoms at age 18 years for the depression outcome.

Path analysis

We conducted path analysis modelling using *Mplus version 7.11*. We controlled for multiple pathways (concurrent and prospective) between psychopathological measures (e.g., depressive symptoms at 12 and 18 years; depressive and psychotic symptoms at 18 years) to determine the

independent associations between BPD and subsequent psychopathologies. We included our weighting variable in the path model.

Results

Descriptive and unadjusted statistics

At age 11-12 years, 6.7% of adolescents reported 5 or more probable/definite symptoms over the past two years. At 18 years, 7.9% had any ICD-10 diagnosis of depression (experienced during the past month), while 4.1% reported experiencing one or more psychotic symptoms since age 12 years. At 22-23 years, 8% reported lifetime clinically relevant hypomanic symptoms. Psychotic and depressive symptoms were strongly associated (Odds Ratio (OR): 5.50; 95% Confidence Interval (CI): 3.20, 9.45). Associations between psychotic experiences and hypomania symptoms (OR: 1.69; 95% CI: 0.82, 3.47) and depression and hypomania symptoms were not significant (OR: 1.44; 95% CI: 0.82, 2.54).

Logistic regression models

Results of the weighted analysis are reported in **Table 1**. BPD symptoms significantly predicted each of the psychopathological outcomes in both unadjusted and adjusted analyses. Associations remained largely unchanged following control for psychosocial confounders (Model 2). Overall, the biggest attenuation effect followed the incorporation of depressive and psychotic symptoms at 12 years (Model 3).

Path analysis

The path model is shown in **Figure 2**. The model had adequate (CFI=0.94) to good ($X^2 = 23.84$, $p = 0.07$; RMSEA=0.02) fit. Four independent trajectories from BPD were evident in the path analysis. First, BPD symptoms were independently associated with clinically relevant depressive symptoms, one or more psychotic symptoms at 12 years, and clinically relevant hypomanic symptoms at 22-23 years. Second, BPD symptoms were indirectly associated with ICD-10 depression (mild, moderate, or severe) at 18 years via depressive symptoms at 12 years. BPD symptoms were not significantly indirectly associated with psychotic symptoms at 18 years via psychotic symptoms at 12 years. However, BPD symptoms were significantly linked to psychotic symptoms at age 12 years, which in turn, were significantly associated with psychotic symptoms at age 18 years (**Table 2; Figure 2**).

Discussion

Our study represents a first step towards explicating the psychopathological sequelae of BPD symptoms (5 or more repeated or very frequent) in a community population. Adolescent BPD symptoms increased the risk of subsequent psychotic symptoms, a diagnosis of depression reported at 18 years, and clinically relevant lifetime hypomanic symptoms reported at 22-23 years. The prospective direct association with depression diagnosis at 18 was not significant following control for all confounders (including inter-relationships between all psychopathological symptoms) in the path analysis. However, BPD was significantly indirectly associated with depression diagnosis via depressive symptoms at 12 years.

The association between adolescent BPD symptoms and subsequent psychotic and hypomanic symptoms are notable given that they have received limited prospective

investigation. It is suggested that many psychiatric disorders are sequentially co-morbid, recurrent, or chronic (Caspi et al., 2014). Our findings suggest that young adolescents with substantial BPD symptomatology are at increased risk of experiencing a range of clinically relevant psychiatric symptoms across several developmental stages (early/late adolescence, early adulthood). Independent developmental pathways linked to hypomania and psychotic symptoms were not likely attributable to symptom overlap between outcomes, as we simultaneously controlled for all associations between each of the psychopathological outcome assessments. These findings are consistent with notions of multifinality (i.e., BPD has divergent outcomes).

Our results are in line with the hypothesis that early BPD symptoms can be seen as an adolescent manifestation of the confluence of internalizing and externalizing (IE) psychopathology on the severity pathway that leads to subsequent major mental disorders (Sharp and Wall, 2018). These outcomes may be determined by the severity level of IE, mediating and moderating contexts, and transactional feedback loops with the manifest syndrome (Beauchaine and Cicchetti, 2016). Indeed, Hayes et al. (2017) hypothesize that the genetic architecture of maladaptive personality traits and serious mental illness may be shared, with emotional instability (a key feature of BPD), in particular, predicting serious mental illness. Maladaptive interpersonal functioning (e.g., self-other relatedness, including maladaptive self-perception and social function), which is another key feature of BPD, may be particularly important as a precursor to other personality pathology (Sharp et al., 2018; Sharp and Wall, 2018). Thus, personality pathology can be considered an important severity indicator in adolescence that should not be ignored.

Previous research suggests three trajectories for individuals with adolescent BPD symptoms: 1) continuation of BPD symptoms over time; 2) remission of psychiatric symptoms; and 3) the development of other disorders (Winsper et al., 2015a). Our analyses highlight there is a risk that individuals develop other types of clinically relevant psychopathology and supports the idea of heterotypic continuity as a developmental pathway. It also supports the notion that adolescents with BPD symptoms are a clinically vulnerable group by virtue of their current symptomatology, but also due to risks of future psychopathology. This helps explain the long-term morbidity associated with the condition, and why the outcomes can be for so devastating into adulthood.

Our study has strengths and limitations. Strengths include the use of data from a large, well-defined birth cohort, with repeated assessments of important psychopathologies covering a developmental period largely neglected in BPD research. Using a validated interview for BPD, we could identify adolescents with 5 or more BPD symptoms, thus creating a variable comparable in composition to the DSM-5 diagnosis for BPD (American Psychiatric Association, 2013). In our community sample, 6.7% of adolescents met our criteria for substantial BPD symptoms. This rate is somewhat higher than the 1.8% (95% CI: 1.2 to 2.5%) reported in adult community populations (Winsper et al., 2019), and is likely attributable to our lower symptom frequency threshold (i.e., inclusion of repeated and very frequent symptom counts). Other small scale community studies with younger populations have suggested a higher prevalence of BPD (e.g., 11% using algorithms for DSM-III-R diagnosis), with a peak in prevalence at 12-13 years of age (Bernstein et al., 1993). This suggests our data handling strategy is likely to have some clinical utility (i.e., in identifying sub-clinical youth at heightened risk of BPD). Whilst our BPD

symptom variable does not equate to a clinician derived BPD diagnosis; it does represent a good balance between clinical and scientific needs. We were able to study a relatively large group of youths demonstrating five or more BPD symptoms, while avoiding the inevitable resource issues associated with providing clinical assessments in epidemiological research. At age 18 years, 7.9% of the sample had any ICD-10 diagnosis of depression consistent with previous epidemiological data (Costello et al., 2005), again supporting the validity of our approach to data handling and analysis. Another strength was our use of advanced analytical methods (e.g., path analysis), which allowed us to understand the prospective connections between psychopathological clusters. Future analyses should consider the use of network analysis to further understand the interconnections between multiple psychopathological and other parameters in studies of adolescent BPD.

There were also limitations. First, while the prospective design enabled us to model predictive pathways based on temporal ordering, some assessments lacked temporal precision, e.g., psychotic symptoms at 18 referred to events occurring since the previous assessment (12 years), and the hypomanic scale referred to lifetime occurrence. However, it should be highlighted that pre-pubertal hypomania is very rare (Kroon et al., 2013), and it is unlikely that respondents would remember symptoms occurring several years ago. Second, there was considerable selective attrition in the cohort reducing statistical power and potentially biasing our results. We weighted both our logistic and path analyses to account for this attrition (Kinner et al., 2007). Third, while we included clinically relevant levels of psychiatric symptoms where possible (e.g., ICD depression diagnosis, hypomanic symptoms according to severity, duration, and impairment), we couldn't include psychotic disorder as the frequency was too low.

Nevertheless, psychotic symptoms are a marker for, and significantly increase risk of, psychotic disorder in adults (Fisher et al., 2013). Fourth, childhood risk factors, including family adversity and physical and sexual abuse were reported by the child's mother. This could have led to issues such as under-reporting as mothers may have been unaware of abuse experiences or were reluctant to report these factors as they could imply neglected care. Thus, there is a small chance that we could have underestimated the impact of confounders on associations between psychopathologies. Further, some of our psychopathological outcomes were assessed via interview, either face-to-face or computerised (i.e., psychotic symptoms reported at 12 and 18 years, and depression symptoms reported at 18 years), and others via self-report postal questionnaire (i.e., depression symptoms reported at 12 years and hypomania symptoms reported at 22-23 years). Thus, there were variations in mode of administration, which could have potentially influenced responses in reference to the different psychopathological outcomes (Bowling, 2005). These differences could have led to an under-estimation of the strength of associations between psychopathologies. Ideally, we would use interview data for all psychopathologies as the gold standard approach to assessing mental disorders. However, this was not possible in due to the considerable resource demands, e.g., young adults assessed at 22-23 years of age likely moved to locations across the country. Fifth, BPD symptoms were only assessed once in this cohort. This is unfortunate and likely reflects the substantial costs involved in administering clinical interviews to very large samples, and the current underfunding of BPD in comparison to other psychiatric disorders (Zimmerman and Gazarian, 2014). Subsequently, we could not examine whether adolescents with BPD symptoms continued to manifest chronic BPD symptoms in early adulthood, or whether associations with other psychopathological outcomes (e.g., psychotic and hypomania symptoms) remained significant following control for

concurrent BPD symptoms. Therefore, it is possible that associations between adolescent psychopathology and subsequent psychotic, depression and hypomania symptomatology were explained by a continuation of BPD symptoms into late adolescence and early adulthood. Clinical studies indicate that most episodes of psychotic and dissociative symptoms in patients with BPD are transient, and of a different structural, functional and physiologic nature to those observed in psychotic disorder (e.g., amygdala over-reactivity versus decreased amygdala activity). This suggests that associations were not solely attributable to concurrent BPD in late adolescence. However, studies do indicate that a subset of BPD patients may experience permanent and more severe psychotic symptoms over time (Barnow et al., 2010). Similarly, clinical studies suggest that BPD and bipolar disorders are independent, though there may be a sub-group of individuals with characterological bipolar disorder, i.e., they demonstrate both BPD and bipolar II symptoms that are less tied to bipolar I disorder (Gunderson et al., 2014). Relatedly, given the overlap between diagnostic clusters of mental disorders, and the fact that those who did not meet criteria for BPD symptoms in early adolescence may have done so subsequently (e.g., at 18 or 22-23 years), it is possible that we measured the same trans-diagnostic symptom pool over several time points. We cannot completely discount this possibility, but it is likely that the reliable and valid measures such as the UK-CI-BPD, CIS-R and HCL are at least to some extent able to accurately differentiate different symptom clusters. Finally, we did not examine the influence of treatment within our analyses. However, in the UK context, services and specialist programmes for adolescents with BPD are very limited and it is unlikely that specific treatment for BPD in adolescence will have had a major influence on our findings, especially given few UK psychiatrists will diagnose BPD before age 18 years.

In conclusion in a large birth cohort study, we found that adolescent syndromal BPD was associated with a range of psychopathological sequelae up to ten years later. Our findings add to the growing literature on the adverse outcomes of adolescent BPD (Winsper et al., 2015a), and should raise clinical awareness that if BPD symptoms are measured in early adolescence, a significant sub-population already appear to have a BPD-like syndrome and these individuals are at risk of a range of future psychopathology. This study raises the possibility that early secondary intervention (Chanen et al., 2014) may help reduce the risk of poor psychopathological outcomes potentially offering an avenue for primary prevention of other major mental disorders. The next step in our investigation is to identify the determinants (e.g., environmental risks) of different developmental trajectories to increase our understanding of the varied outcomes of adolescent BPD (Forbes et al., 2016).

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Conflicts of interest: SM attended a World Psychiatric Association consensus meeting on early intervention sponsored by an unrestricted educational grant from Sonuvion. All other authors declare no conflicts of interest.

Table 1. Weighted unadjusted and adjusted associations between BPD in early adolescence and psychopathological outcomes in late adolescence/early adulthood					
Depression at 18 years		Psychotic symptoms at 18 years		Hypomanic symptoms at 22-23 years	
Odds Ratio (95% CIs)		Odds Ratio (95% CIs)		Odds Ratio (95% CIs)	
Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
<u>Model 1</u> 2.31 (1.90, 2.80)	<u>Model 2</u> 2.09 (1.72, 2.55)	<u>Model 1</u> 3.05 (2.42, 3.86)	<u>Model 2</u> 2.84 (2.24, 3.60)	<u>Model 1</u> 2.90 (2.43, 3.47)	<u>Model 2</u> 2.94 (2.46, 3.51)
	<u>Model 3</u> 1.46 (1.17, 1.82)		<u>Model 3</u> 2.39 (1.85, 3.08)		<u>Model 3</u> 2.96 (2.46, 3.56)
	<u>Model 4</u> 1.30 (1.03, 1.64)		<u>Model 4</u> 2.36 (1.82, 3.06)		<u>Model 4</u> 2.89 (2.40, 3.48)
Analysis weighted for significant predictors of attrition (gender, birthweight, and family adversity); Significant associations in boldface; Results reported in Odds Ratios with 95% Confidence Intervals; Model 2: Adjusted for gender, family adversity, and any abuse in early childhood; Model 3: All psychosocial confounders and additionally controlled for psychotic symptoms and depression at 12 years; Model 4: All confounders in Model 3 and additionally controlled for depression for the psychotic outcome, psychotic symptoms for the depression outcome, and depression and psychotic symptoms for the hypomania outcome.					

Table 2. Direct and indirect associations between BPD, depression, psychotic, and hypomanic symptoms within the final path model

Predictor variables	Psychopathological outcomes				
<u>Direct associations</u>	Depressive symptoms at 12 years	Psychotic symptoms at 12 years	Depression at 18 years	Psychotic symptoms at 18 years	Hypomanic at 22 years
BPD at 11-12 years	0.97 (p<0.001)	0.58 (p<0.001)	0.22 (p=0.28)	0.22 (p=0.34)	0.58 (p<0.01)
Depression at 12 years	N/A	0.32 (p<0.001)^a	0.25 (p<0.01)	0.20 (p=0.07)	N/A ^b
Psychotic symptoms at 12 years	0.32 (p<0.001)^a	N/A	0.02 (p=0.90)	0.34 (p<0.01)	N/A ^b
Depression at 18 years	N/A	N/A	N/A	0.37 (p<0.001)^a	0.03 (p=0.79)
Psychotic symptoms at 18 years	N/A	N/A	0.37 (p<0.001)^a	N/A	0.11 (p=0.30)
<u>Indirect associations</u>					
BPD via depression at 12 years	N/A	N/A	0.24 (p<0.05)	0.20 (p=0.08)	N/A
BPD via psychotic symptoms at 12 years	N/A	N/A	0.01 (p=0.90)	0.20 (p=0.057)	N/A
BPD via depression at 18 years	N/A	N/A	N/A	N/A	0.01 (p=0.80)
BPD via psychotic symptoms at 18 years	N/A	N/A	N/A	N/A	0.02 (p=0.48)

Results reported in probit coefficients: probit coefficients indicate the strength of the relationship between the predictor variable and the probability of group membership, representing the change in the probability of “caseness” associated with a unit change in the independent variable. Analysis weighted for predictors of attrition; ^aThese are correlations; ^bWe did not include these pathways in the final model as it led to saturation and thus no model fit information. However, when included in the model, reported associations did not change; Boldface indicates significant associations

Figure 1. Flow diagram detailing numbers of participants who completed key follow-up assessments during the Avon Longitudinal Study of Parents and Children (ALSPAC)

Figure 2. The final path model including associations between adolescent BPD and subsequent psychopathologies

References

- American Psychiatric Association. (2013) *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.
- Angold A, Costello EJ, Messer SC, et al. (1995) Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International journal of methods in psychiatric research*.
- Angst J, Adolfsson R, Benazzi F, et al. (2005) The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *Journal of affective disorders* 88: 217-233.
- Barnow S, Arens EA, Sieswerda S, et al. (2010) Borderline personality disorder and psychosis: a review. *Current Psychiatry Reports* 12: 186-195.
- Beauchaine TP and Cicchetti D. (2016) A new generation of comorbidity research in the era of neuroscience and Research Domain Criteria. *Development and psychopathology* 28: 891-894.
- Belsky DW, Caspi A, Arseneault L, et al. (2012) Etiological features of borderline personality related characteristics in a birth cohort of 12-year-old children. *Development and psychopathology* 24: 251-265.
- Bernstein DP, Cohen P, Velez CN, et al. (1993) Prevalence and stability of the DSM-III-R personality disorders in a community-based survey of adolescents. *American Journal of Psychiatry* 150: 1237-1237.
- Boyd A, Golding J, Macleod J, et al. (2013) Cohort Profile: The ‘Children of the 90s’—the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology* 42: 111-127.
- Caspi A, Houts RM, Belsky DW, et al. (2014) The p factor one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science* 2: 119-137.
- Chanen AM, Jackson HJ, McGorry PD, et al. (2004) Two-year stability of personality disorder in older adolescent outpatients. *Journal of personality disorders* 18: 526.
- Chanen AM, McCutcheon L and Kerr IB. (2014) HYPE: A Cognitive Analytic Therapy-Based Prevention and Early Intervention Programme for Borderline Personality Disorder. *Handbook of borderline personality disorder in children and adolescents*. Springer, 361-383.
- Cohen P, Chen H, Crawford TN, et al. (2007) Personality disorders in early adolescence and the development of later substance use disorders in the general population. *Drug and Alcohol Dependence* 88: S71-S84.
- Costello EJ, Egger H and Angold A. (2005) 10-year research update review: the epidemiology of child and adolescent psychiatric disorders: I. Methods and public health burden. *Journal of the American Academy of Child & Adolescent Psychiatry* 44: 972-986.
- Fisher HL, Caspi A, Poulton R, et al. (2013) Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychological medicine* 43: 2077-2086.
- Forbes MK, Tackett JL, Markon KE, et al. (2016) Beyond comorbidity: Toward a dimensional and hierarchical approach to understanding psychopathology across the life span. *Development and psychopathology* 28: 971-986.

- George EL, Miklowitz DJ, Richards JA, et al. (2003) The comorbidity of bipolar disorder and axis II personality disorders: prevalence and clinical correlates. *Bipolar disorders* 5: 115-122.
- Grilo CM, McGlashan T and Oldham J. (1998) Course and stability of personality disorders. *Journal of Psychiatric Practice*® 4: 61-75.
- Gunderson JG, Stout RL, Shea MT, et al. (2014) Interactions of borderline personality disorder and mood disorders over ten years. *Journal of Clinical Psychiatry* 75: 829.
- Hayes J, Osborn D, Lewis G, et al. (2017) Association of Late Adolescent Personality With Risk for Subsequent Serious Mental Illness Among Men in a Swedish Nationwide Cohort Study. *JAMA psychiatry*.
- Horwood J, Salvi G, Thomas K, et al. (2008) IQ and non-clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort. *The British Journal of Psychiatry* 193: 185-191.
- Jaffee SR. (2017) Child maltreatment and risk for psychopathology in childhood and adulthood. *Annual review of clinical psychology* 13: 525-551.
- Johnson JG, Cohen P, Skodol AE, et al. (1999) Personality disorders in adolescence and risk of major mental disorders and suicidality during adulthood. *Archives of general psychiatry* 56: 805-811.
- Kaess M, Brunner R and Chanen A. (2014) Borderline personality disorder in adolescence. *Pediatrics* 134: 782-793.
- Kinner SA, Alati R, Najman JM, et al. (2007) Do paternal arrest and imprisonment lead to child behaviour problems and substance use? A longitudinal analysis. *Journal of Child Psychology and Psychiatry* 48: 1148-1156.
- Kroon JS, Wohlfarth TD, Dieleman J, et al. (2013) Incidence rates and risk factors of bipolar disorder in the general population: a population- based cohort study. *Bipolar disorders* 15: 306-313.
- Lewis G, Pelosi AJ, Araya R, et al. (1992) Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychol Med* 22: 465-486.
- Lieb K, Zanarini MC, Schmahl C, et al. (2004) Borderline personality disorder. 364: 453-461.
- Lofgren DP, Bemporad J, King J, et al. (1991) A prospective follow-up study of so-called borderline children. *American Journal of Psychiatry* 148: 1541-1547.
- Marwaha S and Bebbington P. (2015) Mood as a mediator of the link between child sexual abuse and psychosis. *Social psychiatry and psychiatric epidemiology* 50: 661-663.
- Marwaha S, Gordon-Smith K, Broome M, et al. (2016) Affective instability, childhood trauma and major affective disorders. *Journal of affective disorders* 190: 764-771.
- Marwaha S, Winsper C, Bebbington P, et al. (2017) Cannabis use and hypomania in young people: a prospective analysis.
- Sharp C and Fonagy P. (2015) Practitioner Review: Borderline personality disorder in adolescence—recent conceptualization, intervention, and implications for clinical practice. *Journal of Child Psychology and Psychiatry* 56: 1266-1288.
- Sharp C, Goodyer IM and Croudace TJ. (2006) The Short Mood and Feelings Questionnaire (SMFQ): a unidimensional item response theory and categorical data factor analysis of self-report ratings from a community sample of 7-through 11-year-old children. *Journal of abnormal child psychology* 34: 365-377.

- Sharp C, Ha C, Michonski J, et al. (2012) Borderline personality disorder in adolescents: evidence in support of the Childhood Interview for DSM-IV Borderline Personality Disorder in a sample of adolescent inpatients. *Comprehensive psychiatry* 53: 765-774.
- Sharp C, Vanwoerden S and Wall KJPC. (2018) Adolescence as a Sensitive Period for the Development of Personality Disorder. 41: 669-683.
- Sharp C and Wall KJCoip. (2018) Personality pathology grows up: adolescence as a sensitive period. 21: 111-116.
- Singh SP, Winsper C, Wolke D, et al. (2014) School mobility and prospective pathways to psychotic-like symptoms in early adolescence: a prospective birth cohort study. *Journal of the American Academy of Child & Adolescent Psychiatry* 53: 518-527. e511.
- Stapp SD, Smith TD, Morse JQ, et al. (2012) Prospective associations among borderline personality disorder symptoms, interpersonal problems, and aggressive behaviors. *Journal of Interpersonal Violence* 27: 103-124.
- Thompson A, Nelson B, Bechdolf A, et al. (2012) Borderline personality features and development of psychosis in an 'Ultra High Risk'(UHR) population: a case control study. *Early intervention in psychiatry* 6: 247-255.
- Wenning K. (1990) Borderline children: A closer look at diagnosis and treatment. *American Journal of Orthopsychiatry* 60: 225.
- Winsper C, Bilgin A, Thompson A, et al. (2019) The prevalence of personality disorders in the community: a global systematic review and meta-analysis. *The British Journal of Psychiatry*: 1-10.
- Winsper C, Lereya ST, Marwaha S, et al. (2016a) The aetiological and psychopathological validity of borderline personality disorder in youth: A systematic review and meta-analysis. *Clinical psychology review* 44: 13-24.
- Winsper C, Marwaha S, Lereya ST, et al. (2015a) Clinical and psychosocial outcomes of borderline personality disorder in childhood and adolescence: a systematic review. *Psychological medicine* 45: 2237-2251.
- Winsper C, Wolke D, Bryson A, et al. (2016b) School mobility during childhood predicts psychotic symptoms in late adolescence. *Journal of Child Psychology and Psychiatry*.
- Winsper C, Wolke D and Lereya T. (2015b) Prospective associations between prenatal adversities and borderline personality disorder at 11–12 years. *Psychological medicine* 45: 1025-1037.
- Wolke D, Schreier A, Zanarini MC, et al. (2012) Bullied by peers in childhood and borderline personality symptoms at 11 years of age: A prospective study. *Journal of Child Psychology and Psychiatry* 53: 846-855.
- Zammit S, Kounali D, Cannon M, et al. (2013) Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry*.
- Zanarini M and Frankenburg F. (2001) Attainment and maintenance of reliability of Axis I and II disorders over the course of a longitudinal study. *Comprehensive psychiatry* 42: 369–374.
- Zanarini M, Horwood J, Waylen A, et al. (2004) The UK Version of the Childhood Interview for DSM-IV Borderline Personality Disorder (UK-CI-BPD). In: Bristol Uo (ed). Bristol.

- Zanarini M, Horwood J, Wolke D, et al. (2011) Prevalence of DSM-IV borderline personality disorder in two community samples: 6,330 English 11-year olds and 34,653 American adults. *Journal of personality disorders* 25: 607-619.**
- Zimmerman M and Gazarian D. (2014) Is research on borderline personality disorder underfunded by the National Institute of Health? *Psychiatry research* 220: 941-944.**
- Zwierzynska K, Wolke D and Lereya TS. (2013) Peer victimization in childhood and internalizing problems in adolescence: a prospective longitudinal study. *Journal of abnormal child psychology* 41: 309-323.**

