Associations between infant and toddler regulatory problems, childhood co-developing internalising and externalising trajectories, and adolescent depression, psychotic and borderline personality disorder symptoms

Catherine Winsper, Ph.D., Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick; catherine.winsper@warwick. ac.uk;
Ayten Bilgin, Ph.D., Department of Psychology, University of Warwick and Psychologische Hochschule Berlin; ayten.bilgin@warwick.ac.uk;
Dieter Wolke, Ph.D., Dr rer nat h.c., Department of Psychology and Division of Mental Health and Wellbeing
Correspondence: Dieter Wolke, Department of Psychology and Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick, UK, CV4 7AL; email: D.Wolke@warwick.ac.uk; tel: + 44 (0) 2476 573 217
Declaration of Interest: C.W, A.B, and D.W report no conflicts of interest.
Acknowledgements: We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK medical research council and the Wellcome Trust (Grant Ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors. C.W & D.W serve as guarantors for its contents.

Abstract

Background: Early regulatory problems (RPs) are associated with childhood internalising and externalising symptoms. Internalising and externalising symptoms, in turn, are associated with adolescent psychopathology (e.g., personality disorders, depression). We examined whether RPs are directly associated with adolescent psychopathology, or whether associations are indirect via childhood internalising and externalising symptoms.

Methods: We used data from the Avon Longitudinal Study of Parents and Children. Mothers reported on their child's RPs at 6, 15-18 and 24-30 months, and internalising and externalising symptoms at 4, 7, 8 and 9.5 years. Adolescent psychotic, depression and BPD symptoms were assessed at 11-12 years. Children were grouped by their patterns of co-developing internalising and externalising symptoms using parallel process-latent class growth analysis (PP-LCGA). Path analysis was used to examine direct and indirect associations from RPs to the three adolescent outcomes.

Results: There were four groups of children with distinct patterns of co-developing internalising and externalising (INT/EXT) symptoms. Most children (53%) demonstrated low-moderate and stable levels of INT/EXT symptoms. A small proportion (7.7%) evidenced moderate and increasing INT and high stable EXT symptoms: this pattern was strongly predictive of adolescent psychopathology (e.g., depression at 11 years: unadjusted Odds Ratio = 5.62; 95% Confidence Intervals = 3.82, 8.27). The other two groups were differentially associated with adolescent outcomes (i.e., moderate-high increasing INT/moderate decreasing EXT predicted mother-reported depression at 12, while low stable INT/moderate-high stable EXT predicted child-reported depression at 11). In path analysis, RPs at each time-point were significantly indirectly associated with symptoms of BPD and child and mother reported depression symptoms via the most severe class of INT/EXT symptoms.

Conclusions: Consistent with a cascade model of development, RPs are predictive of higher levels of co-developing INT/EXT symptoms, which in turn increase risk of adolescent psychopathology. Clinicians should be aware of, and treat, early RPs to prevent chronic psychopathology.

Keywords: *regulatory problems; internalising and externalising symptoms; parallel process latent class growth analysis; ALSPAC*

Introduction

Regulatory problems (RPs) include excessive crying beyond the colic period of three months (Wolke, Bilgin, & Samara, 2017) and feeding and sleeping problems beyond six months of age (Bilgin & Wolke, 2016). RPs are sometimes transient and without consequence. However, co-occurring and/or persistent RPs can increase the risk of internalising and externalising symptoms and mental disorders across childhood and adolescence (Bilgin et al., 2018; Cook et al., 2019; Hemmi, Wolke, & Schneider, 2011; Hyde, O'Callaghan, Bor, Williams, & Najman, 2012; Toffol et al., 2018; Winsper & Wolke, 2014). The cascade model of development describes how early risk predictors can cumulatively influence maladaptive outcomes over time (Hentges, Graham, Plamondon, Tough, & Madigan, 2019). The "cascade" represents the extent to which differences in emotion or behaviour maximally affect the next most proximate phase of development, which in turn affects the following stage, and so on (Hyde et al., 2012). Within this theoretical framework, early RPs are viewed as the starting point of a trajectory of self-regulatory problems (Winsper & Wolke, 2014), which may manifest as daytime co-occurring internalising and externalising behaviour problems (Williams et al., 2017). These problems, in turn, can increase the risk of a range of psychopathological outcomes including personality disorders (Halperin, Rucklidge, Powers, Miller, & Newcorn, 2011), DSM-IV diagnoses (mood, anxiety, ADHD) and co-morbidity (Bianchi et al., 2017).

Recently researchers have highlighted the importance of identifying early risk pathways for psychopathology (Wiggins, Mitchell, Hyde, & Monk, 2015). However, there is currently a degree of conceptual confusion surrounding the terms used to describe childhood risk profiles (Althoff et al., 2012). There are three key concepts in the developmental psychopathological literature: 1) the childhood dysregulation phenotype or profile; 2) co-developing internalising and externalising symptom profile; and 3) the general psychopathology or "p" factor. The p factor is the broadest of these three concepts and comprises internalising, externalising and thought disorder components (Deutz et al., 2019). Here, we focus on the first two concepts as most relevant to our study (i.e., a chronic pattern of self-regulatory problems across childhood).

The childhood dysregulation profile and co-developing internalising and externalising symptoms are often derived from the same assessment tools (i.e., the Child Behaviour Checklist and Strengths and Difficulties Questionnaire) by combining the emotional symptoms, conduct problems, and hyperactivity-inattention subscales. However, they differ in their terminology and mode of construction. The dysregulation profile (DP) is often derived by simply summing together

emotional (as a marker for emotional dysregulation), conduct problems and hyperactivity (as a marker for behavioural dysregulation) subscales (Deutz et al., 2018; Winsper & Wolke, 2014). In contrast, the co-developing internalising (emotional symptoms subscale) and externalising (conduct and hyperactivity subscales) symptom profile is derived by using sophisticated statistical methods (e.g., Parallel-Process Latent Class Growth Analysis) to model how internalising and externalising symptoms change concurrently over time (Wiggins et al., 2015). The DP has been criticised for its lack of specificity in outcome prediction (Deutz et al., 2018; Jordan, Rescorla, Althoff, & Achenbach, 2016). By modelling how internalising and externalising symptom domains change concurrently (while enabling separate internalising and externalising trajectories) we can elucidate a more nuanced picture of high-risk developmental trajectories (Wiggins et al., 2015). This is important in view of the distinct developmental profiles of internalising and externalising symptoms, e.g., externalising symptoms tend to decrease over childhood (Costello, Copeland, Angold, & Psychiatry, 2011), while internalising symptoms tend to increase for girls and decrease for boys (Nivard et al., 2017).

The current study

It is currently unclear whether early RPs are associated with adolescent psychopathology directly or indirectly via a childhood profile of increased risk (e.g., co-developing internalising and externalising symptoms). To address this research question, we took a two-stage approach (Jung & Wickrama, 2008). In the first stage, we used Parallel Process Latent Class Growth Analysis (PP-LCGA) to identify groups of children based on their longitudinal patterns of co-developing internalising and externalising (INT/EXT) symptoms. In the second stage, we included these derived groups in logistic regression and path analysis to assess the predictors (e.g., RPs, family adversity, maternal mental health), outcomes (e.g., depression, psychotic symptoms), and indirect pathways (e.g., from RPs to adolescent outcomes) of INT/EXT symptom patterns. We addressed the following research questions: 1) Are early RPs directly associated with symptoms of adolescent borderline personality disorder, psychosis and depression? 2) Consistent with a cascade model, are RPs indirectly associated with adolescent psychopathological symptoms via co-developing internalising and externalising symptoms?

Methods

Participants

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a UK birth cohort examining the determinants of development, health and disease. The study is described in detail elsewhere (Boyd et al., 2013). ALSPAC recruited 14,541 pregnant women with expected delivery dates of 1st April 1991 to 31st December 1992. Of the *initial* pregnancies, there were 14,676 foetuses resulting in 14,062 live births; 13,988 children were alive at 1 year of age. A total of 13,978 children formed the original cohort. Ethical approval was obtained from the ALSPAC Law and Ethics committee and the local research ethics committee. From the first trimester of pregnancy, parents completed postal questionnaires about themselves and the study child. Children were invited to annual assessment clinics, including face-to-face interviews, and psychological and physical tests from 7 years onwards. The study website contains details of all data available through a fully searchable dictionary (http://www.bris.ac.uk/alspac/ researchers/data-access/data-dictionary/).

The final sample for the path analysis included adolescents with depression, psychotic, and borderline personality disorder symptom assessments (*N*= 5, 202: 37.2% of original sample; sample size varied very slightly according to whether the child or mother reported depression outcome was included). We compared those lost to follow-up to those retained in the analysis to determine whether attrition was selective (**Supplementary Table 1**). Male gender, black ethnicity, lower birth weight, mother's single status and lower education, parents' manual labour, and family adversity predicted attrition. We conducted a weighted analysis based on the inverse probability of response. We fitted a logistic regression model to calculate the probability of response for each participant (Kinner, Alati, Najman, & Williams, 2007). We then calculated a weight for each participant based on the inverse probability of participating. The pattern and comparative strength of associations were very similar in the weighted to unweighted analysis. We, therefore, report the unweighted analysis (Winsper, Wolke, Bryson, Thompson, & Singh, 2016).

Measures

Adolescent psychopathological outcomes

Depression was assessed with the 13-item Short Moods and Feelings Questionnaire: SMFQ (Angold, Costello, Messer, & Pickles, 1995). The SMFQ is a valid and reliable tool based on DSM-III criteria for depression (Thapar, Collishaw, Potter, & Thapar, 2010). Items are rated on a 3-point scale ('not true'=0; 'sometimes'=1; 'true'=2) and refer to events from the past two weeks, e.g., 'I felt miserable or unhappy." The child completed the SMFQ at 11 years. The mother completed the

SMFQ via postal questionnaires when the child was 12 years. We constructed separate child and mother-reported depression outcomes because of typically low rates of agreement (Ivens & Rehm, 1988). Items were summed for a total score (0-26 points) for each depression variable. The total score was dichotomised at ≥11 to indicate clinically relevant depression (Lereya et al., 2013).

Psychology graduates assessed psychotic symptoms at 12 years using the semi-structured psychosis-like symptoms interview. Adolescents reported whether they had experienced hallucinations, delusions or thought disorders in the previous 6 months (Zammit et al., 2014). Items were rated as "absent," "suspected" or "definitely" present. The average kappa value was 0.72 indicating good inter-rater reliability. We constructed a dichotomous variable representing the definite or suspected presence ≥1 psychotic symptom (Singh, Winsper, Wolke, & Bryson, 2014).

Adolescents were interviewed at 11 years to assess their symptoms of BPD over the past 2 years. Trained psychologists used the semi-structured UK Childhood Interview for DSM-IV Borderline Personality Disorder (Zanarini, Horwood, Waylen, & Wolke, 2004) adapted from the Diagnostic Interview for DSM-IV Personality Disorders (Zanarini, Frankenburg, Sickel, & Yong, 1996). Inter-rater reliability (k) within the current sample ranged from 0.36 to 1.0 (median value 0.88); 86% of the k values were within the excellent range of >0.75 (Zanarini et al., 2011). The UK-CI-BPD comprises nine sections. Each symptom was categorised as definitely present (daily or at least 25% of the time), probably present (symptoms occurring repeatedly) or absent. The dichotomous outcome represented the very frequent or repeated occurrence of ≥5 BPD symptoms and was based on previous studies (Lereya, Winsper, Tang, & Wolke, 2017; Winsper, Wolke, & Lereya, 2015). The BPD outcome does not represent a BPD diagnosis. DSM-5 diagnosis of BPD is based on the presence of 5 or more definite symptoms (American Psychiatric Association, 2013), whereas our outcome was based on the presence of five or more probable (occurring repeatedly) or definite (occurring daily) symptoms.

Internalising and externalising symptoms

Internalising and externalising symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ), which mothers completed when children were 4, 7, 8 & 9.5 years old. The SDQ is a widely used and psychometrically valid behavioural screening tool suitable for community samples (Goodman & Goodman, 2011; Stone, Otten, Engels, Vermulst, & Janssens, 2010). The negative emotionality sub-scale has 5 items (total score of 0-10) examining internalising symptoms (e.g., "child has many worries"). The conduct problems (e.g., "child often cheats or lies") and

hyperactivity (e.g., 'child is easily distracted') subscales have 10 items (i.e., 5 per sub-scale with a total score of 0-20) examining externalising symptoms. We divided the total of these two scales by two to create a common scale (i.e., 0-10). Thus, we had total internalising (0-10) and externalising (0-10) symptom scores for each of the four time-points.

Regulatory Problems (RPs) composite

We constructed RP composites (0= no RPs; 1 = 1 RP; 2 = 2 or 3 RPs) at 6, 15-18 and 24-30 months by summing dichotomous mother-reported sleeping, crying and feeding problem variables (Winsper & Wolke, 2014). Details on individual items and methods of construction are presented in **Supplementary Table 2**.

Confounding variables

We included the following control variables as suggested by the literature: gender (Wiggins et al., 2015), family adversity (Singh et al., 2014), birthweight (Sonuga-Barke et al., 2017) and mother's mental health (Siegenthaler, Munder, & Egger, 2012).

Gender

There were 2, 510 (48%) males and 2, 692 (52%) females in the final sample.

Family adversity

The Family Adversity Index (FAI) comprises 18 items covering the following areas: age of mother at first pregnancy; housing (e.g., crowding, defects); education (mothers and fathers); financial status (e.g., financial difficulties); critical partner relationship (e.g., affection, aggression, emotional or physical cruelty); family size (e.g., >3 children); social network (e.g., support available); prenatal maternal mental health (e.g., anxiety or depression); substance abuse (e.g., drugs or alcohol); and crime (e.g., convictions). The FAI was administered throughout pregnancy at 8, 12, 18- and 32-weeks' gestation and was included as a continuous variable in the path analysis.

Birthweight

Birthweight was included as a dichotomous variable with a threshold of < 2, 500g (Kramer, 1987).

Mother's mental health

Mother's mental health was assessed during early childhood. Anxiety was assessed at 8 weeks and 8, 21 and 33 months using the Crown Crisp Experiential Index (CCEI), which is a validated self-rating inventory (O'Connor, Heron, Glover, & Team, 2002). Mothers with high scores (i.e., ≥9 items) at any of the four time-points were classed as having anxiety symptoms (Winsper et al., 2015). Maternal depression was assessed with the Edinburgh Postnatal Depression Scale (EPDS) at 8 weeks and 8, 21 and 33 months. Mothers were coded as having depression symptoms if they exceeded the cut-point (i.e., ≥13 items) at any time-point (Winsper et al., 2015). As these variables were very strongly associated (Odds Ratio = 24.5), we constructed a mother's mental health variable to represent the presence of anxiety and/or depression during at least one time point.

Analysis plan

We conducted our analysis using a two-stage process as described in Jung and Wickrama (2008). Stage one involved using parallel process-latent class growth analysis (PP-LCGA) to identify groups of children demonstrating similar longitudinal patterns of co-developing internalising and externalising symptoms. We incorporated gender as a covariate in the PP-LCGA. The literature indicates that gender has significant direct effects on internalising and externalising (INT/EXT) symptom development (Wiggins et al., 2015). Therefore, we included gender at this stage of the analysis to avoid misspecification of the INT/EXT classes (Jung and Wickrama, 2008). We did not include the other confounding variables at this point due to the considerable computational intensity required to estimate PP-LCGA models (Wiggins et al., 2015) and to avoid controlling for confounders twice (i.e., we wanted to incorporate these confounders within the path analysis to examine their direct and indirect associations). Once the optimal number of groups were identified, we saved the class assignment information in a data file to allow for further analysis (Jung & Wickrama, 2008).

During stage two, we used the imported INT/EXT classes to examine associations with predictors and outcomes, and indirect effects across development. We first used logistic regression analysis to test: a) the direct (unadjusted) associations between RPs, INT/EXT symptom classes, and adolescent psychopathological symptoms; and b) the associations between RPs and adolescent psychopathological symptoms following adjustment for INT/EXT symptom classes. We then used path analysis to examine direct and indirect (via INT/EXT symptom classes) associations between

RPs and adolescent psychopathological symptoms following control for family adversity, birthweight, and maternal mental health.

Parallel process-latent class growth analysis (PP-LCGA)

We selected PP-LCGA to examine how internalising and externalising symptoms co-develop across childhood, and how this co-development differs between individuals (Nivard et al., 2017; Wiggins et al., 2015). PP-LCGA assigns individuals to groups based on initial levels (intercepts) and changes (slopes) in concurrent internalising and externalising symptoms (Wu, Witkiewitz, McMahon, Dodge, & Group, 2010). Using *Mplus version 7.11* (Muthen & Muthen, 2010) we estimated models with one to six classes and selected the best fitting model based on fit indicators (e.g., Bayesian Information Criterion) and the interpretability of classes (Wiggins et al., 2015). We included all cohort members with at least one internalising and externalising measure (Croudace, Jarvelin, Wadsworth, & Jones, 2003), and used the Full Information Maximum Likelihood (FIML) approach to minimise bias associated with missing data.

Logistic regressions analysis

We conducted logistic regressions in *SPSS version 25*. We examined unadjusted associations between: 1) RPs and classes of internalising and externalising (INT/EXT) symptoms; 2) RPs and adolescent psychopathological symptoms; and 3) classes of INT/EXT symptoms and adolescent psychopathological outcomes. We also conducted adjusted logistic regression analyses to assess associations between RPs and adolescent outcomes following control for INT/EXT symptoms.

Path analysis

We conducted path analysis in *Mplus version 7.11* to examine direct and indirect associations between RPs, INT/EXT symptom classes and adolescent psychopathological symptoms. We selected probit estimation (Winship & Mare, 1983) with the WLSMV estimator (weighted least squares with robust standard errors, mean and variance adjusted). We conducted two path models for RPs at each time-point (6, 15-18 and 24-30 months) with symptoms of BPD, psychotic and child-reported depression in one model and symptoms of BPD, psychotic and mother-reported depression in the other model (6 models in total). We modelled direct and indirect (via INT/EXT symptom classes) pathways from RPs to adolescent psychopathological symptoms, while simultaneously controlling for correlations between outcome variables (i.e., depression, psychotic and borderline personality

disorder symptoms) and confounders (i.e., birthweight, family adversity and maternal mental health). Figures 1a and 1b show the direct and indirect associations modelled in the path analysis.

[Insert Figures 1a and 1b about here]

Results

Descriptive statistics

In total, 12.3% of adolescents reported ≥1 psychotic symptom, 5.6 % reported clinically relevant depression symptoms (2.6 % according to mother-report), and 7.2% reported ≥5 symptoms of BPD. Please see Supplementary Table 3 for the frequencies of individual BPD symptoms. The most common symptoms of BPD were anger, affective instability and impulsivity. The least common were suicidal behaviour and feelings of abandonment. RP frequencies were: 24-30 months (no RPs = 68.9%; 1 RP = 25.3%; 2 or 3 RPs = 5.8%), 15-18 months (no RPs = 70.3%; 1 RP = 22.4%; 2 or 3 RPs = 7.3%), and 6 months (no RPs = 63.7%; 1 RP = 28.5%; 2 or 3 RPs = 7.6%).

Conditional parallel process latent class growth analysis (PP-LCGA): Co-developing internalising and externalising symptom classes

Supplementary Table 4 contains the fit indices for the one to six class models. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) decreased with the addition of each class indicating a better model fit for more classes. This pattern is typically found in large samples (Wiggins et al., 2015). However, decreases in AIC and BIC became considerably smaller from four classes onwards and entropy became smaller. Vuong-Lo-Mendell-Rubin (VLMR) and Lo-Mendell-Rubin-adjusted LRT tests indicated a non-significant (at the $p<.0001$ level) improvement in model fit after 4 classes, thus we selected the four-class model (**Figure 2**).

[Insert Figure 2 about here]

Class one (low-to-moderate and stable INT and EXT symptoms) was the largest class containing 53.0% of the sample and was characterised by initially low and very slightly increasing INT

symptoms and initially moderate and very slightly decreasing EXT symptoms. There were slightly more females in this group (50.7% *vs* 49.3%). Class two (low stable INT and moderate-high stable EXT symptoms) was the second largest class containing 27.0% of the sample. This class was characterised by initially low INT symptoms which increased very slightly, and initially moderate-to high EXT symptoms which decreased very slightly. There were significantly more males in this group (57.5% *vs* 42.5%). Class three (moderate-high increasing INT and moderate decreasing EXT symptoms) contained 12.1% of the sample and had initially moderate-high levels of INT symptoms which increased and initially low-moderate levels of EXT symptoms which declined. There were significantly more females in this group (57.1% *vs* 42.9%). Class four (moderate increasing INT and stable high EXT symptoms) contained 7.7% of the sample and was characterised by moderate-high increasing INT and high stable EXT symptoms. There were significantly more males in this class (61.0% *vs* 39.0%). As some previous studies have reported a three-class model of INT/EXT symptoms (Wiggins et al., 2015), we also tested a three-class model in supplementary analysis to determine whether (and how) results diverged from the four-class model. As observed in the four-class model, there was a large (52%) normative group with low and relatively stable INT/EXT symptoms. Also comparable to the four-class model, the smallest group (9.9%) had high, stable EXT and moderate, increasing INT symptoms. The intermediate group (38.2%) had low stable INT and moderate stable EXT symptoms.

Unadjusted and adjusted logistic regressions: Associations between RPs, internalising and externalising symptom classes, and adolescent psychopathological symptoms

RPs were significantly associated with childhood INT/EXT symptom classes (using class one as the reference group). Odds Ratios (ORs) increased in magnitude as number of RPs increased, and for classes with more severe INT/EXT symptom patterns (**Table 1**).

[Insert Table 1 here]

Each INT/EXT symptoms class (i.e., classes 2, 3 and 4) was significantly associated with adolescent psychopathology. Class 4 demonstrated especially strong associations. We observed a similar dose response pattern in the supplementary analysis for the three-class model (Supplementary Table 7). Direct associations between RPs and adolescent psychotic, depression and BPD symptoms were less

consistent. There were no direct significant associations between RPs at 6 months and adolescent outcomes; however, five out of eight associations were significant for RPs at 15-18 months and seven out of eight associations were significant for RPs at 24-30 months. Most of these direct associations became non-significant following control for the INT/EXT classes (Supplementary Table 5).

Path analysis: Direct and indirect associations between RPs and adolescent psychopathological symptoms

Model fit was good for the path models at each time point (CFI=0.92-0.96; RMSEA=0.025-0.033). Main direct associations are reported in **Table 2**. RPs were not significantly directly associated with adolescent psychotic, depression or BPD symptoms after controlling for all direct and indirect pathways within the model. They were, however, directly significantly associated with each of the INT/EXT symptom classes (**Supplementary Table 6**). Family adversity was significantly directly associated with psychotic and BPD symptoms, and child reported depression symptoms. Class four (moderate increasing INT and stable high EXT symptoms) was significantly associated with BPD symptoms and child and mother reported depression symptoms, but the direct association with psychotic symptoms did not quite reach significance. Class two (low stable INT and moderate-high stable EXT symptoms) was significantly associated with child-reported depression symptoms. Class three (moderate-high increasing INT and moderate decreasing EXT symptoms) was significantly associated with mother-reported depression symptoms. Mother's mental health during early childhood was significantly directly associated with classes three and four. Family adversity was significantly directly associated with classes two and four.

[Insert Table 2 about here]

RPs at each time-point were significantly indirectly associated with adolescent BPD symptoms and child and mother-reported depression symptoms via class four (moderate increasing INT/high stable EXT symptoms). Class two (low stable INT and moderate-high stable EXT symptoms) significantly mediated associations between RPs and child-reported depression. Class three (moderate-high increasing INT and moderate decreasing EXT symptoms) significantly mediated associations between RPs and mother-reported depression (**Table 3**).

[Insert Table 3 about here]

Family adversity was significantly indirectly associated with BPD symptoms and child and mother-reported depression symptoms via class four (**Table 4**). Results also indicated a further two indirect chains comprising four variables: 1) from family adversity to maternal mental health to class four to adolescent outcome (BPD symptoms and depression symptoms respectively); and 2) from family adversity to RPs to class four to adolescent outcome (BPD symptoms and depression symptoms respectively) Full results are not reported in the manuscript.

[Insert Table 4 about here]

Model fit was poorer for the path models in the supplementary path analysis using the three-class model (e.g., RMSEA=0.058, CFI=0.906). Overall, findings were largely comparable to the four-class model: the most severe class of INT/EXT symptoms (i.e., class three) was significantly associated with adolescent BPD symptoms and child and mother-reported depression symptoms (results not reported). Further, RPs were significantly indirectly associated with these outcomes via severe INT/EXT symptom class. In a divergence from the four-class model, class two (low stable INT and moderate stable EXT symptoms) was significantly associated with BPD symptoms, and RPs were significantly indirectly associated adolescent BPD symptoms via this class (see **Supplementary Table 8**).

Discussion

A large community sample was used to test the developmental cascade model by examining the direct and indirect (via internalising and externalising symptoms) associations between early regulatory problems (RPs) and adolescent psychotic, depression and BPD symptoms. Using PP-LCGA, we identified four distinct groups of children who differed in their longitudinal patterns of co-developing internalising and externalising (INT/EXT) symptoms. Consistent with previous studies (Hinnant & El-Sheikh, 2013; Wiggins et al., 2015), we identified a large normative class (i.e., low and relatively stable INT/EXT symptoms) and a small severe class (i.e., moderate increasing INT and stable high EXT symptoms). Our findings of two additional classes (four in total) diverge

from previous work identifying three classes in total (Wiggins et al., 2015), and indicate more nuanced developmental pathways. In path analysis, RPs were not significantly directly associated with adolescent outcomes following control for all other paths in the model. They were, however, significantly indirectly associated with adolescent outcomes via class four (i.e., moderate increasing INT and stable high EXT symptoms).

Before we discuss our findings in more detail, we will focus on methodological and conceptual considerations pertinent to our analysis. In our unadjusted logistic regression analyses, we found that RPs at 15-18 and 24-30 months were mostly significantly associated with adolescent psychotic, depression and BPD symptoms. Conversely, RPs at 6 months were not significantly associated with any of the adolescent outcomes. Within the framework of Baron and Kennys' causal model, the lack of a direct significant association between *X* (i.e., RPs at 6 months) and *Y* (i.e., adolescent outcomes) would preclude testing for mediation of this association (Baron & Kenny, 1986). Indeed, this approach would prompt the question: *can associations that don't exist be mediated* (Hayes, 2009)? A more nuanced understanding of the nature of intervening variables can help clarify this question by distinguishing between "mediating effects" and "indirect effects." Mediating variables are explanatory variables that shed light on the nature of the relationship that exists between two variables. Therefore, if no such relationship exists, there is nothing to be mediated (Mathieu & Taylor, 2006). Indirect effects are a qualitatively different phenomenon to mediation and describe a chain of events whereby *X* is related to *M* and *M* is related to *Y*. In this case, *X* and *Y* are not significantly directly related, but are indirectly related through significant relationships with linking mechanisms (Mathieu & Taylor, 2006). The implications of this model are that significant indirect effects can occur in the absence of significant total or direct effects (Rucker, Preacher, Tormala, & Petty, 2011). We found this to be the case with RPs at 6 months which were indirectly, but not directly associated with adolescent outcomes. This seems plausible when we consider the strong associations between *X* and *M* (RPs at 6 months and INT/EXT symptoms) and *M* and *Y* (INT/EXT symptoms and adolescent outcomes), and in view of the cascade model of development which states that differences in emotion and behaviour maximally affect the next most proximate phase of development, which in turn affects the following stage, and so on (Hyde et al., 2012). Overall, our results support that chronic and severe INT/EXT symptoms play an important intervening role in linking RPs from 15-18 and 24-30 months to adolescent psychopathological outcomes. Findings regarding links between RPs at 6 months and adolescent outcomes are more tentative.

Chronic and severe co-developing INT/EXT symptoms (i.e., class four) were significantly directly associated with adolescent BPD symptoms and child and mother-reported depression symptoms, and RPs at each time-point were significantly indirectly associated with these adolescent outcomes via severe co-developing INT/EXT symptoms. As discussed previously, there is some conceptual confusion surrounding terms such as "emotional and behavioural dysregulation," and "internalising and externalising symptoms," which are often assessed with the same tools (e.g., SDQ). We interpret our findings as indicating that children demonstrating elevated and chronic co-developing internalising and externalising symptoms (as indicative of emotional and behavioural dysregulation) have been caught in a cascade of dysregulation beginning with early regulatory problems (or perhaps even earlier, e.g., prenatal experiences) and culminating in adolescent BPD and depression symptoms (Hyde et al., 2012). We found, for example, that family adversity during pregnancy was significantly indirectly associated with adolescent psychopathology via an increased risk of RPs and subsequent INT/EXT symptoms. While the chronic and severe co-developing INT/EXT symptoms phenotype may have genetic roots (Nobile et al., 2016), specific outcomes are likely dependent on continuous interactions between the child and environment (Wiggins et al., 2015; Winsper, Hall, Strauss, & Wolke, 2017). For example, it is plausible that maternal psychopathology could reduce parenting skills which likely impact on the child's ability to improve self-regulation skills over time (Eyden, Winsper, Wolke, Broome, & MacCallum, 2016; Smith, 2004).

We identified additional developmental trajectories according to class of INT/EXT symptoms. Our PP-LCGA confirmed that developmental patterns of INT/EXT symptoms are differentially associated with gender. We found that male gender significantly predicted class two (low stable INT and moderate-high stable EXT symptoms) and class 4 (moderate increasing INT and stable high EXT symptoms). Conversely, female gender significantly predicted class 3 (moderate-high increasing INT and moderate decreasing EXT symptoms). In path analysis, mother's mental health problems were significantly associated with membership in classes three (moderate-high increasing INT and moderate decreasing EXT symptoms) and four (moderate increasing INT/stable high EXT), but not class two (low stable INT and moderate-high stable EXT symptoms). Class two was significantly directly and indirectly (from RPs) associated with child-reported depression symptoms at 11 years, while class three was significantly directly and indirectly (from RPs) associated with mother-reported depression symptoms at 12 years. In contrast, class four was significantly directly and indirectly associated with BPD symptoms and child and mother-reported depression symptoms.

It is unclear why youths in class two (i.e., those who exhibited higher externalising than internalising symptoms) developed child-reported depression symptoms over time. It could be related to the distress caused by the consequences of externalising behaviours, e.g., problematic social relationships or reduced academic progress (Winsper, 2012). Another potential explanation is that children in class two already had a tendency towards feelings of depression causing them to act out (Laukkanen, Hakko, Riipinen, & Riala, 2016), hence mothers were aware of, and reported, their child's externalising (but not internalising) symptoms.

Consistent with previous work, children with increasing trajectories of INT (but not EXT) symptoms (i.e., class three) were more likely to develop depression symptoms (Toumbourou, Williams, Letcher, Sanson, & Smart, 2011), but not psychotic or BPD symptoms. Externalising symptoms decreased over time, while internalising symptoms continued to increase in this group. This suggests that chronic internalising symptoms predict depression, but not other disorders, unless they are accompanied by concurrently elevated levels of externalising symptoms.

We did not find any significant associations (direct or indirect) with psychotic symptoms in the path analysis. While we found significant direct associations between RPs and INT/EXT classes and psychotic symptoms in the unadjusted logistic regression analysis, these were of lower magnitude than the associations with BPD and depression symptoms (this could in part relate to the lower threshold for positive psychotic symptoms, i.e., ≥1 symptom). It is therefore perhaps unsurprising that these associations became non-significant in the path analysis following control for all confounders. Clemmensen et al. (2016) similarly found that the significant association between early RPs and adolescent psychotic symptoms became non-significant following control for other factors including low family income and concurrent mental disorders.

This prospective study has several strengths including the large sample size, adjustment for important confounders, repeated assessments of RPs and internalising and externalising symptoms, and the assessment of adolescent psychopathological outcomes using validated tools. By using PP-LCGA, we were able to examine nuanced pathways rather than assuming that internalising and externalising symptoms follow the same developmental pattern. Further, our use of path analysis enabled us to simultaneously control for all associations between variables, allowing us to identify several independent pathways to adolescent psychopathology. There are also limitations. First, there was selective attrition. Nonetheless, in our weighted analysis based on the variables associated with selective drop-out, the patterns and comparative strength of associations were very similar to the unweighted analysis. This is consistent with previous studies showing that drop-out rates may have

little impact on the strength of prospective associations (Wolke et al., 2009). Second, RPs, internalising and externalising symptoms and depression symptoms (at some time-points) were assessed via mother report. While questionnaire measures are considered less robust than observational measures, they have the benefit of capturing behaviours over time and are more feasible in large scale epidemiological studies. However, some of the associations could have been inflated by shared measure variance (e.g., associations between RPs and mother-reported depression symptoms).

Consistent with the cascade model of development, RPs occurring as early as 6 months of age were significantly associated with adolescent BPD and depression symptoms via an increased risk of severe and increasing INT and EXT symptoms. We also observed additional indirect pathways to adolescent psychopathology for children evidencing less severe but elevated and/or increasing patterns of internalising or externalising symptoms across childhood. Consistent with the theory of multifinality (Cicchetti & Rogosch, 1996), early regulatory problems appear to lead to several different maladaptive trajectories with various psychopathological outcomes. Clinicians should be aware that RPs starting in infancy may indicate an early vulnerability, and thus warrant treatment during the infant and toddler years to prevent a developmental cascade culminating in chronic self-regulatory problems and psychopathology. Initiatives providing parenting and family support could help reduce the exacerbation of regulatory problems across childhood through adolescence (Smith, 2004). Future research may seek to further examine the environmental determinants (e.g., parenting; peer bullying) of the multifinal outcomes of early RPs.

References

Althoff, R. R., Ayer, L. A., Crehan, E. T., Rettew, D. C., Baer, J. R., & Hudziak, J. J. (2012). Temperamental profiles of dysregulated children. *Child Psychiatry & Human Development, 43*, 511-522.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (5th edition).* Arlington, VA, US: American Psychiatric Publishing.

Angold, A., Costello, E. J., Messer, S. C., & Pickles, A. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research, 5,* 237-249.

Bianchi, V., Brambilla, P., Garzitto, M., Colombo, P., Fornasari, L., Bellina, M., . . . & Nobile, M. (2017). Latent classes of emotional and behavioural problems in epidemiological and referred samples and their relations to DSM-IV diagnoses. *European Child and Adolescent Psychiatry, 26*, 549-557.

Bilgin, A., Baumann, N., Jaekel, J., Breeman, L. D., Bartmann, P., Bäuml, J. G., . . . Wolke, D. (2018). Early crying, sleeping, and feeding problems and trajectories of attention problems from childhood to adulthood. *Child Development*. doi: 10.1111/cdev.13155

Bilgin, A., & Wolke, D. (2016). Regulatory problems in very preterm and full-term infants over the first 18 months. *Journal of Developmental Behavioral Pediatrics, 37*, 298-305.

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., . . . Smith, G. D. (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.

Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology, 8*, 597-600.

Clemmensen, L., Van Os, J., Drukker, M., Munkholm, A., Rimvall, M., Vaever, M., . . . Jeppesen, P. (2016). Psychotic experiences and hyper-theory-of-mind in preadolescence–a birth cohort study. *Psychological Medicine, 46*, 87-101.

Cook, F., Giallo, R., Hiscock, H., Mensah, F., Sanchez, K., & Reilly, S. (2019). Infant regulation and child mental health concerns: a longitudinal study. *Pediatrics, 143*, e20180977.

Costello, E. J., Copeland, W., & Angold, A. (2011). Trends in psychopathology across the adolescent years: what changes when children become adolescents, and when adolescents become adults? *Journal of Child Psychology & Psychiatry, 52*, 1015-1025.

Croudace, T. J., Jarvelin, M.-R., Wadsworth, M. E., & Jones, P. B. (2003). Developmental typology of trajectories to nighttime bladder control: epidemiologic application of longitudinal latent class analysis. *American Journal of Epidemiology, 157*, 834-842.

Deutz, M. H., Geeraerts, S. B., Belsky, J., Deković, M., van Baar, A. L., Prinzie, P…… & Patalay, P. (2019). General Psychopathology and Dysregulation Profile in a Longitudinal Community Sample: Stability, Antecedents and Outcomes. *Child Psychiatry & Human Development*, doi.org/10.1007 /s1057 8-019-00916 -2

Deutz, M. H., Shi, Q., Vossen, H. G., Huijding, J., Prinzie, P., Deković, M., . . . & Woltering, S. (2018). Evaluation of the Strengths and Difficulties Questionnaire-Dysregulation Profile (SDQ-DP). *Psychological Assessment, 30*, 1174-1185.

Eyden, J., Winsper, C., Wolke, D., Broome, M. R., & MacCallum, F. (2016). A systematic review of the parenting and outcomes experienced by offspring of mothers with borderline personality pathology: Potential mechanisms and clinical implications. *Clinical Psychology Review, 47*, 85-105.

Goodman, A., & Goodman, R. (2011). Population mean scores predict child mental disorder rates: validating SDQ prevalence estimators in Britain. *Journal of Child Psychology and Psychiatry, 52*, 100-108.

Halperin, J. M., Rucklidge, J. J., Powers, R. L., Miller, C. J., & Newcorn, J. H. (2011). Childhood CBCL bipolar profile and adolescent/young adult personality disorders: a 9-year follow-up. *Journal of Affective Disorders, 130*, 155-161.

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Communication Monographs, 76*, 408-420.

Hemmi, M. H., Wolke, D., & Schneider, S. (2011). Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioural outcomes in childhood: a meta-analysis. *Archives of Disease in Childhood, 96*, 622-629.

Hentges, R. F., Graham, S. A., Plamondon, A., Tough, S., & Madigan, S. (2019). A developmental cascade from prenatal stress to child internalizing and externalizing problems. *Journal of Pediatric Psychology*, doi: 10.1093/jpepsy/jsz044.

Hinnant, J. B., & El-Sheikh, M. (2013). Codevelopment of externalizing and internalizing symptoms in middle to late childhood: Sex, baseline respiratory sinus arrhythmia, and respiratory sinus arrhythmia reactivity as predictors. *Development and Psychopathology, 25*, 419-436.

Hyde, R., O'Callaghan, M. J., Bor, W., Williams, G. M., & Najman, J. M. J. P. (2012). Long-term outcomes of infant behavioral dysregulation. Pediatrics, *130,* e1243-e1251.

Ivens, C., & Rehm, L. P. (1988). Assessment of childhood depression: correspondence between reports by child, mother, and father. *Journal of the American Academy of Child & Adolescent Psychiatry, 27*, 738-741.

Jordan, P., Rescorla, L. A., Althoff, R. R., & Achenbach, T. M. (2016). International comparisons of the youth self-report dysregulation profile: latent class analyses in 34 societies. *Journal of the American Academy of Child & Adolescent Psychiatry, 55*, 1046-1053.

Jung, T., & Wickrama, K. (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass, 2*, 302-317.

Kenny, D. A., & Judd, C. M. (2014). Power anomalies in testing mediation. *Psychological Science, 25*, 334-339.

Kinner, S. A., Alati, R., Najman, J. M., & Williams, G. M. (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.

Kramer, M. S. (1987). Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the World Health Organization, 65*, 663-737.

Laukkanen, M., Hakko, H., Riipinen, P., & Riala, K. (2016). Does family structure play a role in depression in adolescents admitted to psychiatric inpatient Care? *Child Psychiatry & Human Development, 47*, 918-924.

Lereya, S. T., Winsper, C., Heron, J., Lewis, G., Gunnell, D., Fisher, H. L., & Wolke, D. (2013). Being bullied during childhood and the prospective pathways to self-harm in late adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 52*, 608-618.

Lereya, S. T., Winsper, C., Tang, N. K., & Wolke, D. (2017). Sleep problems in childhood and borderline personality disorder symptoms in early adolescence. *Journal of Abnormal Child Psychology, 45*, 193-206.

Mathieu, J. E., & Taylor, S. R. (2006). Clarifying conditions and decision points for mediational type inferences in organizational behavior. *Journal of Organizational Behavior, 27*, 1031-1056.

Muthen, L. K., & Muthen, B. O. (2010). *Mplus Statistical Analysis with Latent Variables User's Guide. Sixth Edition*. Los Angeles: Muthen & Muthen.

Nivard, M. G., Lubke, G. H., Dolan, C. V., Evans, D. M., Pourcain, B. S., Munafo, M.R.,& Middeldorp, C.M. (2017). Joint developmental trajectories of internalizing and externalizing disorders between childhood and adolescence. *Development and Psychopathology, 29*, 919-928.

Nobile, M., Bianchi, V., Monzani, D., Beri, S., Bellina, M., Greco, A., . . . & Giorda, R. (2016). Effect of family structure and TPH2 G-703T on the stability of dysregulation profile throughout adolescence. *Journal of Affective Disorders, 190*, 576-584.

O'Connor, T. G., Heron, J., Glover, V., & Team, A. S. (2002). Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *Journal of the American Academy of Child & Adolescent Psychiatry, 41*, 1470-1477.

Rucker, D. D., Preacher, K. J., Tormala, Z. L., & Petty, R. E. (2011). Mediation analysis in social psychology: Current practices and new recommendations. *Social and Personality Psychology Compass, 5*, 359-371.

Sharp, C., Ha, C., Michonski, J., Venta, A., & Carbone, C. (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.

Siegenthaler, E., Munder, T., & Egger, M. (2012). Effect of preventive interventions in mentally ill parents on the mental health of the offspring: systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*, 8-17.

Singh, S. P., Winsper, C., Wolke, D., & Bryson, A. (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.

Smith, M. (2004). Parental mental health: disruptions to parenting and outcomes for children. *Child & Family Social Work, 9*, 3-11.

Sonuga-Barke, E. J., Kennedy, M., Kumsta, R., Knights, N., Golm, D., Rutter, M., ...& Kreppner, J. (2017). Child-to-adult neurodevelopmental and mental health trajectories after early life deprivation: the young adult follow-up of the longitudinal English and Romanian Adoptees study. *The Lancet, 389*, 1539-1548.

Stone, L. L., Otten, R., Engels, R. C., Vermulst, A. A., & Janssens, J. M. (2010). Psychometric properties of the parent and teacher versions of the strengths and difficulties questionnaire for 4-to 12-year-olds: a review. *Clinical Child and Family Psychology Review, 13*, 254-274.

Thapar, A., Collishaw, S., Potter, R., & Thapar, A. K. (2010). Managing and preventing depression in adolescents. *BMJ, 340*, 254-258.

Toffol, E., Rantalainen, V., Lahti-Pulkkinen, M., Girchenko, P., Lahti, J., Tuovinen, S., . . . & Hämäläinen, E. (2018). Infant regulatory behavior problems during first month of life and neurobehavioral outcomes in early childhood. *European Child & Adolescent Psychiatry, 28,* 847-859.

Toumbourou, J. W., Williams, I., Letcher, P., Sanson, A., & Smart, D. (2011). Developmental trajectories of internalising behaviour in the prediction of adolescent depressive symptoms. *Australian Journal of Psychology, 63,* 214-223.

Wiggins, J. L., Mitchell, C., Hyde, L. W., & Monk, C. S. (2015). Identifying early pathways of risk and resilience: The codevelopment of internalizing and externalizing symptoms and the role of harsh parenting. *Development and Psychopathology, 27,* 1295-1312.

Winship, C., & Mare, R. D. (1983). Structural equations and path analysis for discrete data. *American Journal of Sociology*, 89, 54-110.

Winsper, C., Hall, J., Strauss, V. Y., & Wolke, D. (2017). Aetiological pathways to Borderline Personality Disorder symptoms in early adolescence: childhood dysregulated behaviour, maladaptive parenting and bully victimisation. *Borderline Personality Disorder and Emotion Dysregulation, DOI 10.1186/s40479-017-0060-x*

Winsper, C., & Wolke, D. (2014). Infant and toddler crying, sleeping and feeding problems and trajectories of dysregulated behavior across childhood. *Journal of Abnormal Child Psychology, 42,* 831-843.

Winsper, C., Wolke, D., Bryson, A., Thompson, A., & Singh, S. P. (2016). School mobility during childhood predicts psychotic symptoms in late adolescence. *Journal of Child Psychology and Psychiatry, 57,* 957-966.

Winsper, C., Wolke, D., & Lereya, T. (2015). Prospective associations between prenatal adversities and borderline personality disorder at 11–12 years. *Psychological Medicine, 45,* 1025-1037.

Wolke, D., Bilgin, A., & Samara, M. (2017). Systematic review and meta-analysis: fussing and crying durations and prevalence of colic in infants. *The Journal of Pediatrics, 185,* 55-61.

Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *The British Journal of Psychiatry, 195*, 249-256.

Wu, J., Witkiewitz, K., McMahon, R. J., Dodge, K. A., & Conduct Problems Prevention Research Group. (2010). A parallel process growth mixture model of conduct problems and substance use with risky sexual behavior. *Drug and Alcohol Dependence, 111*, 207-214.

Zammit, S., Kounali, D., Cannon, M., David, A. S., Gunnell, D., Heron, J., . . . & Wolke, D. (2014). 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, 170,* 742-750.

Zanarini, M., Frankenburg, F., Sickel, A., & Yong, L. (1996). *The Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV).* McLean Hospital: Belmont, MA.

Zanarini, M., Horwood, J., Waylen, A., & Wolke, D. (2004). The UK Version of the Childhood Interview for DSM-IV Borderline Personality Disorder (UK-CI-BPD). University of Bristol: Bristol, UK.

Zanarini, M., Horwood, J., Wolke, D., Waylen, A., Fitzmaurice, G., & Grant, B. (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.

Figure 1a. Diagrammatic representation of the main direct associations modelled in the path analysis (attached as PDF file)

Figure 1b. Diagrammatic representation of main indirect associations modelled in the path analysis (attached as PDF file)

Figure 2. Parallel Process Latent Class Growth Analysis (PP-LCGA) of co-developing internalising and externalising trajectories (attached as PDF file)

Table 1. Unadjusted multinomial logistic regression associations between regulatory problems (RPs) and childhood internalising (INT) and externalising (EXT) symptom classes (4-class solution) from 4 to 9.5 years			
RPs	**INT/EXT classes**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
		1 RP	**2 or 3 RPs**

6 months	Class 1 (low stable INT/EXT)	[reference]	[reference]
	Class 2 (low INT moderate increasing EXT)	**1.22 (1.05, 1.43)**	1.29 (0.98, 1.70)
	Class 3 (moderate increasing INT, decreasing EXT)	**1.57 (1.29, 1.90)**	**1.97 (1.44, 2.70)**
	Class 4 (severe and stable INT/EXT symptoms)	**1.81 (1.38, 2.37)**	**2.83 (1.91, 4.18)**
15-18 months	Class 1 (low stable INT/EXT)	[reference]	[reference]
	Class 2 (low INT moderate increasing EXT)	**1.62 (1.37, 1.92)**	**2.60 (1.99, 3.40)**
	Class 3 (moderate increasing INT, decreasing EXT)	**1.97 (1.60, 2.41)**	**2.63 (1.88, 3.66)**
	Class 4 (severe and stable INT/EXT symptoms)	**2.41 (1.83, 3.18)**	**4.76 (3.25, 6.97)**
24-30 months	Class 1 (low stable INT/EXT)	[reference]	[reference]
	Class 2 (low INT moderate increasing EXT)	**1.70 (1.45, 2.00)**	**2.29 (1.69, 3.12)**
	Class 3 (moderate increasing INT, decreasing EXT)	**2.45 (2.01, 2.98)**	**2.91 (2.01, 4.21)**
	Class 4 (severe and stable INT/EXT symptoms)	**2.35 (1.78, 3.09)**	**6.10 (4.11, 9.04)**

Table 2. Unstandardised probit coefficients (β) for the main direct associations between family adversity, birth weight, RPs at 6, 15-18 and 24-30 months, internalising and externalising (INT/EXT) symptom classes (4-class solution) and adolescent BPD, psychotic and depression symptoms

	BPD symptoms at 11 years (child report)			**Psychotic symptoms at 12 years (child report)**			**Depression symptoms at 11 years (child report)**			**Depression symptoms at 12 years (mother report)**		
	β	**SE**	***P***	**B**	**SE**	***P***	**β**	**SE**	***P***	**β**	**SE**	***P***
6 Months												
Family Adversity	**0.049**	**0.021**	**0.017**	**0.057**	**0.018**	**0.001**	**0.080**	**0.021**	**0.000**	0.039	0.034	0.250
RPs at 6 months	-0.071	0.037	0.057	0.019	0.031	0.533	0.007	0.039	0.864	-0.039	0.057	0.500
INT/EXT class 2	**0.075**	**0.038**	**0.049**	0.036	0.032	0.267	**0.104**	**0.042**	**0.012**	-0.090	0.069	0.194
INT/EXT class 3	0.061	0.044	0.161	0.069	0.036	0.058	0.033	0.047	0.487	**0.298**	**0.065**	**0.000**
INT/EXT class 4	**0.223**	**0.050**	**0.000**	**0.088**	**0.044**	**0.049**	**0.251**	**0.053**	**0.000**	**0.531**	**0.076**	**0.000**
15- 18 Months												
Family Adversity	**0.047**	**0.021**	**0.022**	**0.056**	**0.018**	**0.002**	**0.082**	**0.021**	**0.000**	0.033	0.034	0.330
RPs 15-18 months	0.005	0.040	0.900	0.027	0.031	0.388	-0.013	0.041	0.754	0.061	0.060	0.310
INT/EXT class 2	0.068	0.039	0.076	0.030	0.032	0.355	**0.099**	**0.042**	**0.018**	-0.108	0.071	0.128
INT/EXT class 3	0.052	0.044	0.241	0.067	0.037	0.066	0.032	0.047	0.497	**0.289**	**0.064**	**0.000**
INT/EXT class 4	**0.210**	**0.051**	**0.000**	0.084	0.044	0.057	**0.250**	**0.054**	**0.000**	**0.519**	**0.079**	**0.000**
24-30 Months												
Family Adversity	**0.047**	**0.021**	**0.021**	**0.054**	**0.018**	**0.002**	**0.079**	**0.021**	**0.000**	0.040	0.034	0.240
RPs at 24-30 months	-0.004	0.039	0.921	0.054	0.031	0.086	0.014	0.042	0.745	-0.003	0.058	0.954
INT/EXT class 2	0.071	0.038	0.066	0.030	0.033	0.364	**0.099**	**0.042**	**0.019**	-0.101	0.070	0.150
INT/EXT class 3	0.057	0.045	0.203	0.064	0.037	0.080	0.033	0.047	0.477	**0.284**	**0.064**	**0.000**

INT/EXT class 4	**0.215**	**0.051**	**0.000**	0.082	0.045	0.069	**0.251**	**0.055**	**0.000**	**0.519**	**0.077**	**0.000**
Model Fit Indices												
6 Months	Chi Square = 53.14, p=0.0000; RMSEA=0.025; CFI=0.96											
15-18 Months	Chi Square = 84.67, p=0.0000; RMSEA=0.034; CFI=0.94											
24-30 Months	Chi Square = 81.99, p=0.0000; RMSEA=0.033; CFI=0.92											
B=probit coefficient; SE=standard error; P=probability; family adversity assessed with the family adversity index (FAI); RPs assessed at 6, 15-18 and 24-30 months and entered as an ordinal variable; EXT/INT trajectory classes across childhood entered as categorical (i.e., dummy) variables; Two separate path models run: one with mother reported depression and one with child reported depression, all other variables identical												

Table 3. Unstandardised probit coefficients (β) for the indirect associations between RPs at 6, 15-18 and 24-30 months and adolescent BPD, psychotic and depression symptoms at 11-12 years via internalising and externalising (INT/EXT) trajectories (4-class solution)												
	BPD symptoms at 11 years (child report)			**Psychotic symptoms at 12 years (child report)**			**Depression symptoms at 11 years (child report)**			**Depression symptoms at 12 years (mother report)**		
	β	**SE**	***P***	**B**	**SE**	***P***	**β**	**SE**	***P***	**β**	**SE**	***P***
RPs @ 6 Months												
Total effect	-0.027	0.036	0.453	0.042	0.029	0.150	0.053	0.038	0.162	0.067	0.058	0.248
Total indirect effect	**0.045**	**0.011**	**0.000**	**0.023**	**0.008**	**0.005**	**0.046**	**0.013**	**0.000**	**0.105**	**0.025**	**0.000**
Direct effect	-0.071	0.037	0.057	0.019	0.031	0.533	0.007	0.039	0.864	-0.039	0.057	0.500
Via INT/EXT class 2	0.000	0.002	0.845	0.000	0.001	0.846	0.001	0.003	0.844	-0.002	0.003	0.549
Via INT/EXT class 3	0.008	0.011	0.186	0.009	0.005	0.082	0.004	0.006	0.491	**0.032**	**0.011**	**0.004**
Via INT/EXT class 4	**0.037**	**0.037**	**0.001**	0.014	0.008	0.067	**0.041**	**0.013**	**0.001**	**0.074**	**0.024**	**0.002**
RPs @ 15- 18 Months												
Total effect	0.062	0.036	0.085	0.056	0.030	0.057	0.053	0.040	0.183	**0.169**	**0.059**	**0.004**
Total indirect effect	**0.057**	**0.012**	**0.000**	**0.029**	**0.009**	**0.002**	**0.066**	**0.013**	**0.000**	**0.108**	**0.024**	**0.000**
Direct effect	0.005	0.040	0.900	0.027	0.031	0.388	-0.013	0.041	0.754	0.061	0.060	0.310
Via INT/EXT class 2	0.008	0.005	0.094	0.003	0.004	0.365	**0.011**	**0.005**	**0.034**	-0.012	0.009	0.158
Via INT/EXT class 3	0.007	0.006	0.250	0.009	0.005	0.083	0.004	0.006	0.503	**0.033**	**0.012**	**0.005**
Via INT/EXT class 4	**0.042**	**0.012**	**0.001**	0.017	0.009	0.073	**0.050**	**0.014**	**0.000**	**0.087**	**0.024**	**0.000**
RPs @ 24-30 Months												
Total effect	0.061	0.036	0.086	**0.087**	**0.030**	**0.003**	**0.085**	**0.039**	**0.031**	**0.143**	**0.058**	**0.014**
Total indirect effect	**0.065**	**0.014**	**0.000**	**0.033**	**0.011**	**0.003**	**0.071**	**0.015**	**0.000**	**0.146**	**0.026**	**0.000**
Direct effect	-0.004	0.039	0.921	0.054	0.031	0.086	0.014	0.042	0.745	-0.003	0.058	0.954
Via INT/EXT class 2	0.006	0.004	0.096	0.003	0.003	0.375	**0.009**	**0.004**	**0.047**	-0.009	0.007	0.194
Via INT/EXT class 3	0.011	0.008	0.208	0.012	0.007	0.092	0.006	0.009	0.480	**0.050**	**0.014**	**0.001**

Via INT/EXT class 4	**0.048**	**0.014**	**0.000**	0.018	0.011	0.081	**0.056**	**0.015**	**0.000**	**0.105**	**0.026**	**0.000**
B=probit coefficient; SE=standard error; P=probability; family adversity assessed with the family adversity index (FAI); RPs assessed at 6, 15-18 and 24-30 months and entered as an ordinal variable; INT/EXT classes entered as dummy variables (with class one as the reference)												

Table 4. Unstandardised probit coefficients (β) for the indirect associations between family adversity and adolescent BPD, psychotic and depression symptoms at 11-12 years via trajectories												
	BPD symptoms at 11 years (child report)			**Psychotic symptoms at 12 years (child report)**			**Depression symptoms at 11 years (child report)**			**Depression symptoms at 12 years (mother report)**		
	β	**SE**	***P***	**B**	**SE**	***P***	**β**	**SE**	***P***	**β**	**SE**	***P***
Family adversity												
Total effect	**0.093**	**0.019**	**0.000**	**0.080**	**0.016**	**0.000**	**0.135**	**0.020**	**0.000**	**0.144**	**0.032**	**0.000**
Total indirect effect	**0.046**	**0.009**	**0.000**	**0.026**	**0.008**	**0.001**	**0.055**	**0.010**	**0.000**	**0.104**	**0.018**	**0.000**
Direct effect	**0.047**	**0.021**	**0.021**	**0.054**	**0.018**	**0.002**	**0.079**	**0.021**	**0.000**	0.040	0.034	0.240
Via INT/EXT class 2	0.004	0.003	0.096	0.002	0.002	0.377	**0.006**	**0.003**	**0.044**	-0.007	0.005	0.172
Via INT/EXT class 3	-0.001	0.001	0.494	-0.001	0.001	0.459	-0.001	0.001	0.590	-0.004	0.006	0.495
Via INT/EXT class 4	**0.023**	**0.007**	**0.001**	0.009	0.005	0.085	**0.027**	**0.008**	**0.001**	**0.059**	**0.014**	**0.000**
B=probit coefficient; SE=standard error; P=probability; family adversity assessed with the family adversity index (FAI); Based on the model for RPs at 24-30 months												