1   **ADHD symptom trajectories across childhood and early adolescence and risk for**

2   **hypomanic symptoms in young adulthood**

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18   **Abstract**

19   **Background:** There is increasing evidence that childhood Attention-Deficit Hyperactivity

20   Disorder (ADHD) elevates risk of later Bipolar spectrum Disorder (BD). However, it remains

21   unclear whether different trajectories of ADHD symptoms confer differential risk for BD.

22   **Methods:** Data from the Avon Longitudinal Study of Parents and Children were available from

23   7811 children at age 8 years, 7435 at 10, 6798 at 13, and 1217 at 21-23 years. ADHD symptoms

24   were assessed at 8, 10, and 13 years with the Development and Well-Being

25   Assessment. Clinically significant hypomanic symptoms (CSHS) at 21-23 years were assessed

26   using the Hypomania Symptom Checklist (HCL-32). Group trajectories of ADHD and its

27   subtypes were estimated using latent class growth analysis. The prospective associations between

28   different ADHD trajectories and CSHS were tested using logistic regression analysis.

29   **Results:** Persistently high, increasing, remitting, and persistently low ADHD symptom

30   trajectories were identified for the three ADHD-related categories. Individuals with persistently

31   high and increasing levels of ADHD symptoms had increased odds of CSHS compared to

32   persistently low class. Sensitivity analyses validated these results. In separate analyses,

33   persistently high levels of hyperactivity and inattentive, and increasing levels of inattentive

34   symptoms were also independently associated with CSHS.

35   **Conclusions:** Young people with a longitudinal pattern of high and increasing ADHD symptoms

36   are at higher risk for developing CSHS in young adulthood compared to individuals with low

37   symptom patterns. These two trajectories in childhood and adolescence may represent distinct

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38   phenotypic risk profiles for subsequently developing BD and be clinically significant targets for

39   prevention and treatment of BD.

40   *Keywords:* ADHD; hypomania; LCGA; trajectories; ALSPAC

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1- Introduction

There is growing evidence suggesting that bipolar disorder (BD) is preceded by childhood ADHD [1,2]. Mania shares many overlapping symptoms with ADHD, such as irritability, increased activity, aggression, problems in social situations, disinhibition, and/or distractibility. It is estimated that up to 1 in 13 patients with ADHD have comorbid BD, up to 1 in 6 patients with BD have comorbid ADHD in adult populations [4] and that about 10% of children and adolescents with ADHD will develop BD [5]. Further, young people with comorbid ADHD and hypomania, or BD, have an increased risk of suicide [6], more psychiatric hospitalizations, less treatment adherence, higher rates of additional psychopathology [5,7] and an earlier age of onset [4] than individuals without such comorbidity. A recent study also found that most offspring of BD parents did not develop BD, but those with preschool ADHD were at particularly high risk for developing BD [8].

Most studies investigating the association between ADHD and BD development have been limited by measuring ADHD either at one time point or by simply reporting the diagnostic proportions for the sample at various follow-up times. This method does not capture intraindividual variability in ADHD symptoms or their longitudinal course and could mask a potentially complex association or mechanism. The presence of subgroups may also explain apparent divergent results within the literature. [9–11] This is also important as ADHD is a neurodevelopmental disorder starting early in life and developing with a highly variable trajectory.[12–16] It remains unclear whether different trajectories of ADHD symptoms confer differential risk for development of BD. Further, although modest correlations between adolescent hypomanic and hyperactivity symptoms have been reported, recent research has detected higher estimates for genetic risk factors between hypomania and symptoms of

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67   hyperactivity (10%-25%) than with inattention (6%-16%).[1] Another study found that BD was

68   associated with inattentive and combined but not with hyperactive ADHD presentations.[17]

69   Thus, since the ADHD symptom domains of hyperactivity and inattention may be differentially

70   associated with BD and there are incongruent findings in the literature, ideally these domains

71   need to be further investigated separately.

72   Understanding unique trajectories of ADHD symptoms and how these subgroups

73   influence the development of BD could help identify at-risk groups and could guide specific

74   interventions. One way to identify the earliest clinical manifestations of BD is to study

75   hypomanic symptoms, a common feature of BD in youth which often heralds a subsequent

76   manic episode [18] Recent research has found that traits of ADHD across childhood and

77   adolescence were associated with adolescent hypomania [1] Significant, modest correlations

78   between adolescent hypomanic and hyperactivity symptoms have also been reported [19,20]

79   Given the existing knowledge gaps, we sought to characterize ADHD symptom

80   trajectories across childhood and early adolescence from age 8 to 13, and to describe their

81   prospective associated risk for subsequent hypomanic symptoms assessed between 21-23 years

82   old. We also sought to distinguish inattention from hyperactivity to further examine the origins

83   of the ADHD-BD overlap and investigate the prospective relationship between subtypes of

84   ADHD (hyperactivity and inattentive symptoms) and hypomanic symptoms.

85   **Materials and Methods**

86   **2.1 Participants**

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87   The current study used data from the Avon Longitudinal Study of Parents and Children

88   (ALSPAC), an ongoing longitudinal UK birth cohort study designed to investigate the factors

89   associated with the development, health, and disease during childhood and beyond.[21–23] All

90   women resident in Avon, UK, with expected dates of delivery between 1 April 1991 and 31

91   December 1992 were contacted and eligible for participation.[24] The study cohort consisted of

92   14,541 pregnancies and 13,988 children still alive at 1 year of age (see Supplement, for further

93   details and Figure S1 for a flow chart detailing sample definition). Ethical approval was obtained

94   from the ALSPAC Law and Ethics committee and the local research ethics committees.

95   Informed consent was obtained from the parents of the children.

96   **2.2 Measures**

97   *ADHD across childhood and adolescence*

98   ADHD at the age of 8, 10, and 13 was assessed using parental reports of the Development and

99   Wellbeing Assessment (DAWBA). DAWBA is a validated instrument including both structured

100   and semi-structured questions related to the International Classification of Diseases-10 (ICD-10)

101   and Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) diagnostic

102   criteria.[25] See Supplement for additional details on all measures. Items used for calculating the

103   total scores for ADHD, and the total scores for its subtypes (inattention and hyperactivity) to obtain

104   the trajectories can be found in Supplementary-Table 1. ADHD items prevalence in the cohort can

105   be found in Supplementary-Table 2.

106   *Clinically Significant Hypomanic symptoms in young people*

107   Study participants completed the Hypomania Checklist Questionnaire (HCL-32), a self-report

108   measure of lifetime experience of manic symptoms[26] comprising 32 items when they were 21-

109 23 years old. Consistent with previous work,[27] we constructed a dichotomous clinically

110 significant hypomanic symptoms variable; a) those with a symptom score of 14 or more (out of

111 32) were classed as having hypomania if they also reported b) at least one incident of "negative

112 consequences" or of "negative plus positive consequences," as a result of hypomanic symptoms,

113 c) that mood changes caused a reaction in people close to the participant and d) that symptoms

114 lasted for "4 days" or more. HCL-32 item prevalence in the cohort can be found in

115 Supplementary-Table 3.

116 **2.3 Confounders**

117 Child's sex, and ethnicity were reported by the mother. Multiple adverse childhood experiences

118 including but not limited to family psychopathology, socioeconomic status and childhood abuse

119 were assessed using the Family Adversity Index (FAI) during pregnancy and at 2 and 4 years

120 (see Methods-Supplementary).

121 Borderline features were assessed using a face-to-face semi – structured interview, which was the

122 Childhood Interview for DSM-IV Borderline Personality Disorder: UK Version (CI-BPD-UK),

123 based on the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders

124 [28] at 11 years old (see further details in Methods-Supplement). We controlled for BPD traits as

125 its highly associated with both ADHD and BD.[29–31]

126 **2.4 Statistical Analysis**

127 A multi-staged analysis plan was developed. In the first stage, we described the normative

128 patterns of ADHD, subtypes of ADHD (hyperactivity only and inattention only), hypomanic

129 symptoms and covariates across childhood, adolescence, and young adulthood using descriptive

130 analysis implemented in SPSS, v29.

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131   In the second stage as a primary analysis, we conducted latent class growth analyses

132   (LCGA) using Mplus, v8 to potentially identify differing levels of ADHD symptoms across

133   childhood and adolescence. We also conducted separate LCGAs for the subgroups of ADHD as

134   a secondary analysis. The variables that were included in the LCGA analysis were DAWBA

135   scores of ADHD at ages 8, 10, and 13 years. Several models were fitted by increasing the

136   number of classes [32] from 2 to 6 classes. The best-fitting classification model was chosen

137   using the following parameters: lower sample size–adjusted Bayesian information criteria,

138   significant Vuong-Lo-Mendell-Rubin and Lo, Mendell, and Rubin likelihood ratio tests, higher

139   entropy value, and the proportion of individuals in each class.[32] Missing values due to attrition

140   were handled by the full information maximum likelihood estimation method.[33]

141   In the third stage, we conducted logistic regression analyses to explore the associations

142   between ADHD trajectories and hypomania. Among 15645 participants in the original sample of

143   ALSPAC, 13951 participants were lost to follow-up at age 21-23 years. Therefore, to deal with

144   missingness which was unlikely to be missing at random, we conducted weighted analysis using

145   inverse probability to account for those lost to follow-up (See Supplementary-Methods).

146   Characteristics associated with attrition at 21-23 years old were being a male, having a younger

147   mother who had lower socioeconomic levels, and had higher scores on FAI (see Supplementary-

148   Table 4). Using the variables associated with selective dropout as the factors to predict

149   missingness in our analysis sample, we fitted a logistic regression model (nonresponse vs

150   response outcome) to determine weights for each individual using the inverse probability of

151   response. The regression coefficients from this model were used to determine probability

152   weights for the covariates in the primary and secondary analyses. Subsequently, unadjusted, and

153   adjusted associations between ADHD (primary analyses) and subgroups of ADHD (secondary

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154 analyses) trajectories, and hypomanic symptoms in young adulthood were assessed using

155 separate logistic regression analysis (i.e., three separate analyses). Additionally, we conducted

156 sensitivity analyses to investigate whether reducing four HCL-32 items that are similar to ADHD

157 items (i.e., talking fast, easily distracted, more energetic, and physically more active) would

158 affect the results.

159 ## 2- Results

160 Table 1 shows the frequencies and descriptive values of the variables of interest in this study.

161 **3.1 Primary Analyses**

162 ***Latent Classes of ADHD***

163 Table 2 shows the values of log-likelihood VLMR, ABIC, and number of other parameters for

164 all models assessed. Overall, a 4-class model offered the best model fit and theoretical

165 explanation (see Supplementary).

166 Figure 1 shows the four trajectory classes: persistently low (66.1%, N=6294), with ADHD

167 symptoms that remained low at all time points; adolescence-increasing (10.3%, N=981), with

168 symptoms that began to increase later in adolescence; persistently high (9.1%, N=865), with

169 childhood onset ADHD symptoms that persisted into adolescence, with a very high probability

170 of clinically significant ADHD symptoms at age 13; and remitting (14.5%, N=1381), with

171 clinically significant ADHD symptoms that began in childhood and remitted by adolescence.

172 ***ADHD Classes and risk for clinically significant hypomanic symptoms***

173 The weighted adjusted logistic regression model (with persistent low ADHD symptom levels as

174 the reference) showed that persistently high levels of ADHD symptoms (OR=2.36; CI

175   95%=1.12-4.99; p=0.024) and increasing levels of ADHD symptoms (OR=3.60; CI 95%=1.92-

176   6.74; p<0.001) were significantly associated with clinically significant hypomanic symptoms at

177   the age of 21-23 compared to persistently low class (Table 3).

178   **Sensitivity Analyses**

179   Removal of hypomania items that were similar to ADHD items (four HCL-32 items; being more

180   easily distracted, talking more, feeling more energetic and more active, and being physically

181   more active) did not affect the results (Supplementary-Table 5).

182   **3.2 Secondary analyses**

183   *Latent Classes of Inattentive Symptoms and risk for clinically significant hypomanic*

184   *symptoms*

185   Overall, a 4-class model offered the best fit and theoretical explanation (see Table 2,

186   Supplementary, Table S6 and Table S7). Figure S2 shows the four trajectory classes: persistently

187   low (63.8%, N=6099); increasing (15.5%, N=1486), persistently high (10.1%, N=963), and

188   remitting (6.5%, N=1014).

189   The weighted adjusted logistic regression model (with persistent low levels as the

190   reference) showed that persistently high levels class (OR=2.47; CI 95%=1.07-5.70; p=0.034) and

191   increasing levels class (OR=3.25; CI 95%=1.32-8.04; p=0.011) were significantly associated

192   with clinically significant hypomanic symptoms at age 21-23, compared to persistently low class

193   (see Table 3).

194   *Latent Classes of Hyperactivity Symptoms and risk clinically significant for hypomanic*

195   *symptoms*

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196   Overall, a 4-class model offered the best fit and theoretical explanation. We selected the 4-class

197   model as this provided the best fit to the data and theoretical interpretation for hyperactivity (see

198   Table 2 and Supplementary). Figure S3 shows the four trajectory classes: persistently low

199   (74.3%, N=7129); increasing (7.7%, N=735), persistently high (7.5%, N=722), and remitting

200   (10.5%, N=1011).

201   The weighted adjusted logistic regression model (with persistent low levels as the

202   reference) showed that only persistently high levels class was significantly associated with

203   clinically significant hypomanic symptoms at age 21-23 (OR=3.47, CI 95%=1.69-7.12, p<0.001;

204   Table 3) compared to persistently low class.

205   4 - Discussion

206   To our knowledge, this is the first study to examine the extent to which, and how ADHD

207   trajectories across childhood and adolescence, including ADHD subtypes, are associated with

208   later clinically significant hypomanic symptoms. First, we identified a group of individuals

209   characterized by persistently high, increasing, remitting and persistently low levels of ADHD,

210   inattentive and hyperactivity symptoms across childhood and adolescence. Second, we found

211   that persistently high levels and increasing levels of ADHD were independently associated with

212   clinically significant hypomanic symptoms at the age of 21-23. Third, persistently high levels of

213   hyperactivity and inattentive symptoms and increasing inattentive symptoms were also

214   independently associated with subsequent clinically significant hypomanic symptoms.

215   Our results suggest that tracking ADHD symptoms over time in childhood and

216   adolescence may help identify individuals at risk for clinically significant hypomanic symptoms.

217   More specifically, our findings indicate that children and adolescents with persistently high

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218   ADHD symptoms (including hyperactivity and inattentive domains) and a greater cumulative

219   burden of ADHD symptoms (including inattention domain only) are at higher risk of developing

220   clinically significant hypomanic symptoms in young adulthood. The chronic levels of ADHD

221   symptom trajectories may be reflecting children with ADHD with possibly developing BD, since

222   young people with ADHD plus BD compared to those with ADHD alone have greater number of

223   ADHD symptoms.[34] What we add to these findings is that even sub-threshold ADHD

224   symptoms in childhood increasing in time could be a risk factor for developing clinically

225   significant hypomanic symptoms later in life. Based on our results, chronicity and increasing

226   levels could be critical to identify at-risk populations for BD and the dose response signal adds

227   validity to these findings.

228   When looked at the ADHD sub-domain classes, persistently high inattention and

229   persistently high hyperactivity were significantly associated with clinically significant

230   hypomanic symptoms. Interestingly, increasing inattentive levels were also significantly

231   associated with clinically significant hypomanic symptoms but increasing hyperactivity levels

232   were not. This is partly in line with previous research in which they found persistently high

233   hyperactivity and inattention levels classes had the worst manic symptom severity scores.[35]

234   Further, although they did not find a remitting class for inattentive levels, they did find for

235   hyperactivity symptom trajectories suggesting that hyperactivity symptoms wane more over

236   time. They added that the remitting trajectory was associated with the highest rate of ADHD and

237   lowest rate of bipolar diagnoses. Building on these previous findings, our study adds that both

238   ADHD sub-domains with the most favorable (persistently low) and remitting trajectory classes

239   had the lowest risk for subsequent clinically significant hypomanic symptoms and both ADHD

240   sub-domains wane over time. A pattern of inattention symptoms that are both chronically high

241 and increasing over time appears to be particularly impactful in developing hypomanic

242 symptoms.

243   There are many potential mechanisms by which ADHD symptoms may either lead to

244 hypomanic symptoms or reflect comorbidity. Whilst there are some common symptomatic

245 features in both conditions, diagnostic criterion overlap may not entirely explain the comorbidity

246 of both.[36] It has also been found that some shared clinical features are due to shared genetic

247 factors.[37] For example, a twin study found that more than a quarter of the variance for

248 hypomania was associated with shared genetic risk factors for ADHD traits and environmental

249 influences appeared to have a negligible role in the associations between the two disorders.[1]

250 Another large cohort study found that BD polygenic risk scores were strongly associated with

251 childhood ADHD.[38] Additionally, a cross-disorder meta-analysis of the existing genome-wide

252 association studies[39] (GWAS) provided evidence for genetic overlap between ADHD and BD

253 such as G protein-coupled signalling already known for their role in hyperactivity and emotional

254 behaviours. Further, another recent GWAS study[40] provided five novel risk loci showing

255 concordant directions of effect for ADHD and BD. Future research is needed to clarify whether

256 mechanisms driving associations between ADHD symptoms and hypomanic symptoms may

257 differ depending on the pattern of ADHD symptoms that young people experience over time,

258 including its subtypes. In line with previous research[1] our findings are unlikely to be

259 explainable by symptom overlap given that exclusion of ADHD-like symptoms from the HCL

260 variable did not modify our results.

261   There are several implications arising from the current findings. First, the present

262 findings suggest that childhood and adolescent ADHD symptom trajectories, including its

263 subtypes may confer risk for clinically significant hypomanic symptoms in young adulthood.

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264   Practitioners and patients would be best served in completing multiple assessments of ADHD

265   symptoms over time to identify individuals who are most at risk of future BD. Formally

266   classifying child trajectories to target the reduction in high-risk trajectories and encourage

267   preventative treatments is a critical next step.[41] This is crucial also because treatment earlier

268   in the illness course is more effective.[42,43] If replicated in individuals entering health service

269   systems, the results can substantially help refine clinical staging models.[44] Future longitudinal

270   research is needed to demonstrate the complex patterns of emergence of psychopathology in

271   youth at-risk for BD, along with their homotypic and heterotypic continuity, within a

272   developmental framework utilising multidisciplinary approaches.[45] Additionally, given the

273   multidimensional nature of most mental disorders[46,47], transdiagnosticity of these associations

274   should also be examined.[48–51] This way, robust specific risk trajectories might also be

275   identified. In the same vein, future research should also investigate the potential underlying

276   mechanisms of the observed associations. Previous research have suggested that a history or

277   current diagnosis of ADHD should be taken into account as a possible predictor of mixed or

278   bipolar depression in patients with a major depressive episode (MDE).[52] For example, a study

279   looking at the prevalence of ADHD in adult patients with BD observed a higher frequency of

280   atypical depression (i.e., hypersomnia, hyperphagia, and increased appetite and weight gain) and

281   a lower frequency of melancholic depression in the patients of the BD + ADHD group [53].

282   Another study found that mixed features during current MDE, earlier onset of depression before

283   the age of 20, higher number of previous depressive and mood episodes, shorter duration of

284   current MDE, and psychotic symptoms were more common in patients with comorbid major

285   depression and ADHD comparing to the remaining sample [54]. Thus, one of the potential

286   mechanisms future studies could investigate may be clinical characteristics suggestive of a

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287   bipolar depression diathesis (e.g., atypical depression features, psychotic symptoms, abrupt onset

288   and offset, non-response to antidepressants, or antidepressant emergent elation, and family

289   history of BD).

290   Our study has several limitations. First, despite our methods and results meeting several

291   of the Bradford Hill criteria,[55] we have not demonstrated causation. Second, our cohort

292   consisted of prepubertal children who tend to exhibit non-clinical symptomatology and derive

293   from genetically heterogenous families. Therefore, our results may differ from young people

294   who are seen in clinical settings. Third, ALSPAC has only one assessment timepoint of

295   hypomanic symptoms. That is why, a baseline measure against which to compare stability

296   symptoms over time was not available. Further, the HCL-32 was used as a measure of lifetime

297   clinically significant hypomanic symptoms, but this will not always equate with a clinical

298   diagnosis of hypomania and hypomanic symptoms were not clinically verified in the cohort.[56]

299   The HCL-32 was self-reported, and this may have diminished the accuracy of the data due to

300   recall biases. There is also a lack of chronology of hypomanic symptoms. Although we used a

301   well-recognized cut-off score for lifetime hypomanic symptoms to improve the capacity of the

302   HCL to identify clinical levels, amplified by measures of duration and impact on functioning, the

303   combination of self-reports, parent reports and clinical structured interviews would be the ideal

304   approach to increase the predictive value of our findings than the use of a single scale.[57] That

305   is why, replicating these findings in help-seeking clinical populations utilising both screening

306   tools and clinical structured interviews is warranted. Fourth, only parent-reported data was

307   available for all the ADHD assessments; however, symptoms may differ across settings and in

308   interaction with different informants such as teachers and peers.[58] Fifth, we were only able to

309   look at ADHD symptoms from age 8 to 13. However, the trajectory classes we have observed are

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310   in line with the highly dynamic changes in ADHD presentation from childhood to adulthood

311   evident in the previous literature.[16,59,60] Sixth, the ALSPAC cohort was recruited in one

312   region in Southwest England comprising mainly White participants, and therefore our findings

313   may not generalize to other settings or birth cohorts. Additionally, although inverse probability

314   weighting partially addressed cohort-specific patterns of non-response by adjusting samples to

315   better represent the initial population, we cannot dismiss the biases that might stem from

316   unmeasured factors that may influence missingness.[61] Seventh, although we focused on the

317   associations with clinically significant hypomanic symptoms, given the multidimensional nature

318   of most mental disorders,[44,48,50,62] the same risk trajectories observed here may be

319   associated with multiple types of disorders. Eight, there is the risk of residual confounding, as it

320   is the case with all observational analyses. For example, childhood ADHD increase the risk of

321   developing substance-related disorders[63–65] and there is a higher risk of developing BD in

322   children and adolescents with ADHD with comorbid substance use disorders (SUDs).[66,67]

323   Past or current substance misuse may also confound the reliability of bipolar self-assessment

324   screening[68] as SUDs can mimic affective episodes.[69] Cannabis use, particularly, may

325   compound dopaminergic signalling in adolescence and lead to an increased propensity to

326   experience hypomanic symptomatology.[70] Additionally, the psychostimulant methylphenidate,

327   one of the most widely used medications for ADHD, may increase the risk of treatment-

328   emergent mania in patients suffering from BD when it is used without a concomitant mood-

329   stabilizing treatment.[71] However, it must also be noted that the available evidence with regards

330   to manic switch risk with commonly used ADHD medications is limited and somewhat

331   inconsistent.[72] For example, one study found that children with ADHD who were prescribed

332   long-term methylphenidate (i.e., more than 365 days) had a lower risk of being diagnosed with

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333   BD.[73] Additionally, given the similar cognitive impairments in BD and ADHD,[72] if the

334   observed associations between persistent and increasing inattention trajectories and clinically

335   significant hypomanic symptoms are replicated in high-risk samples, identifying effective pro-

336   cognitive treatments alongside mood stabilisers might be a helpful early intervention strategy for

337   cognitive impairments. Lastly, although we were not able to control for ADHD medication use,

338   evidence coming from other UK cohort studies highlight that the proportion of children with

339   ADHD using medication remains lower than in North America, East Asia, France and Central

340   Europe[74,75] possibly due to stigma and lack of recognition of the condition[76] and resource

341   limitations.[77] Further, most of those who stop ADHD medication in adolescence do not have

342   their prescriptions resumed in early adulthood.[78,79] That is why, ADHD medication use might

343   have had a negligible role in the associations we observed.

344   Conclusions

345   We identified a pattern of chronically high ADHD and increasing ADHD symptoms across

346   childhood and early adolescence as independent risk factors for clinically significant hypomanic

347   symptoms in young adulthood compared to persistently low and decreasing levels. We have also

348   found that a pattern of chronically high hyperactivity and inattention and increasing inattention

349   levels were also independent risk factor for clinically significant hypomanic symptoms. These

350   ADHD symptom profiles and trajectories represent a new and critical way of identifying at risk

351   populations for BD. Further validation in help seeking clinical populations is warranted.

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370 **Conflict of Interest Disclosures:** None

371 **Data Availability:** ALSPAC data used within this study are accessible on request via an online

372 proposal form. Please see http://www.bristol.ac.uk/alspac/researchers/access/ for further details.

373 Please note that the ALSPAC website contains details of all data that are available through a

374 fully searchable data dictionary and variable search tool

375 (http://www.bristol.ac.uk/alspac/researchers/our-data/).

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References

[1] Hosang GM, Lichtenstein P, Ronald A, Lundström S, Taylor MJ. Association of Genetic and Environmental Risks for Attention-Deficit/Hyperactivity Disorder with Hypomanic Symptoms in Youths. JAMA Psychiatry 2019;76:1150–8. https://doi.org/10.1001/jamapsychiatry.2019.1949.

[2] Meier SM, Pavlova B, Dalsgaard S, Nordentoft M, Mors O, Mortensen PB, et al. Attention-deficit hyperactivity disorder and anxiety disorders as precursors of bipolar disorder onset in adulthood. British Journal of Psychiatry 2018;213:555–60. https://doi.org/10.1192/bjp.2018.111.

[3] Kent L, Craddock N. Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? J Affect Disord 2003;73:211–21. https://doi.org/10.1016/S0165-0327(02)00092-7.

[4] Schiweck C, Arteaga-Henriquez G, Aichholzer M, Edwin Thanarajah S, Vargas-Cáceres S, Matura S, et al. Comorbidity of ADHD and adult bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev 2021;124:100–23. https://doi.org/10.1016/j.neubiorev.2021.01.017.

[5] Brancati GE, Perugi G, Milone A, Masi G, Sesso G. Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of prospective studies. J Affect Disord 2021;293:186–96. https://doi.org/10.1016/j.jad.2021.06.033.

[6] Moran L V., Guvenek-Cokol PE, Perlis. RH. Attention-Deficit/Hyperactivity Disorder, Hypomania, and Bipolar Disorder in Youth. JAMA Psychiatry 2019;76:1119–21. https://doi.org/10.2307/3088897.

[7] Serrano E, Ezpeleta L, Castro-Fornieles J. Comorbidity and Phenomenology of Bipolar Disorder in Children With ADHD. J Atten Disord 2013;17:330–8. https://doi.org/10.1177/1087054711427553.

[8] Birmaher B, Merranko J, Hafeman D, Goldstein BI, Diler R, Levenson JC, et al. A Longitudinal Study of Psychiatric Disorders in Offspring of Parents With Bipolar Disorder From Preschool to Adolescence. J Am Acad Child Adolesc Psychiatry 2021;60:1419–29. https://doi.org/10.1016/j.jaac.2021.02.023.

[9] Brancati GE, Perugi G, Milone A, Masi G, Sesso G. Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of prospective studies. J Affect Disord 2021;293:186–96. https://doi.org/10.1016/j.jad.2021.06.033.

[10] Tillman R, Geller B. Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: Rate, risk, and predictors. Dev Psychopathol 2006;18:1037–53. https://doi.org/10.1017/S0954579406060512.

[11] Arnold LE, Van Meter AR, Fristad MA, Youngstrom EA, Birmaher BB, Findling RL, et al. Development of bipolar disorder and other comorbidity among youth with attention-deficit/hyperactivity disorder. J Child Psychol Psychiatry 2020;61:175–81. https://doi.org/10.1111/jcpp.13122.

[12] Breda V, Rohde LA, Menezes AMB, Anselmi L, Caye A, Rovaris DL, et al. The neurodevelopmental nature of attention-deficit hyperactivity disorder in adults. British Journal of Psychiatry 2021;218:43–50. https://doi.org/10.1192/bjp.2020.200.

[13] Brinksma DM, Hoekstra PJ, de Bildt A, Buitelaar JK, van den Hoofdakker BJ, Hartman CA, et al. Parental rejection in early adolescence predicts a persistent ADHD symptom trajectory across adolescence. Eur Child Adolesc Psychiatry 2023;32:139–53. https://doi.org/10.1007/s00787-021-01844-0.

[14] Murray AL, Booth T, Eisner M, Auyeung B, Murray G, Ribeaud D. Sex differences in ADHD trajectories across childhood and adolescence. Dev Sci 2019;22:1–11. https://doi.org/10.1111/desc.12721.

[15] Murray AL, Hall HA, Speyer LG, Carter L, Mirman D, Caye A, et al. Developmental trajectories of ADHD symptoms in a large population-representative longitudinal study. Psychol Med 2022;52:3590–6. https://doi.org/10.1017/S0033291721000349.

[16] Franke B, Michelini G, Asherson P, Banaschewski T, Bilbow A, Buitelaar JK, et al. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. European Neuropsychopharmacology 2018;28:1059–88. https://doi.org/10.1016/j.euroneuro.2018.08.001.

[17] Friedrichs B, Igl W, Larsson H, Larsson JO. Coexisting psychiatric problems and stressful life events in adults with symptoms of ADHD-A large swedish population-based study of twins. J Atten Disord 2012;16:13–22. https://doi.org/10.1177/1087054710376909.

[18] Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. The Lancet 2016;387:1561–72. https://doi.org/10.1016/S0140-6736(15)00241-X.

[19] Hosang GM, Cardno AG, Freeman D, Ronald A. Characterization and structure of hypomania in a British nonclinical adolescent sample. J Affect Disord 2017;207:228–35. https://doi.org/10.1016/j.jad.2016.08.033.

[20] Holtmann M, Pörtner F, Duketis E, Flechtner HH, Angst J, Lehmkuhl G. Validation of the Hypomania Checklist (HCL-32) in a nonclinical sample of German adolescents. J Adolesc 2009;32:1075–88. https://doi.org/10.1016/j.adolescence.2009.03.004.

[21] Northstone K, Ben Shlomo Y, Teyhan A, Hill A, Groom A, Mumme M, et al. The Avon Longitudinal Study of Parents and children ALSPAC G0 Partners: A cohort profile. Wellcome Open Res 2023;8:37. https://doi.org/10.12688/wellcomeopenres.18782.2.

[22] Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort profile: The 'Children of the 90s'-The index offspring of the avon longitudinal study of parents and children. Int J Epidemiol 2013;42:111–27. https://doi.org/10.1093/ije/dys064.

[23] Fraser A, Macdonald-wallis C, Tilling K, Boyd A, Golding J, Davey smith G, et al. Cohort profile: The avon longitudinal study of parents and children: ALSPAC mothers cohort. Int J Epidemiol 2013;42:97–110. https://doi.org/10.1093/ije/dys066.

[24] Golding G, Pembrey P, Jones J. ALSPAC - The Avon Longitudinal Study of Parents and Children I. Study methodology. Paediatr Perinat Epidemiol 2001;15:74–87. https://doi.org/10.1046/j.1365-3016.2001.00325.x.

[25] Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: Description and initial validation of an integrated assessement of child and adolescent psychopathology. J Child Psychol Psychiatry 2000;41:645–55. https://doi.org/10.1017/S0021963099005909.

467	[26]	Angst J, Cassano G. The mood spectrum: Improving the diagnosis of bipolar disoder.
468		Bipolar Disorders, Supplement 2005;7:4–12. https://doi.org/10.1111/j.1399-
469		5618.2005.00210.x.
470	[27]	Marwaha S, Winsper C, Bebbington P, Smith D. Cannabis use and hypomania in
471		young people: A prospective analysis. Schizophr Bull 2018;44:1267–74.
472		https://doi.org/10.1093/schbul/sbx158.
473	[28]	Zanarini MC. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-
474		BPD): A continuous measure of DSM-IV borderline psychopathology. J Pers Disord
475		2003;17:233–42. https://doi.org/10.1521/pedi.17.3.233.22147.
476	[29]	Baryshnikov I, Aaltonen K, Koivisto M, Näätänen P, Karpov B, Melartin T, et al.
477		Differences and overlap in self-reported symptoms of bipolar disorder and borderline
478		personality disorder. European Psychiatry 2015;30:914–9.
479		https://doi.org/10.1016/j.eurpsy.2015.08.002.
480	[30]	Mistry S, Zammit S, Price VE, Jones HJ, Smith DJ. Borderline personality and
481		attention-deficit hyperactivity traits in childhood are associated with hypomanic
482		features in early adulthood. J Affect Disord 2017;221:246–53.
483		https://doi.org/10.1016/j.jad.2017.06.039.
484	[31]	Durdurak BB, Altaweel N, Upthegrove R, Marwaha S. Understanding the
485		development of bipolar disorder and borderline personality disorder in young people:
486		a meta-review of systematic reviews. Psychol Med 2022;52:3769–82.
487		https://doi.org/10.1017/S0033291722003002.
488	[32]	Jung T, Wickrama KAS. An Introduction to Latent Class Growth Analysis and
489		Growth Mixture Modeling. Soc Personal Psychol Compass 2008;2:302–17.
490		https://doi.org/10.1111/j.1751-9004.2007.00054.x.
491	[33]	Wardenaar KJ. Latent class growth analysis and growth mixture modeling using R: A
492		tutorial for two R-packages and a comparison with Mplus. PsyArXiv 2022:1–23.
493	[34]	Wilens TE, Biederman J, Wozniak J, Gunawardene S, Wong J, Monuteaux M. Can
494		adults with attention-deficit/hyperactivity disorder be distinguished from those with
495		comorbid bipolar disorder? Findings from a sample of clinically referred adults. Biol
496		Psychiatry 2003;54:1–8. https://doi.org/10.1016/S0006-3223(02)01666-9.
497	[35]	Arnold LE, Ganocy SJ, Mount K, Youngstrom EA, Frazier T, Fristad M, et al. Three-
498		year latent class trajectories of attention-deficit/hyperactivity disorder (ADHD)
499		symptoms in a clinical sample not selected for ADHD. J Am Acad Child Adolesc
500		Psychiatry 2014;53:745–60. https://doi.org/10.1016/j.jaac.2014.03.007.
501	[36]	Hosang GM, Lichtenstein P, Ronald A, Lundström S, Taylor MJ. Association of
502		Genetic and Environmental Risks for Attention-Deficit/Hyperactivity Disorder with
503		Hypomanic Symptoms in Youths. JAMA Psychiatry 2019;76:1150–8.
504		https://doi.org/10.1001/jamapsychiatry.2019.1949.
505	[37]	Faraone S V., Larsson H. Genetics of attention deficit hyperactivity disorder. Mol
506		Psychiatry 2019;24:562–75. https://doi.org/10.1038/s41380-018-0070-0.
507	[38]	Mistry S, Escott-Price V, Florio AD, Smith DJ, Zammit S. Genetic risk for bipolar
508		disorder and psychopathology from childhood to early adulthood. J Affect Disord
509		2019;246:633–9. https://doi.org/10.1016/j.jad.2018.12.091.
510	[39]	van Hulzen KJE, Scholz CJ, Franke B, Ripke S, Klein M, McQuillin A, et al. Genetic
511		Overlap Between Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder:

21

512   Evidence From Genome-wide Association Study Meta-analysis. Biol Psychiatry
513   2017;82:634–41. https://doi.org/10.1016/j.biopsych.2016.08.040.

514   [40]   O'Connell KS, Shadrin A, Bahrami S, Smeland OB, Bettella F, Frei O, et al.
515   Identification of genetic overlap and novel risk loci for attention-deficit/hyperactivity
516   disorder and bipolar disorder. Mol Psychiatry 2021;26:4055–65.
517   https://doi.org/10.1038/s41380-019-0613-z.

518   [41]   Shore L, Toumbourou JW, Lewis AJ, Kremer P. Review: Longitudinal trajectories of
519   child and adolescent depressive symptoms and their predictors – a systematic review
520   and meta-analysis. Child Adolesc Ment Health 2018;23:107–20.
521   https://doi.org/10.1111/camh.12220.

522   [42]   Berk M, Post R, Ratheesh A, Gliddon E, Singh A, Vieta E, et al. Staging in bipolar
523   disorder: from theoretical framework to clinical utility. World Psychiatry
524   2017;16:236–44. https://doi.org/10.1002/wps.20441.

525   [43]   Nierenberg AA, Agustini B, Köhler-Forsberg O, Cusin C, Katz D, Sylvia LG, et al.
526   Diagnosis and Treatment of Bipolar Disorder: A Review. JAMA 2023;330:1370–80.
527   https://doi.org/10.1001/jama.2023.18588.

528   [44]   Shah JL, Jones N, van Os J, McGorry PD, Güloksüz S. Early intervention service
529   systems for youth mental health: integrating pluripotentiality, clinical staging, and
530   transdiagnostic lessons from early psychosis. Lancet Psychiatry 2022;9:413–22.
531   https://doi.org/10.1016/S2215-0366(21)00467-3.

532   [45]   Manchia M, Vieta E, Smeland OB, Altimus C, Bechdolf A, Bellivier F, et al.
533   Translating big data to better treatment in bipolar disorder - a manifesto for
534   coordinated action. European Neuropsychopharmacology 2020;36:121–36.
535   https://doi.org/10.1016/j.euroneuro.2020.05.006.

536   [46]   Piazza GG, Allegrini AG, Eley TC, Epskamp S, Fried E, Isvoranu AM, et al.
537   Polygenic Scores and Networks of Psychopathology Symptoms. JAMA Psychiatry
538   2024;81:902–10. https://doi.org/10.1001/jamapsychiatry.2024.1403.

539   [47]   Stefan Leucht M, Jim van Os M, Markus Jäger M, John M. Davis M. Prioritization of
540   Psychopathological Symptoms and Clinical Characterization in Psychiatric
541   Diagnoses A Narrative Review 2024:1–10.
542   https://doi.org/10.1001/jamapsychiatry.2024.2652.

543   [48]   Arribas M, Oliver D, Patel R, Kornblum D, Shetty H, Damiani S, et al. A
544   transdiagnostic prodrome for severe mental disorders: an electronic health record
545   study. Mol Psychiatry 2024. https://doi.org/10.1038/s41380-024-02533-5.

546   [49]   Destrée L, McGorry P, Chanen A, Ratheesh A, Davey C, Polari A, et al.
547   Transdiagnostic risk identification: A validation study of the Clinical High At Risk
548   Mental State (CHARMS) criteria. Psychiatry Res 2024;333.
549   https://doi.org/10.1016/j.psychres.2024.115745.

550   [50]   Scott J, Iorfino F, Capon W, Crouse J, Nelson B, Chanen AM, et al. Staging 2.0:
551   refining transdiagnostic clinical staging frameworks to enhance reliability and utility
552   for youth mental health. Lancet Psychiatry 2024;11:461–71.
553   https://doi.org/10.1016/S2215-0366(24)00060-9.

554   [51]   Shah JL, Scott J, McGorry PD, Cross SPM, Keshavan MS, Nelson B, et al.
555   Transdiagnostic clinical staging in youth mental health: a first international
556   consensus statement. World Psychiatry 2020;19:233–42.
557   https://doi.org/10.1002/wps.20745.

22

558　[52]　Purper-Ouakil D, Porfirio MC, Le Strat Y, Falissard B, Gorwood P, Masi G. What do
559　　　　 childhood attention deficit/hyperactivity symptoms in depressed adults tell us about
560　　　　 the bipolar spectrum? Psychiatry Res 2017;249:244–51.
561　　　　 https://doi.org/10.1016/j.psychres.2016.12.055.
562　[53]　Torres I, Gómez N, Colom F, Jiménez E, Bosch R, Bonnín CM, et al. Bipolar
563　　　　 disorder with comorbid attention-deficit and hyperactivity disorder. Main clinical
564　　　　 features and clues for an accurate diagnosis. Acta Psychiatr Scand 2015;132:389–99.
565　　　　 https://doi.org/10.1111/acps.12426.
566　[54]　Vannucchi G, Medda P, Pallucchini A, Bertelli M, Angst J, Azorin JM, et al. The
567　　　　 relationship between attention deficit hyperactivity disorder, bipolarity and mixed
568　　　　 features in major depressive patients: Evidence from the BRIDGE-II-Mix Study. J
569　　　　 Affect Disord 2019;246:346–54. https://doi.org/10.1016/j.jad.2018.12.089.
570　[55]　Hill AB. The Environment and Disease: Association or causation? Proc R Soc Med
571　　　　 1965:295–300.
572　[56]　Marwaha S, Winsper C, Bebbington P, Smith D. Cannabis use and hypomania in
573　　　　 young people: A prospective analysis. Schizophr Bull 2018;44:1267–74.
574　　　　 https://doi.org/10.1093/schbul/sbx158.
575　[57]　Vieta E, Salagre E, Grande I, Carvalho AF, Fernandes BS, Berk M, et al. Early
576　　　　 intervention in Bipolar disorder. American Journal of Psychiatry 2018;175:411–26.
577　　　　 https://doi.org/10.1176/appi.ajp.2017.17090972.
578　[58]　Murray AL, Booth T, Auyeung B, Eisner M, Ribeaud D, Obsuth I. Outcomes of
579　　　　 ADHD Symptoms in Late Adolescence: Are Developmental Subtypes Important? J
580　　　　 Atten Disord 2020;24:113–25. https://doi.org/10.1177/1087054718790588.
581　[59]　Murray AL, Hall HA, Speyer LG, Carter L, Mirman D, Caye A, et al. Developmental
582　　　　 trajectories of ADHD symptoms in a large population-representative longitudinal
583　　　　 study. vol. 52. 2022. https://doi.org/10.1017/S0033291721000349.
584　[60]　Rice F, Riglin L, Thapar AK, Heron J, Anney R, O'Donovan MC, et al.
585　　　　 Characterizing Developmental Trajectories and the Role of Neuropsychiatric Genetic
586　　　　 Risk Variants in Early-Onset Depression. JAMA Psychiatry 2019;76:306–13.
587　　　　 https://doi.org/10.1001/jamapsychiatry.2018.3338.
588　[61]　Armitage JM, Kwong ASF, Tseliou F, Sellers R, Blakey R, Anthony R, et al. Cross-
589　　　　 cohort change in parent-reported emotional problem trajectories across childhood and
590　　　　 adolescence in the UK. Lancet Psychiatry 2023;10:509–17.
591　　　　 https://doi.org/10.1016/S2215-0366(23)00175-X.
592　[62]　McGorry PD, Hartmann JA, Spooner R, Nelson B. Beyond the "at risk mental state"
593　　　　 concept: transitioning to transdiagnostic psychiatry. World Psychiatry 2018;17:133–
594　　　　 42. https://doi.org/10.1002/wps.20514.
595　[63]　Groenman AP, Janssen TWP, Oosterlaan J. Childhood Psychiatric Disorders as Risk
596　　　　 Factor for Subsequent Substance Abuse: A Meta-Analysis. J Am Acad Child Adolesc
597　　　　 Psychiatry 2017;56:556–69. https://doi.org/10.1016/j.jaac.2017.05.004.
598　[64]　Ottosen C, Petersen L, Larsen JT, Dalsgaard S. Gender Differences in Associations
599　　　　 between Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder. J Am
600　　　　 Acad Child Adolesc Psychiatry 2016;55:227-234.e4.
601　　　　 https://doi.org/10.1016/j.jaac.2015.12.010.

[65] Skoglund C, Chen Q, Franck J, Lichtenstein P, Larsson H. Attention-Deficit/Hyperactivity Disorder and Risk for Substance Use Disorders in Relatives. Biol Psychiatry 2015;77:880–6. https://doi.org/10.1016/j.biopsych.2014.10.006.

[66] Lalli M, Brouillette K, Kapczinski F, de Azevedo Cardoso T. Substance use as a risk factor for bipolar disorder: A systematic review. J Psychiatr Res 2021;144:285–95. https://doi.org/10.1016/j.jpsychires.2021.10.012.

[67] Salvi V, Ribuoli E, Servasi M, Orsolini L, Volpe U. Adhd and bipolar disorder in adulthood: Clinical and treatment implications. Medicina (Lithuania) 2021;57:1–11. https://doi.org/10.3390/medicina57050466.

[68] Goldberg JF, Garakani A, Ackerman SH. Clinician-rated versus self-rated screening for bipolar disorder among inpatients with mood symptoms and substance misuse. Journal of Clinical Psychiatry 2012;73:1525–30. https://doi.org/10.4088/JCP.12m07926.

[69] Carvalho AF, Firth J, Vieta E. Bipolar Disorder Bipolar Disorder 2016. New England Journal of Medicine 2020;383:58–66. https://doi.org/10.1056/NEJMra1906193.

[70] Marwaha S, Winsper C, Bebbington P, Smith D. Cannabis use and hypomania in young people: A prospective analysis. Schizophr Bull 2018;44:1267–74. https://doi.org/10.1093/schbul/sbx158.

[71] Viktorin A, Rydén E, Thase ME, Chang Z, Lundholm C, D'Onofrio BM, et al. The risk of treatment-emergent mania with methylphenidate in bipolar disorder. American Journal of Psychiatry 2017;174:341–8. https://doi.org/10.1176/appi.ajp.2016.16040467.

[72] Miskowiak KW, Obel ZK, Guglielmo R, Bonnin C del M, Bowie CR, Balanzá-Martínez V, et al. Efficacy and safety of established and off-label ADHD drug therapies for cognitive impairment or attention-deficit hyperactivity disorder symptoms in bipolar disorder: A systematic review by the ISBD Targeting Cognition Task Force. Bipolar Disord 2024;26:216–39. https://doi.org/10.1111/bdi.13414.

[73] Wang LJ, Shyu YC, Yuan SS, Yang CJ, Yang KC, Lee TL, et al. Attention-deficit hyperactivity disorder, its pharmacotherapy, and the risk of developing bipolar disorder: A nationwide population-based study in Taiwan. J Psychiatr Res 2016;72:6–14. https://doi.org/10.1016/j.jpsychires.2015.10.014.

[74] Raman SR, Man KKC, Bahmanyar S, Berard A, Bilder S, Boukhris T, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. Lancet Psychiatry 2018;5:824–35. https://doi.org/10.1016/S2215-0366(18)30293-1.

[75] Russell AE, Ford T, Russell G. Barriers and predictors of medication use for childhood ADHD: findings from a UK population-representative cohort. Soc Psychiatry Psychiatr Epidemiol 2019;54:1555–64. https://doi.org/10.1007/s00127-019-01720-y.

[76] Young S, Asherson P, Lloyd T, Absoud M, Arif M, Colley WA, et al. Failure of Healthcare Provision for Attention-Deficit/Hyperactivity Disorder in the United Kingdom: A Consensus Statement. Front Psychiatry 2021;12:1–16. https://doi.org/10.3389/fpsyt.2021.649399.

[77] Asherson P, Leaver L, Adamou M, Arif M, Askey G, Butler M, et al. Mainstreaming adult ADHD into primary care in the UK: guidance, practice, and best practice

647   recommendations. BMC Psychiatry 2022;22:1–20. https://doi.org/10.1186/s12888-
648   022-04290-7.

649   [78] Newlove-Delgado T, Ford TJ, Hamilton W, Janssens A, Stein K, Ukoumunne OC.
650   Resumption of attention-deficit hyperactivity disorder medication in early adulthood:
651   findings from a UK primary care prescribing study. Eur Child Adolesc Psychiatry
652   2019;28:1589–96. https://doi.org/10.1007/s00787-019-01325-5.

653   [79] Newlove-Delgado T, Hamilton W, Ford TJ, Stein K, Ukoumunne OC. Prescribing
654   for young people with attention deficit hyperactivity disorder in UK primary care:
655   analysis of data from the Clinical Practice Research Datalink. ADHD Attention
656   Deficit and Hyperactivity Disorders 2019;11:255–62. https://doi.org/10.1007/s12402-
657   019-00288-6.

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659

660 **Figure 1. Four Class Model ADHD Symptoms -** Developmental course of Development and
661 Wellbeing Assessment (DAWBA) ADHD from 8 to 13 years old.
662
663

ADHD 4 CLASS TRAJECTORIES
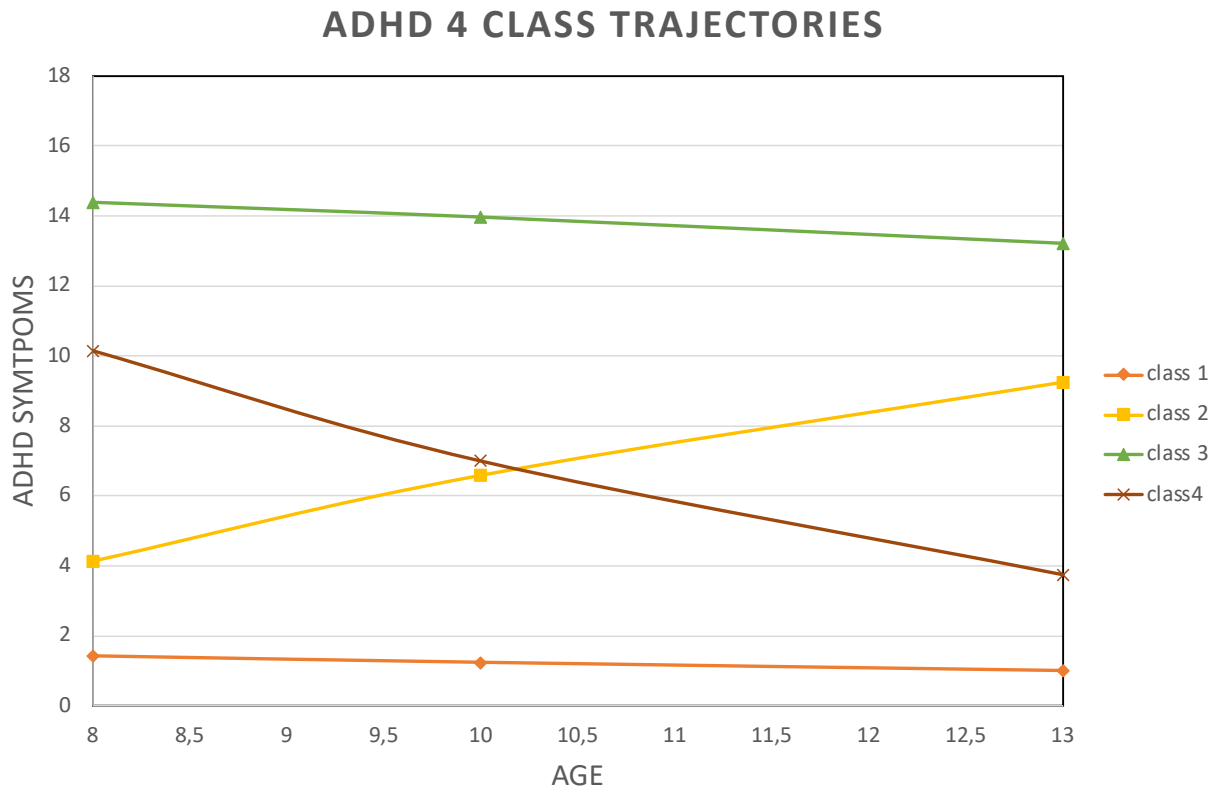
664
665 The latent class growth analyses detected a best model fit for 4 classes. Class 1 (orange line on
666 the bottom) represents individuals with persistent low levels of ADHD across time points. Class
667 2 (yellow line) represents individuals with increasing levels of ADHD. Class 3 (green line on the
668 top) represents individuals with persistent high levels of ADHD. Class 4 (brown line) represents
669 individuals with decreasing levels of inattentiveness.
670
671
672

26

673 **Table 1**. Descriptive values of sociodemographic variables, ADHD symptom trajectories, and
674 clinically significant hypomanic symptoms in ALSPAC Cohort[a]
675

Variable	Mean (SD)	No. (%)
Child's Sex		
Female	-	7348 (8.9)
Male	-	7691 (51.1)
Ethnicity		
White	-	12062 (97.4)
Bangladeshi	-	7 (0.1)
Black African	-	11 (0.1)
Black Caribbean	-	76 (0.6)
Black Other	-	44 (0.4)
Chinese	-	30 (0.2)
Indian	-	54 (0.4)
Pakistani	-	22 (0.2)
Other	-	82 (0.7)
FAI, total scores[b]	4.38 (4.31)	-
BPD symptoms at 11 years, total score	0.35 (0.86)	-
DAWBA ADHD symptoms at 8 years total score (n=7811), mean (SD)	4.21 (5.07)	-
DAWBA ADHD symptoms at 10 years total score (n=7435), mean (SD)	3.87 (4.91)	-
DAWBA ADHD symptoms at 13 years total score (n=6798), mean (SD)	3.42 (4.59)	-
Hypomanic symptoms total score at 21-23 years[c]	15.14 (16.00)	-
Clinically significant hypomanic symptoms at 21-23 years		
Yes	-	25 (1.8)
No	-	1348 (98.2)

676
677
678 Note: ADHD = Attention Deficit/hyperactivity disorder; BPD = Borderline Personality Disorder; DAWBA =
679 Development and Well-Being Assessment; SD, Standard Deviation.
680
681 [a] Unweighted descriptive values for the total sample.
682
683 [b]The total Family Adversity Index scores for 3 time-points (i.e., during pregnancy, age 2 years, and age 4 years)
684 were summed.
685
686 [c] Participants were asked to consider a time when they were in a "high or hyper" state and endorse a number of
687 statements about their emotions, thoughts, and behaviours at that time.
688
689
690

691 **Table 2.** BIC, VLMR Likelihood Test p Values, and Entropy for Classes 2–6 of the DAWBA
692 Scores of ADHD, Inattentive Only, and Hyperactivity Only

Composite Score of ADHD	AIC	BIC	ABIC	VLMR P-Value	LMRALT P-Value	Entropy
2 classes	121631.994	121689.284	121663.861	0.0000	0.0000	0.898
3 classes	118935.147	119013.921	118978.964	0.0000	0.0000	0.865
4 classes	117185.608	117285.865	117285.865	0.0000	0.0000	0.848
5 classes	116292.692	116414.433	116360.410	0.0549	0.0593	0.834
Hyperactivity Only						
2 classes	92437.058	92494.411	92468.988	0.0000	0.0000	0.927
3 classes	89626.816	89705.678	89670.721	0.0000	0.0000	0.893
4 classes	87450.031	87550.400	87505.910	0.0038	0.0045	0.875
5 classes	85894.420	86016.296	85962.273	0.1924	0.1997	0.859
Inattentive Only						
2 classes	100774.221	100831.546	100806.123	0.0000	0.0000	0.898
3 classes	98851.228	98930.049	98895.093	0.0000	0.0000	0.833
4 classes	95529.744	95630.062	95585.572	0.0000	0.0000	0.853
5 classes	94702.548	94824.362	94770.339	0.0061	0.0071	0.833

693
694 Abbreviations: ABIC, Sample-size Adjusted Bayesian Information Criterion; AIC, Akaike Information Criterion;
695 ADHD; Attention deficit/hyperactivity disorder; BIC, Bayesian information criterion; DAWBA, Development and
696 Well-Being Assessment; VLMR, Vuong-Lo-Mendell-Rubin; LMRALT, Lo-Mendell-Rubin Adjusted LRT Test P-
697 Value.
698
699
700

701 **Table 3.** Associations of Latent Classes of ADHD, Hyperactivity Only, and Inattention Only and
702 Risk of Clinically Significant Hypomanic Symptoms at 21-23 Years[a]
703

	Unadjusted Model			Adjusted Model		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
ADHD composite score						
Persistently low class (Ref)	-	-	<0.001			<0.001
Remitting class	0.00	0.00	0.992	0.00	0.00	0.990
Increasing class	3.88	2.12-7.08	<0.001	3.60	1.92-6.74	<0.001
Persistently high class	3.26	1.65-6.45	<0.001	2.36	1.12-4.99	0.024
Child's sex	-	-	-	1.18	0.68-2.04	0.560
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.19	1.13-1.25	<0.001
BPD traits at 11 years	-	-	-	1.26	1.07-1.49	0.007
Hyperactivity Only						
Persistently low levels (Ref)	-	-	<0.001	-	-	0.005
Remitting class	0.00	0.00	0.992	0.00	0.00	0.991
Increasing class	2.03	0.91-4.53	0.084	0.92	0.35-2.43	0.868
Persistently high class	4.77	2.44-9.29	<0.001	3.47	1.69-7.12	<0.001
Child's sex	-	-	-	0.97	0.55-1.71	0.911
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.14	1.09-1.20	<0.001
BPD traits at 11 years	-	-	-	1.20	1.00-1.44	0.048
Inattentive Only						
Persistently low levels (Ref)	-	-	0.011	-	-	0.039
Remitting class	0.00	0.00	0.995	0.00	0.00	0.995
Increasing class	3.58	1.47-8.70	0.005	3.25	1.32-8.04	0.011
Persistently high class	2.75	1.26-6.00	0.011	2.47	1.07-5.70	0.034
Child's sex	-	-	-	0.51	0.24-1.09	0.082
Child's ethnicity	-	-	-	0.00	0.00	0.997
Family Adversity Index	-	-	-	0.93	0.84-1.04	0.211
BPD traits at 11 years	-	-	-	1.37	1.10-1.70	0.004

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705 Note: ADHD = Attention Deficit/hyperactivity disorder; BPD = Borderline Personality Disorder; DAWBA =
706 Development and Well-Being Assessment; OR = Odds Ratio.
707
708 [a] All analyses were weighted for sex, ethnicity, maternal age, maternal socioeconomic status, preterm delivery,
709 birthweight and family adversity; Adjusted Model: associations adjusted for child's sex, child's ethnicity, family
710 adversity scores during pregnancy, at 2 years of age and 4 years of age, and BPD traits at 11 years.
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