information services
gwasanaethau gwybodaeth

1   **Title:** Childhood trauma as a mediator of the association between autistic traits and psychotic

2   experiences: evidence from the ALSPAC birth cohort

3   **Running title:** Autistic traits and psychotic experiences

4

5   **Authors:**

6   Christina Dardani[1*], Rik Schalbroeck[2,3,4*], Paul Madley-Dowd[1], Hannah J. Jones[1,5,6], Daniela

7   Strelchuk[1], Gemma Hammerton[1,5], Jazz Croft[1], Sarah A. Sullivan[1,6], Stan Zammit[1,6,7], Jean-Paul

8   Selten[2,3], Dheeraj Rai[1,6,8]

9

10   **Affiliations:**

11   [1] Population Health Sciences, Bristol Medical School, University of Bristol, UK.

12   [2] Rivierduinen Institute for Mental Healthcare, Leiden, The Netherlands.

13   [3] School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands.

14   [4] Section of Nuclear Medicine, Department of Radiology, Leiden University Medical Center, Leiden,

15   The Netherlands.

16   [5] Medical Research Council Integrative Epidemiology Unit, Bristol Medical School, University of

17   Bristol, UK.

18   [6] National Institute for Health Research, Bristol Biomedical Research Centre, University Hospitals

19   Bristol NHS Foundation Trust, University of Bristol, Bristol, UK.

20   [7] Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK.

21   [8] Avon and Wiltshire Partnership NHS Mental Health Trust, Bath, UK.

22   * Joint first authors

23

24   **Corresponding author**:

25   Rik Schalbroeck: Rivierduinen Institute for Mental Healthcare, Sandifortdreef 19, 2333ZZ Leiden,

26   The Netherlands, r.schalbroeck@rivierduinen.nl

27

28   **Wordcount abstract (max. 250)**: 248

29   **Wordcount main text, acknowledgments, and figure legend (max. 4000):** 3984

30   **Figures and Tables**: 4

31 **Abstract**

32 **Background and hypothesis**: Little is known on whether associations between childhood autistic

33 traits and psychotic experiences persist into adulthood and whether genetic confounding and

34 childhood trauma influence them. Here we investigate the associations between childhood autistic

35 traits and psychotic experiences until young adulthood and assess the influence of schizophrenia

36 polygenic risk and childhood traumatic experiences, using the Avon Longitudinal Study of Parents

37 and Children (ALSPAC) population-based birth cohort.

38

39 **Study design:** We used a measure of broad autistic traits (autism factor mean score), and four

40 dichotomised measures of autistic traits capturing social communication difficulties (age 7), repetitive

41 behaviours (age 5), sociability (age 3), and pragmatic language (age 9). Psychotic experiences were

42 assessed at ages 18 and 24 using the semi-structured Psychosis-Like Symptoms interview (PLIKSi).

43 Traumatic experiences between ages 5 to 11 were assessed with questionnaires and interviews

44 administered to children and parents at multiple ages.

45

46 **Study results:** Broad autistic traits, as well as social communication difficulties, were associated with

47 psychotic experiences that were distressing and/or frequent until age 24 (autism factor mean score, n

48 = 3,707: OR 1.19, 95%CI 1.01–1.39; social communication difficulties, n = 3,384: OR 1.54, 95%CI

49 0.97–2.45). Childhood trauma mediated a substantial proportion of the identified associations (~28%

50 and 36% respectively, maximum n = 3,577). Schizophrenia polygenic risk did not appear to confound

51 the associations. Multiple imputation analyses (maximum n = 13,105) yielded comparable results.

52

53 **Conclusions**: Childhood trauma may be an important, potentially modifiable pathway between

54 autistic features and later onset of psychotic psychopathology.

55

56 **Keywords**: Autism, psychosis, childhood trauma, polygenic risk

Introduction

Autistic individuals are at an increased risk of developing a psychotic disorder[1]. An increasing number of studies also indicate that sub-clinical psychotic experiences are more common in individuals with autistic traits in the general population. This association has been observed in cross-sectional studies[2,3] and in studies that followed children with autistic traits to a maximum of age 18 years[4-7]. Although psychotic experiences in adolescence are usually transient and of no clinical concern, persistent psychotic experiences have been associated with distress and poor mental health outcomes[8,9], including the development of psychotic disorder[10]. Little is currently known on whether the associations between autistic traits and psychotic experiences persist into adulthood.

There is evidence suggesting a shared genetic basis between autism and psychotic disorders[11]. For instance, several common and rare genetic variants have been found to be associated with both autism and psychotic disorder[12], genome-wide association studies (GWAS) have shown a strong genetic correlation between autism and schizophrenia[13], and common polygenic risk for autism has been associated with increased odds of psychotic experiences in the general population[14].

However, the risk of psychosis in autism may also be influenced by environmental factors[11]. A history of childhood trauma (in the form of exposure to abuse, neglect, and bullying) is one of the most consistently reported environmental risk factors for psychotic experiences and psychotic disorder[15,16]. Socio-communicative differences may make individuals with autistic features vulnerable to childhood traumatic experiences, which may be exacerbated by reduced access to social support[17-20]. Indeed, there is evidence that childhood maltreatment and/or bullying victimization is more common in autistic individuals[21,22], individuals with autistic traits[23,24], and individuals with higher autism polygenic risk scores (PRS)[25].

Few studies have examined whether childhood trauma influences the risk of psychosis in individuals with autistic traits. One study of college students found that a self-reported history of trauma did not explain the association between autistic and schizotypal traits[23], but the retrospective design was prone to recall bias and precluded causal inferences. A longitudinal study reported that adjusting for bullying victimization did not alter the association between childhood autistic traits and psychotic

3

84 experiences, but formal mediation analysis was not conducted[4]. In contrast, a recent longitudinal study

85 reported that bullying victimization mediated the association between autistic traits and psychotic

86 experiences in adolescents, although other traumatic experiences were not assessed[26]. Therefore, it

87 remains unclear whether and to what extent trauma mediates the association between autistic traits

88 and psychotic experiences.

89 Using data from a UK population-based birth cohort, we examined (i) whether autistic traits assessed

90 between ages 3 and 9 were associated with psychotic experiences measured at ages 18 and 24, (ii) the

91 extent to which any identified association was mediated by trauma experienced between ages 5 and

92 11, and (iii) the possible confounding influence of several child and family factors including

93 schizophrenia PRS.

94

Methods

Participants

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based cohort study of children born to 14,541 pregnant mothers residing in the former county of Avon, United Kingdom, with an expected delivery date between 1 April 1991 and 31 December 1992. Of these pregnancies, there were 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, eligible samples who did not join the study initially were contacted, and additional participants were recruited. This resulted in a total of 15,454 pregnancies and 15,589 fetuses, of which 14,901 were alive at 1 year of age. Depending on the analysis conducted, we restricted our sample to participants with complete data on autistic traits, traumatic experiences, psychotic experiences, confounders, and/or schizophrenia PRS (Supplementary Figure 1).

Further information on the ALSPAC cohort is available on the ALSPAC website (http://www.bristol.ac.uk/alspac) and elsewhere[27,28]. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Some data were collected using REDCap[29,30].

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

Measures

Autistic traits

In accordance with previous studies in the ALSPAC cohort[31], we used a measure of broad autistic traits, estimated as the mean score of seven factors identified in a previous factor analysis of 93 available measures related to autism. Additionally, we used four measures of autistic traits, which were independent predictors of an autism diagnosis. These included social communication difficulties

5

121 assessed with the Social Communication Disorder Checklist (SCDC) at age 7 years[32], difficulties in

122 pragmatic language use assessed with the coherence subscale of the Children's Communication

123 Checklist at age 9 years[33], sociability assessed with a subscale of the Emotionality, Activity and

124 Sociability Temperament Scale at age 3 years[34], and repetitive behaviour assessed with measures

125 obtained from the Development and Well-Being Assessment at age 5 years[35]. Participants who had

126 scores within the approximately highest 10% of the measure distribution were classified as being

127 'case positive' for the autistic trait[36].

Psychotic experiences

129 Psychotic experiences were assessed at ages 18 and 24 using the semi-structured Psychosis-Like

130 Symptoms interview (PLIKSi), administered by trained psychologists, and scored according to criteria

131 predefined by the World Health Organization[37]. The PLIKSi consists of 12 core questions covering

132 hallucinations, delusions, and thought interference. Participants were asked about experiences that had

133 occurred since age 12 years. Psychotic experiences were considered present if, at ages 18 and/or 24

134 years, one or more of the experiences was rated by the interviewer as suspected or definitely present,

135 and if this was not attributable to falling asleep or waking up, fever, or substance use. We additionally

136 examined psychotic experiences that had been distressing and/or frequent, since these experiences are

137 more clinically-relevant and predictive of psychotic disorder[38]. Moreover, in subsequent sensitivity

138 analyses we excluded reports of tactile hallucinations, which might be difficult to distinguish from the

139 heightened tactile perception often seen in autism[39].

Childhood trauma

141 The measures of childhood trauma and their associations with psychotic experiences have been

142 described in detail elsewhere[16]. In brief, we used a measure of childhood trauma between ages 5 and

143 11 based on responses to 57 questions from questionnaires and interviews about domestic violence

144 (regular acts of physical violence taking place in the home), physical abuse (physical harm to the

145 participant from caregivers or other adults), emotional abuse (emotional cruelty to the participant

146 from caregivers or other adults), emotional neglect (caregivers not taking an interest in the

147 participant's life), sexual abuse (adults or older children forcing the participant into sexual activity,

148 including attempts to do so), and bullying victimization (regular name-calling, blackmail, or assault

149 by peers). Measures of sexual, physical, and emotional abuse, assessed contemporaneously by the

150 participant and their caregivers between participant ages 5 to 11, were supplemented with data from a

151 participant-completed questionnaire at age 22, as all data on sexual abuse, and most data on physical

152 and emotional abuse prior to age 11, were based on parental report. Each type of trauma was coded as

153 present or not, and a single trauma variable was created representing exposure to any type of trauma[16].

154 *Confounders*

155 Confounders were considered on the basis of existing evidence suggesting associations with autistic

156 traits, traumatic events and psychotic experiences[24,27,40]. These included child sex (male/female),

157 maternal parity (≤1 child versus ≥2 children), major financial problems in the family when the child

158 was 8 months old (yes/no), maternal highest educational attainment (32 weeks gestation), maternal

159 age (at delivery), maternal Crown-Crisp anxiety scores[41] (18 weeks gestation), maternal depression

160 measured with the Edinburgh Postnatal Depression Scale[42] (EPDS; 18 weeks gestation scores ≥13),

161 and child IQ scores at age 8 assessed with the Wechsler Intelligence Scale for Children third edition[43]

162 (WISC-III). In mediation analyses, four assumptions are made with respect to confounding. These

163 include no unmeasured confounders for any of the paths and no measured or unmeasured confounder

164 for the association between mediator and outcome which lies on the causal pathway from the

165 exposure. In the current analyses, the above confounders were assumed to potentially confound all

166 paths.

167 We also examined the potential confounding role of schizophrenia PRS. In children with available

168 genotype data in ALSPAC, we calculated schizophrenia PRS using GWAS summary data for

169 schizophrenia[44] as our discovery sample (details available in Supplementary Methods 1). We used

170 scores corresponding to a 0.05 *p*-value threshold, as it has been found to optimally capture

171 schizophrenia liability across different samples[44].

172 **Statistical analyses**

173 Statistical analyses were conducted in STATA/MP version 15. We compared individuals with and

174 without autistic traits on confounder data, traumatic experiences, and psychotic experiences using

175 Pearson χ^2-test, independent-samples t-tests, and logistic regression analyses.

176 Using logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (95% CIs) for

177 the associations between the five measures of autistic traits in childhood and psychotic experiences in

178 young adulthood. We performed crude models and confounder-adjusted analyses, including a separate

179 analysis adjusting for schizophrenia PRS in the sample with available genotype data.

180 Mediation analyses were performed in cases that there was evidence of association between the

181 exposure(s) of the interest and the outcomes. Mediation analyses were performed using the g-formula

182 package in STATA[45]. We used the parametric g-formula using Monte Carlo simulations to estimate

183 the natural direct effect (NDE) of autistic traits on psychotic experiences, and the natural indirect

184 effect (NIE) that was mediated via traumatic experiences between ages 5 to 11. We performed

185 unadjusted as well as adjusted models for confounders and for schizophrenia PRS (Figure 1).

186 Corresponding 95% CIs were estimated using the standard errors from 1000 non-parametric bootstrap

187 resamples. The proportion mediated (PM) was calculated as[46]: $[(OR_{NDE}*(OR_{NIE}-1)) / (OR_{NDE}*OR_{NIE} -$

188 $1)]*100$.

189 **Missing data**

190 We performed multiple imputation by chained equations[47], using the STATA *ice* command.

191 Confounder, mediator and outcome data were imputed for the sample with complete data on each

192 autistic trait exposure. Provided the missing at random (MAR) assumption is met, multiple imputation

193 (MI) can produce unbiased estimates even when the proportion of missing data is large. Specifically,

194 previous work using simulations, found that for data with a MAR data pattern, multiple imputation

195 can provide unbiased estimates even when the proportion of missing data is as high as 90%[48]. We

196 created 100 imputed datasets using information from variables included in our analyses as well as

197 auxiliary variables associated with the variables of interest and attrition, to make the MAR assumption

198 plausible[49]. Based on established guidelines on auxiliary variables selection[50], we entered in the

199 models those variables presenting the lowest missingness in the ALSPAC cohort ranging from 13% to

200   16% (Supplementary Methods 2). We used linear regression models for imputation of normally

201   distributed variables, logistic regression models for binary variables, and the inbuilt *match* command

202   for predictive mean matching to impute non-normal continuously distributed variables. Considering

203   that the MAR assumption is not directly testable, in the context of the present study we conducted a

204   sensitivity analysis in cases that there was evidence of association between an exposure of interest and

205   our primary outcome, psychotic experiences assessed at ages 18 and/or 24. Specifically, we assumed

206   that all participants with missing data on the primary outcome variable, presented the outcome (i.e.,

207   psychotic experiences at ages 18 and/or 24). We imputed covariates following the process described

208   above and we ran crude and adjusted for covariates logistic regression models to test the association

209   between the exposures and the outcome. This allowed us to scrutinise the association estimates across

210   complete case, imputed data, and under the scenario that the MAR assumption was completely

211   violated.

212   In the case of mediation analyses, we used the inbuilt g-formula imputation commands[45], allowing

213   simultaneous imputation of missing data and mediation analyses, entering in the models the same

214   auxiliary variables we used for the association analyses.

215

Results

Sample characteristics

The maximum available sample size before imputation was 3,707 for the analyses examining the associations between autistic traits and psychotic experiences, and 3,577 for the mediation analyses (Supplementary Figure 1). Children scoring highest on all the autistic traits were more likely to be male, present lower total IQ scores (Table 1), and experience trauma between ages 5–11 (only exception sociability; Supplementary Tables 1 & 2).

Approximately 23–25% of the sample had complete data on exposure, outcome and confounders. Participants with complete data were more likely to be female, have a higher socioeconomic background, and present higher total IQ scores, while they were less likely to have experienced childhood trauma and psychotic experiences, compared to those with incomplete data (Supplementary Tables 3 & 4). After imputing data, the maximum sample size for our analyses was 13,105 individuals.

Autistic traits and psychotic experiences

As shown in Table 2, there was evidence of associations between autism factor mean score and psychotic experiences (OR_{CRUDE} = 1.13, 95%CI 1.02–1.26, p = 0.03) as well as distressing and/or frequent psychotic experiences (OR_{CRUDE} = 1.20, 95%CI 1.04–1.38, p = 0.01). The associations remained of comparable magnitude when we adjusted for confounders ($OR_{ADJUSTED}$ = 1.09, 95%CI 0.97–1.23, p = 0.15; $OR_{ADJUSTED}$ = 1.19, 95%CI 1.01–1.39, p = 0.03) or schizophrenia polygenic risk (Supplementary Table 5), or restricted to psychotic experiences without tactile hallucinations (Table 2).

Additionally, we found evidence of associations between social communication difficulties and psychotic experiences (OR_{CRUDE} = 1.43, 95%CI 1.01–2.03, p = 0.04) as well as distressing and/or frequent psychotic experiences (OR_{CRUDE} = 1.60, 95%CI 1.02–2.52, p = 0.04). Effect estimates were of comparable magnitude when we adjusted for confounders ($OR_{ADJUSTED}$ = 1.34, 95%CI 0.94–1.91, p = 0.11; $OR_{ADJUSTED}$ = 1.54, 95%CI 0.97–2.45, p = 0.07) or schizophrenia polygenic risk

242   (Supplementary Table 5), or restricted to psychotic experiences without tactile hallucinations (Table

243   2).

244   The imputed data analysis supported the identified associations (Supplementary Table 6), as estimates

245   were of comparable magnitude to the primary analyses, and with higher precision.

246   There was less evidence of an association between repetitive behaviour, pragmatic language, and

247   sociability with any psychotic experiences measure (Table 2). On this basis, we conducted sensitivity

248   analyses under the scenario that the MAR assumption was completely violated, using social

249   communication difficulties and autism factor mean score, considering that they were the exposures

250   presenting the strongest associations with the outcome. Specifically, in a sample of n=8,106

251   participants with complete data on social communication difficulties, 3,702 had missing data on the

252   outcome and were recoded as having psychotic experiences (Supplementary Tables 7 & 8). Similarly,

253   in a sample of n=13,105 participants with complete data on autism factor mean score, 7,600

254   participants had missing data on psychotic experiences and were recoded as having psychotic

255   experiences (Supplementary Tables 9 & 10). Logistic regression analyses yielded confidence intervals

256   that were overlapping, and in most cases completely bounded, across sensitivity, complete case, and

257   imputed data analyses (Supplementary Tables 11 & 12).

258   **Mediation analysis**

259   The results of the mediation analyses are shown in Table 3. Autism factor mean score, social

260   communication difficulties, and psychotic experiences were associated with traumatic experiences at

261   ages 5 to 11 (Supplementary Tables 1 & 2).

262   There was evidence to suggest that the associations between autism factor mean score and psychotic

263   experiences were mediated by childhood traumatic experiences in crude and adjusted for confounder

264   models (NIE OR$_{CRUDE}$ = 1.06, 95%CI 1.03–1.08, p < 0.001, PM = 45%; NIE OR$_{ADJUSTED}$ = 1.04,

265   95%CI 1.02–1.06, p < 0.001, PM = 41%). Analyses with distressing and/or frequent psychotic

266   experiences yielded comparable natural indirect effect estimates (NIE OR$_{CRUDE}$ = 1.07, 95%CI 1.04–

267   1.1, p < 0.001, PM = 35%; NIE OR$_{ADJUSTED}$ = 1.05, 95%CI 1.02–1.07, p < 0.001, PM = 28%).

268   Additionally, we found evidence consistent with a mediating effect of childhood traumatic

269   experiences in the associations between social communication difficulties and psychotic experiences

270   in crude and adjusted models (NIE OR_{CRUDE} = 1.15, 95%CI 1.08–1.22, p < 0.001, PM = 41%; NIE

271    $OR_{ADJUSTED}$ = 1.11, 95%CI 1.05–1.18, p < 0.001, PM = 38%). Comparable natural indirect effect

272   estimates were identified in analyses assessing distressing and/or frequent psychotic experiences (NIE

273   OR_{CRUDE} = 1.18, 95%CI 1.09–1.27, p < 0.001, PM = 40%; NIE $OR_{ADJUSTED}$ = 1.15, 95%CI 1.06–1.23

274   p < 0.001, PM = 36%).

275   Results of the mediation analyses were similar when we assessed associations with psychotic

276   experiences excluding tactile hallucinations, adjusted for schizophrenia PRS, or imputed missing data

277   (Supplementary Tables 13–15).

278

Discussion

Using population-based birth cohort data, we examined the association between autistic traits in childhood and psychotic experiences in adulthood, and the potential mediating role of traumatic experiences. We found that broad autistic traits, as captured by autism factor mean score, and social communication difficulties were associated with psychotic experiences up to age 24. There was limited evidence to suggest associations between measures of repetitive behaviour, pragmatic language, or sociability and psychotic experiences. The relationship between autism factor mean score, social communication difficulties and psychotic experiences was substantially mediated by traumatic experiences in early childhood, and not confounded by schizophrenia PRS.

Our longitudinal study is the first to show a relationship between childhood autistic traits and psychotic experiences up to age 24 years. It extends two previous ALSPAC studies which found that psychotic experiences at age 12 years were more common in autistic children or children with autistic traits[4,5]. However, these studies also observed associations with measures of repetitive behaviours and pragmatic language[5]. Two other cohort studies observed weaker or no evidence for a relationship between autistic traits and psychotic experiences, with one study reporting only modest correlations between autistic traits at ages 8–16 years and psychotic experiences at age 16 years[7], and the other reporting weak associations between autistic traits at ages 9 or 12 years and psychotic experiences at ages 15 or 18 years[6]. One possibility is that varying operationalizations of autistic traits might account for discrepant results. For instance, children with social communication difficulties might be especially prone to developing persistent psychotic experiences because they encounter more problems in social relationships than individuals exhibiting repetitive behaviours, and consequently, factors such as increased feelings of isolation, distrust, and defeat might make those individuals more vulnerable to developing psychosis[51,52].

Among children scoring positively on the measures of autism mean factor score or social communication difficulties, point estimates for the occurrence of distressing and/or frequent psychotic experiences in early adulthood were particularly high. Notably, three previous studies have also shown that (for as of yet unknown reasons) autistic individuals reported more distress when

13

306 experiencing psychotic symptoms than non-autistic peers[9,53,54]. These distressing and/or frequent

307 psychotic experiences appear to be most strongly related to negative mental health consequences,

308 such as the development of psychotic disorder[38]. Still, thus far there has been little work examining

309 how these psychotic experiences can be best identified and addressed in individuals with autistic

310 traits, and more work is needed in this area.

311 The association between autistic traits and psychotic experience was not strongly influenced by

312 schizophrenia PRS, but substantially mediated by interpersonal trauma in childhood. These findings

313 are consistent with the idea that the association between autism and psychosis is influenced by

314 environmental factors and not the sole result of a shared genetic liability. The experience of trauma in

315 childhood is a well-established risk factor for psychosis[15,55]. However, despite reports of elevated rates

316 of trauma in autistic individuals or individuals with autistic traits[22,56], studies of its mental health

317 consequences are lacking[57]. Our findings indicate that trauma may be an important, potentially

318 modifiable pathway between autistic features and later onset of psychotic experiences, and more work

319 is necessary to examine how (the consequences of) trauma can best be prevented, identified, or treated

320 in autistic individuals. For instance, there is early work showing that eye movement desensitization

321 and reprocessing (EMDR) can be safely and effectively used among individuals with a psychotic

322 disorder[58], and its efficacy for autistic individuals with psychotic symptoms could be assessed.

323 Additionally, elucidating the mechanisms through which traumatic experiences lead to psychosis,

324 building on work in non-autistic populations[52,55,59], can be an important avenue for future research.

325 Of note, with regards to the causal pathways tested in this study, there was a partial overlap in the

326 ages at which autistic traits and childhood trauma were measured. This exposure-mediator overlap

327 might preclude strong causal inferences, as autistic-like traits might have been exacerbated by

328 exposure to traumatic events. Indeed, detrimental effects of childhood adversity on social cognitive

329 functioning have been reported[60]. However, it is worth noting that in the ALSPAC cohort, social

330 communication difficulties are associated with autism PRS, suggesting developmental origins[24]. In

331 addition, social communication difficulties in the ALSPAC cohort seem to be relatively stable over

332 time for male as well as female participants[3]. These studies support the idea that particularly social

333 communication difficulties measured in the context of the present study do not necessarily stem from

334 trauma exposure alone but reflect autism-related difficulties.

335 Strengths of our study include its longitudinal design and long-term follow-up in a general

336 population-based cohort. The study also has limitations. First, our complete-records analysis might

337 have been influenced by a lower statistical power and/or selection bias due to attrition. However,

338 analyses using imputed data yielded comparable results to the complete-records analyses. Second,

339 multiple imputation is a widely used approach to address missing data, but it presents important

340 pitfalls that should be acknowledged. The most important is that the method requires the MAR

341 assumption to hold. Since the MAR assumption is not directly testable the possibility of biased

342 estimates cannot be excluded. However, we followed established guidelines to include auxiliary

343 variables and make the MAR assumption more plausible, while in addition, we performed sensitivity

344 analyses to test the association estimates in the extreme scenario that the MAR assumption was

345 completely violated. Third, a substantial number of models were run to examine the association

346 between autistic traits and psychotic experiences, which could increase the likelihood of false-positive

347 findings. However, it is important to note the consistency of the association estimates across analyses

348 and that the vast majority of the tests conducted were conducted in order to test the robustness of our

349 findings and overcome limitations of previous studies investigating psychotic outcomes. Fourth,

350 traumatic experiences were measured with a combination of parental- and self-reports. Parents are

351 likely to underreport the occurrence of traumatic events, whereas retrospective self-reports might

352 overestimate (due to recall bias) or underestimate (due to non-differential measurement error) trauma

353 prevalence. Finally, as in every observational analysis, the possibility of residual confounding cannot

354 be excluded.

355 Future studies are expected to further elucidate present findings. Specifically, the increasing

356 availability of large multi-ethnic ancestry samples with extensive information on childhood

357 neurodevelopment, life events and adulthood psychopathology can provide valuable insights into the

358 complex relationship between autism and psychosis. A particularly promising avenue for research

359 would be the investigation of whether specific trauma types mediate the pathways linking autistic

360   traits to a range of adverse mental health outcomes, including negative and positive psychotic

361   symptoms, depressive symptoms, and anxiety.

362   In conclusion, broad autistic traits and especially social communication difficulties in childhood

363   appear to be associated with psychotic experiences until young adulthood. This association is unlikely

364   explained by genetic risk as captured by current schizophrenia PRS. Childhood trauma constitutes a

365   potentially modifiable environmental risk factor for psychosis in autistic individuals that warrants

366   further attention in research and clinical practice.

References

1. Lai M-C, Kassee C, Besney R, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *Lancet Psychiatry.* 2019;6(10):819-829.

2. Zhou H-Y, Yang H-X, Gong J-B, et al. Revisiting the overlap between autistic and schizotypal traits in the non-clinical population using meta-analysis and network analysis. *Schizophr Res.* 2019;212:6-14.

3. Martinez AP, Wickham S, Rowse G, Milne E, Bentall RP. Robust association between autistic traits and psychotic-like experiences in the adult general population: epidemiological study from the 2007 Adult Psychiatric Morbidity Survey and replication with the 2014 APMS. *Psychol Med.* 2020;online ahead of print:1-7.

4. Bevan-Jones R, Thapar A, Lewis G, Zammit S. The association between early autistic traits and psychotic experiences in adolescence. *Schizophr Res.* 2012;135(1-3):164-169.

5. Sullivan S, Rai D, Golding J, Zammit S, Steer C. The association between autism spectrum disorder and psychotic experiences in the Avon longitudinal study of parents and children (ALSPAC) birth cohort. *J Am Acad Child Adolesc Psychiatry.* 2013;52(8):806-814.

6. Cederlöf M, Pettersson E, Sariaslan A, et al. The association between childhood autistic traits and adolescent psychotic experiences is explained by general neuropsychiatric problems. *Am J Med Genet.* 2016;171(2):153-159.

7. Taylor MJ, Robinson EB, Happé F, Bolton P, Freeman D, Ronald A. A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. *Mol Autism.* 2015;6(1):44.

8. Demirkaya SK, Tutkunkardaş MD, Mukaddes NM. Assessment of suicidality in children and adolescents with diagnosis of high functioning autism spectrum disorder in a Turkish clinical sample. *Neuropsychiatr Dis Treat.* 2016;12:2921.

9.   Van der Linden K, Simons C, van Amelsvoort T, Marcelis M. Lifetime and momentary psychotic experiences in adult males and females with an autism spectrum disorder. *Front Psychiatry.* 2020;11:766.

10. Foss-Feig JH, Velthorst E, Smith L, et al. Clinical profiles and conversion rates among young individuals with autism spectrum disorder who present to clinical high risk for psychosis services. *J Am Acad Child Adolesc Psychiatry.* 2019;58(6):582-588.

11. Chisholm K, Lin A, Abu-Akel A, Wood SJ. The association between autism and schizophrenia spectrum disorders: A review of eight alternate models of co-occurrence. *Neurosci Biobehav Rev.* 2015;55:173-183.

12. Muhle RA, Reed HE, Stratigos KA, Veenstra-VanderWeele J. The emerging clinical neuroscience of autism spectrum disorder: a review. *JAMA Psychiatry.* 2018;75(5):514-523.

13. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell.* 2019;179(7):1469-1482. e1411.

14. Legge SE, Jones HJ, Kendall KM, et al. Association of genetic liability to psychotic experiences with neuropsychotic disorders and traits. *JAMA Psychiatry.* 2019;76(12):1256-1265.

15. Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophr Bull.* 2012;38(4):661-671.

16. Croft J, Heron J, Teufel C, et al. Association of trauma type, age of exposure, and frequency in childhood and adolescence with psychotic experiences in early adulthood. *JAMA Psychiatry.* 2019;76(1):79-86.

17. Humphrey N, Symes W. Responses to bullying and use of social support among pupils with autism spectrum disorders (ASDs) in mainstream schools: A qualitative study. *J Res Spec Educ.* 2010;10(2):82-90.

18. Sevlever M, Roth ME, Gillis JM. Sexual abuse and offending in autism spectrum disorders. *Sex Disabil.* 2013;31(2):189-200.

19. Kerns CM, Newschaffer CJ, Berkowitz SJ. Traumatic childhood events and autism spectrum disorder. *J Autism Dev Disord.* 2015;45(11):3475-3486.

20. Novin S, Broekhof E, Rieffe C. Bidirectional relationships between bullying, victimization and emotion experience in boys with and without autism. *Autism.* 2019;23(3):796-800.

21. Schroeder JH, Cappadocia MC, Bebko JM, Pepler DJ, Weiss JA. Shedding light on a pervasive problem: A review of research on bullying experiences among children with autism spectrum disorders. *J Autism Dev Disord.* 2014;44(7):1520-1534.

22. McDonnell CG, Boan AD, Bradley CC, Seay KD, Charles JM, Carpenter LA. Child maltreatment in autism spectrum disorder and intellectual disability: results from a population-based sample. *J Child Psychol Psychiatry.* 2019;60(5):576-584.

23. Gong J-b, Wang Y, Lui SS, Cheung EF, Chan RC. Childhood trauma is not a confounder of the overlap between autistic and schizotypal traits: A study in a non-clinical adult sample. *Psychiatry Res.* 2017;257:111-117.

24. Rai D, Culpin I, Heuvelman H, et al. Association of autistic traits with depression from childhood to age 18 years. *JAMA Psychiatry.* 2018;75(8):835-843.

25. Warrier V, Baron-Cohen S. Childhood trauma, life-time self-harm, and suicidal behaviour and ideation are associated with polygenic scores for autism. *Mol Psychiatry.* 2019:1-15.

26. Stanyon D, Yamasaki S, Ando S, et al. The role of bullying victimization in the pathway between autistic traits and psychotic experiences in adolescence: data from the Tokyo Teen Cohort study. *Schizophr Res.* 2022;239:111-115.

27. Fraser A, Macdonald-Wallis C, Tilling K, et al. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol.* 2013;42(1):97-110.

28. Boyd A, Golding J, Macleod 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(1):111-127.

29. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform.* 2019;95:103208.

30.   Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.

31.   Steer CD, Golding J, Bolton PF. Traits contributing to the autistic spectrum. *PLoS One.* 2010;5(9):e12633.

32.   Skuse DH, Mandy WP, Scourfield J. Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. *Br J Psychiatry.* 2005;187(6):568-572.

33.   Bishop DV. Development of the Children's Communication Checklist (CCC): A method for assessing qualitative aspects of communicative impairment in children. *J Child Psychol Psychiatry.* 1998;39(6):879-891.

34.   Buss AH, Plomin R. *Temperament (PLE: Emotion): Early developing personality traits.* Psychology Press; 2014.

35.   Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry.* 2000;41(5):645-655.

36.   Guyatt AL, Heron J, Knight BLC, Golding J, Rai D. Digit ratio and autism spectrum disorders in the Avon Longitudinal Study of Parents and Children: a birth cohort study. *BMJ Open.* 2015;5(8):e007433.

37.   World Health Organization (WHO) Division of Mental Health. *Schedules for Clinical Assessment in Neuropsychiatry.* Washington, DC: American Psychiatric Press; 1994.

38.   Sullivan SA, Kounali D, Cannon M, et al. A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. *Am J Psychiatry.* 2020;177(4):308-317.

39.   Robertson CE, Baron-Cohen S. Sensory perception in autism. *Nat Rev Neurosci.* 2017;18(11):671.

40.   Maclean MJ, Sims S, Bower C, Leonard H, Stanley FJ, O'Donnell M. Maltreatment risk among children with disabilities. *Pediatrics.* 2017;139(4).

41. Crown S, Crisp A. A short clinical diagnostic self-rating scale for psychoneurotic patients: The Middlesex Hospital Questionnaire (MHQ). *Br J Psychiatry.* 1966;112(490):917-923.

42. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987;150(6):782-786.

43. Wechsler D, Golombok S, Rust J. *Weschler Intelligence Scale for Children (WISC-III UK).* 3 ed: The Psychological Corporation; 1992.

44. Trubetskoy V, Pardiñas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature.* 2022;604(7906):502-508.

45. Daniel RM, De Stavola BL, Cousens SN. gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula. *Stat J.* 2011;11(4):479-517.

46. VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol.* 2010;172(12):1339-1348.

47. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. *J Stat Softw.* 2011;45(4):1-20.

48. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. *J Clin Epidemiol.* 2019;110:63-73.

49. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338.

50. Lee KJ, Tilling KM, Cornish RP, et al. Framework for the treatment and reporting of missing data in observational studies: The Treatment And Reporting of Missing data in Observational Studies framework. *J Clin Epidemiol.* 2021;134:79-88.

51. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet.* 2014;383(9929):1677-1687.

52. Selten J-P, van der Ven E, Rutten BP, Cantor-Graae E. The social defeat hypothesis of schizophrenia: an update. *Schizophr Bull.* 2013;39(6):1180-1186.

53. Milne E, Dickinson A, Smith R. Adults with autism spectrum conditions experience increased levels of anomalous perception. *PLoS One.* 2017;12(5):e0177804.

54. Jutla A, Donohue MR, Veenstra-VanderWeele J, Foss-Feig JH. Reported autism diagnosis strongly predicts psychotic-like experiences in the Adolescent Brain Cognitive Development cohort. *Eur Child Adolesc Psychiatry.* 2021;online ahead of print:1-10.

55. Alameda L, Rodriguez V, Carr E, et al. A systematic review on mediators between adversity and psychosis: potential targets for treatment. *Psychol Med.* 2020;50(12):1966-1976.

56. Roberts AL, Koenen KC, Lyall K, Robinson EB, Weisskopf MG. Association of autistic traits in adulthood with childhood abuse, interpersonal victimization, and posttraumatic stress. *Child Abuse Negl.* 2015;45:135-142.

57. Hoover DW. The effects of psychological trauma on children with autism spectrum disorders: a research review. *Rev J Autism Dev Disord.* 2015;2(3):287-299.

58. De Bont P, De Jongh A, Van den Berg D. Psychosis: an emerging field for EMDR research and therapy. *J EMDR Pract Res.* 2019;13(4):313-324.

59. Bloomfield MA, Chang T, Woodl MJ, et al. Psychological processes mediating the association between developmental trauma and specific psychotic symptoms in adults: a systematic review and meta-analysis. *World Psychiatry.* 2021;20(1):107-123.

60. Rodriguez V, Aas M, Vorontsova N, et al. Exploring the interplay between adversity, neurocognition, social cognition, and functional outcome in people with psychosis: a narrative review. *Front Psychiatry.* 2021;12:237.

61. St Pourcain B, Robinson EB, Anttila V, et al. ASD and schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. *Mol Psychiatry.* 2018;23(2):263-270.

Tables & Figures

Figure 1. Schematic depiction of the mediation analyses, indicating potential indirect effects between exposure (autistic traits) and outcome (psychotic experiences) (solid black lines), potential direct effects (dashed black line), and potential confounding (grey lines). Although exposure and mediators overlap, the rationale of the analyses was based on the neurodevelopmental origins of autistic traits, i.e. that they are present since birth, regardless of assessment age. This is supported by previous studies in the ALSPAC cohort, suggesting associations between autism polygenic risk and the autistic measures used in the present analyses[24,61].

Table 1. Characteristics of individuals with and without autistic traits[1].

Variable	Autism factor mean score[2] (n = 5,800)			Social communication difficulties (n = 5,106)			Repetitive behaviours (n = 5,127)			Pragmatic language (n = 5,086)			Sociability (n = 5,434)		
	Yes	No	p-value[3]	Yes	No	p-value[3]	Yes	No	p-value[3]	Yes	No	p-value[3]	Yes	No	p-value[3]
Total n (%)	457 (7.9)	5,343 (92.1)	N/A	461 (9.0)	4,645 (91.0)	N/A	313 (6.1)	4,814 (93.9)	N/A	450 (8.9)	4,636 (91.2)	N/A	600 (11.0)	4,834 (89.0)	N/A
Male sex, n (%)	330 (72.2)	2,571 (48.1)	<0.001	298 (64.4)	2,257 (48.6)	<0.001	194 (62.0)	2,377 (49.4)	<0.001	284 (63.1)	2,250 (48.5)	<0.001	354 (59.0)	2,379 (49.2)	<0.001
Parity (<=1 child), n (%)	354 (77.5)	4,449 (83.3)	0.002	367 (79.6)	3,888 (83.7)	0.02	259 (82.8)	4,011 (83.3)	0.79	369 (82.0)	3,873 (83.5)	0.40	491 (81.8)	4,024 (83.2)	0.39
Maternal educational attainment (university degree), n (%)	70 (15.3)	904 (16.9)	0.38	71 (15.4)	841 (18.1)	0.15	59 (18.9)	836 (17.4)	0.50	75 (16.7)	825 (17.8)	0.55	91 (15.2)	834 (17.3)	0.20
Mother's age at delivery, mean (SD)	29.2 (4.6)	29.4 (4.4)	0.51	29.2 (4.6)	29.5 (4.4)	0.11	29.4 (4.5)	29.5 (4.4)	0.60	29.5 (4.3)	29.5 (4.4)	0.91	29.2 (4.3)	29.4 (4.4)	0.33
Maternal depression during pregnancy (EPDS >= 12), n (%)	99 (21.7)	716 (13.4)	<0.001	102 (22.1)	590 (12.7)	<0.001	60 (19.2)	628 (13.1)	0.002	90 (20.0)	604 (13.3)	<0.001	88 (14.7)	649 (13.4)	0.40
Total IQ score (WISC-III), mean (SD)	93.6 (18.1)	105.8 (15.9)	<0.001	99.6 (19.1)	106.2 (15.9)	<0.001	101.8 (18.4)	105.7 (16.2)	<0.001	96.1 (17.9)	106.5 (15.8)	<0.001	103.4 (15.9)	105.2 (16.5)	0.01
Maternal anxiety during pregnancy, mean (SD)	5.4 (3.6)	4.5 (3.3)	<0.001	5.4 (3.6)	4.48 (3.3)	<0.001	5.7 (3.4)	4.5 (3.3)	<0.001	5.2 (3.6)	4.5 (3.3)	<0.001	4.6 (3.4)	4.6 (3.3)	0.92
Major financial problems (present), n (%)	81 (17.7)	705 (13.2)	0.01	91 (19.7)	575 (12.4)	<0.001	48 (15.3)	614 (12.8)	0.19	63 (14.0)	591 (12.8)	0.45	79 (13.2)	642 (13.3)	0.94

SD, standard deviation; EPDS, Edinburgh Postnatal Depression Scale; IQ, Intelligence Quotient; WISC-III, Wechsler Intelligence Scale for Children third edition.

[1] Characteristics are shown for observations with complete data on exposure and confounders.

[2] Dichotomised (worst 10th percentile) for the purposes of the sample descriptive statistics.

[3] The p-values for n (%) and mean (SD) are based on Pearson χ2 test and independent-samples t-test, respectively.

Table 2. Associations between autistic traits and psychotic experiences[1].

Exposure	n	Including tactile hallucinations								Excluding tactile hallucinations							
		Psychotic experiences at age 18/24				Psychotic experiences at age 18/24, distressing and/or frequent				Psychotic experiences at age 18/24				Psychotic experiences at age 18/24, distressing and/or frequent			
		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Autism factor mean score	3,707	1.13 (1.02–1.26)	0.03	1.09 (0.97–1.23)	0.15	1.20 (1.04–1.38)	0.01	1.19 (1.01–1.39)	0.03	1.15 (1.03–1.28)	0.01	1.09 (0.96–1.23)	0.17	1.18 (1.02–1.36)	0.03	1.14 (0.97–1.35)	0.11
Social communication difficulties	3,384	1.43 (1.01–2.03)	0.04	1.34 (0.94–1.91)	0.11	1.60 (1.02–2.52)	0.04	1.54 (0.97–2.45)	0.07	1.49 (1.04–2.12)	0.03	1.36 (0.95–1.96)	0.10	1.69 (1.07–2.67)	0.02	1.61 (1.01–2.56)	0.05
Repetitive behaviour	3,397	0.98 (0.63–1.54)	0.94	0.94 (0.60–1.48)	0.78	1.17 (0.65–2.09)	0.61	1.14 (0.64–2.06)	0.66	0.98 (0.61–1.56)	0.74	0.92 (0.58–1.48)	0.74	1.13 (0.62–2.06)	0.70	1.09 (0.59–2.01)	0.78
Sociability	3,536	1.28 (0.94–1.73)	0.12	1.27 (0.94–1.73)	0.12	1.31 (0.87–1.98)	0.20	1.33 (0.88–2.02)	0.18	1.25 (0.92–1.72)	0.16	1.25 (0.91–1.71)	0.18	1.20 (0.78–1.86)	0.40	1.22 (0.79–1.88)	0.38
Pragmatic language	3,409	1.08 (0.75–1.55)	0.68	1.00 (0.69–1.45)	0.99	1.45 (0.92–2.28)	0.11	1.37 (0.85–2.18)	0.19	1.15 (0.80–1.66)	0.45	1.04 (0.71–1.52)	0.82	1.54 (0.98–2.42)	0.06	1.43 (0.89–2.29)	0.14

OR, odds ratio; CI, confidence interval.

[1] Estimates based on observations with complete data on exposure, outcome, and confounders.

[2] Adjusted for child sex (male/female), parity ($\leq$ 1 child versus $\geq$ 2 children), major financial problems in the family when the child was 8 months old (yes/no), maternal highest educational attainment, maternal age (at delivery), maternal Crown-Crisp anxiety scores (18 weeks gestation), maternal depression measured with the Edinburgh Postnatal Depression Scale (EPDS; 18 weeks gestation scores $\geq$ 13), and child IQ scores at age 8 assessed with the Wechsler Intelligence Scale for Children third edition (WISC-III).

Table 3. Results of the mediation analyses with childhood trauma for the associations between autism mean factor score, social communication difficulties and psychotic experiences.

Estimate	Unadjusted		Adjusted[2]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Exposure: Autism mean factor score; Outcome: psychotic experiences until age 24 (n = 3,577)				
Natural direct effect	1.08 (0.97–1.21)	0.18	1.06 (0.94–1.20)	0.36
Natural indirect effect	1.06 (1.03–1.08)	<0.001	1.04 (1.02–1.06)	<0.001
Total effect	1.14 (1.02–1.28)	0.02	1.10 (0.97–1.25)	0.14
Proportion mediated	45%		41%	
Exposure: Autism mean factor score; Outcome: psychotic experiences until age 24 distressing/frequent (n = 3,577)				
Natural direct effect	1.15 (0.98–1.35)	0.10	1.15 (0.96–1.37)	0.12
Natural indirect effect	1.07 (1.04–1.10)	<0.001	1.05 (1.02–1.07)	<0.001
Total effect	1.23 (1.04–1.44)	0.01	1.20 (1.01–1.44)	0.04
Proportion mediated	35%		28%	
Exposure: Social communication difficulties; Outcome: psychotic experiences until age 24 (n = 3,326)				
Natural direct effect	1.27 (0.90–1.80)	0.17	1.22 (0.86–1.73)	0.26
Natural indirect effect	1.15 (1.08–1.22)	<0.001	1.11 (1.05–1.18)	<0.001
Total effect	1.46 (1.03–2.06)	0.03	1.36 (0.96–1.92)	0.08
Proportion mediated	41%		38%	
Exposure: Social communication difficulties; Outcome: psychotic experiences until age 24 distressing/frequent (n = 3,326)				
Natural direct effect	1.38 (0.87–2.18)	0.17	1.37 (0.87–2.15)	0.18
Natural indirect effect	1.18 (1.09–1.27)	<0.001	1.15 (1.06–1.23)	<0.001
Total effect	1.62 (1.03–2.55)	0.04	1.57 (1.00–2.45)	0.05
Proportion mediated	40%		36%	

OR, odds ratio; CI, confidence interval.

[1] Estimates based on observations with complete data on exposure, mediator, outcome, and confounders.

[2] Adjusted for the following confounders: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.