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Reported autism diagnosis is associated with psychotic-like symptoms in the Adolescent Brain Cognitive Development cohort

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Abstract

Although the schizophrenia (SCZ) rate is increased in autism spectrum disorder (ASD), it is difficult to identify which ASD youth will develop psychosis. We explored the relationship between ASD and emerging psychotic-like experiences (PLS) in a sample of 9,127 youth aged 9–11 from the Adolescent Brain Cognitive Development (ABCD) cohort. We predicted that parent-reported ASD would be associated with PLS severity, and that ASD youth with PLS (ASD+/PLS+) would differ from ASD youth without PLS (ASD+/PLS−) and youth with PLS but not ASD (ASD−/PLS+) in cognitive function. We fit regression models that included parent-reported ASD, family history of psychosis, lifetime trauma, executive function, processing speed, working memory, age, sex, race, ethnicity, and income-to-needs ratio as predictors of Prodromal Questionnaire – Brief Child (PQ-BC) distress score, a continuous index of PLS severity. We assessed cognitive differences using regression models with ASD/PLS status and relevant covariates as predictors of NIH Toolbox measures. ASD increased raw PQ-BC distress scores by 2.47 points (95% CI 1.33 – 3.61), an effect at least as large as black race (1.27 points, 95% CI 0.75 – 1.78), family history of psychosis (1.05 points, 95% CI 0.56 – 1.54), and Latinx ethnicity (0.99 points, 95% CI 0.53 – 1.45. We did not identify differences in cognition for ASD+/PLS+ youth relative to other groups. Our finding of association between ASD and PLS in youth is consistent with previous literature and adds new information in suggesting that ASD may be a strong risk factor for PLS even compared to established SCZ risk factors.

Introduction

Schizophrenia (SCZ) and autism spectrum disorder (ASD) are separate diagnoses that in some respects show clear divergence. SCZ, typically diagnosed in late adolescence or early adulthood [1], is characterized by psychotic symptoms [2] and tends to be associated with

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progressive functional and cognitive decline [3]. ASD, typically diagnosed in childhood, is characterized by the combined presence of social communication deficits and restricted or repetitive behaviors [4] and tends either to have a stable course or to show clinical improvement with time [5].

Despite these clear differences, SCZ and ASD also have notable similarities. Both have an impact on social skills, with impaired social communication an important cause of long-term disability in SCZ [6] and a core ASD deficit. Both are characterized by deficits in non-social cognition, sharing impairments in executive function[7, 8], processing speed [9, 10] and working memory [11, 12].

Consistent with this, genome-wide association data demonstrate robust shared risk between SCZ and ASD [13]. Recent meta-analytic findings suggest that individuals with ASD are 3 to 4 times more likely to develop SCZ than members of the general population [14, 15].

Whether ASD is also a risk factor for the clinical high risk for psychosis (CHR) syndrome is an important question. Although the CHR syndrome progresses to frank SCZ in just one-fourth of cases within 36 months of its identification [16], even CHR youth who do not progress continue to have pronounced social and cognitive impairment [17] and may benefit from specialized attention.

Recent findings suggest that ASD youth with CHR show a symptom pattern and rate of conversion to psychosis similar to the general CHR population, yet may be under-referred to CHR clinical settings [18]. This may in part stem from the dearth of research exploring the nature and extent of the relationship between ASD and early psychotic-like experiences.

In particular, the effect of ASD relative to other putative risk factors for SCZ or psychotic-like experiences, such as family history of psychosis [19, 20], childhood trauma [21], or race [22, 23], is unknown. It is also unknown whether ASD children with psychotic-like experiences show a pattern of impairment in executive function, working memory and processing speed dissociable from the patterns seen in children with ASD alone or psychotic-like experiences alone.

We sought to address these gaps in knowledge by investigating ASD and psychotic-like experiences in a large national sample of 9- to 11-year-olds. We hypothesized that (1) an ASD diagnosis would be associated with severity of psychotic-like experiences, and (2) executive function, working memory, and processing speed impairment would differ among ASD children with psychotic-like experiences, ASD children without psychotic-like experiences, and children with psychotic-like experiences but not ASD.

Method

Study sample

Our study drew from the Adolescent Brain Cognitive Development (ABCD; RRID:SCR_015769) study cohort. The ABCD study's design and recruitment strategy have been described elsewhere [24, 25], but in brief, the study recruited 11,875 children from 21 sites across the United States, with a goal of obtaining a representative cross-section of U.S.

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youth aged 9 to 11 to follow longitudinally over ten years into early adulthood. The ABCD study was approved by the institutional review board at each participating site.

We used baseline cross-sectional data collected from each ABCD participant between September 2016 and October 2018. We excluded 2,748 participants missing data for any of the following variables: ASD diagnosis, psychotic-like experience rating, family history of psychosis, age-adjusted standard scores for NIH toolbox measures of cognition, trauma history, age, sex, race, ethnicity, household income, number of people in the household, history of speech delay, maternal age at birth, and paternal age at birth (see Table S1 for missingness by variable). This yielded a sample of 9,127 youth.

Assessment measures

ASD: As the ABCD study did not collect ASD-specific measures at baseline, we ascertained ASD based on whether a participant's parent(s) reported an existing ASD diagnosis during the screening interview. Note that we interrogated the validity of this ascertainment method by estimating a logistic regression model, ancillary to our main analysis, in which we examined whether variables known to be associated with an ASD diagnosis (including speech delay, male sex, and older parental age) were associated in our sample with parent report of ASD diagnosis during screening.

Psychotic-like experiences: We identified psychotic-like experiences using the Prodromal Questionnaire - Brief Child version (PQ-BC). The PQ-BC is an adapted version of the Prodromal Questionnaire - Brief (PQ-B), a 21-item screening questionnaire for individual psychotic-like experiences in adolescents and adults. Each PQ-B item asks about the presence of a psychotic-like experience and then has the respondent rate, on a five-point scale, how much distress it causes if present [26]. [27] has previously described the PQ-BC's development and psychometric properties. Briefly, however, the adapted measure retains the PQ-B's 21 items, but uses simplified, child-appropriate wording. To ensure that children understand the questions posed, these items are administered as an interview rather than a questionnaire, with the distress scale paired with a visual response analog.

The PQ-BC, like the PQ-B, is scored by deriving two indices. For the "total" score, ranging from 0 to 21, one point is assigned per symptom endorsed. For the "distress" score, ranging from 0 to 105, 1 to 5 points are assigned per symptom endorsed, based on a distress rating (where 1 indicates "no distress" and 5 "severe distress") [26, 27]. As psychotic-like experiences seem to be most predictive of CHR when associated with distress, [28] we focused on the PQ-BC distress score.

We analyzed the distress score in two ways: 1) by using the score itself as a continuous indicator of psychotic-like experience severity, and 2) by using an empirical cutoff of a score ≥ 2 standard deviations above the mean to represent the binary presence of "likely significant" psychotic-like experiences. We chose this cutoff because no studies have yet recommended a meaningful PQ-BC cutoff, and the applicability of previous recommendations for the PQ-B [26, 28, 29] to a younger population is not clear.

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Family history of psychosis: We defined family history of psychosis as a response of "yes" to the question "Has any blood relative of your child ever had a period lasting six months when they saw visions or heard voices or thought people were spying on them or plotting against them?"

Cognitive measures: The ABCD cognitive assessment [30] included three NIH Toolbox Cognition Battery instruments with direct relevance to our study hypotheses: Dimensional Change Card Sort (RRID:SCR_003616), [31, 32], Pattern Comparison Processing Speed (RRID:SCR_003623) [33], and List Sorting Working Memory (RRID:SCR_003626) [34]. These are continuous measures of executive function, processing speed, and working memory respectively. A fourth NIH Toolbox Cognition Battery instrument, the Picture Vocabulary Test (RRID:SCR_000166), is a continuous measure of receptive vocabulary, and is the primary language measure included in the NIH Toolbox [35]. We incorporated the Picture Vocabulary Test into our baseline comparisons between ASD and non-ASD participants to verify that the groups had comparable language levels. All NIH Toolbox measures mentioned above have shown adequate convergent and discriminant validity in children, as well as good reliability[32–34].

Trauma history: Each participant's parent(s) received the traumatic events section of the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL) structured interview [36]. This entails a series of yes/no questions about whether the participant has ever had certain lifetime traumatic experiences. From these data we derived a continuous "trauma index" for each participant representing the number of traumatic experiences endorsed.

Demographic variables: Of the demographic variables in the ABCD dataset [37], we included age at evaluation and sex assigned at birth as reported. Small numbers of participants for racial groups other than white or black required us to create an "other" racial group for statistical analysis. This group included Chinese, Filipinx, Indian, Japanese, Korean, Vietnamese, Native American, Native Alaskan, Native Hawaiian, Guamanian, Samoan, "other Asian," and "other Pacific Islander" participants, as well as "other race," "unknown race," and multiracial participants. We included ethnicity as a binary variable (Latinx vs. non-Latinx) independent from race.

We derived an income-to-needs ratio for each participant by dividing their reported household income by the poverty threshold for their reported family size in the year they were interviewed[38].

Other variables: We used a reported history of speech delay (defined as a parent response of "later" to the question "Would you say his/her speech development was earlier, average, or later than most other children?"), maternal age at birth, and paternal age at birth in our ancillary analysis of ASD predictors.

Statistical approach

We compared participants with and without ASD across the variables described above. For continuous variables, we used Welch's two-sided *t*-test, and for categorical variables we

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used Pearson's χ^2. For each group of tests, we used the Benjamini-Hochberg procedure for false discovery rate (FDR) correction.

To ascertain whether ASD diagnosis was associated with psychotic-like experiences (hypothesis 1), we estimated two regression models. The first was a linear regression against continuous PQ-BC distress score. The second was a binary logistic regression against a PQ-BC distress cutoff ≥ 2 standard deviations above the mean. Both models had a multilevel ("mixed-effect") structure, with family unit and ABCD recruitment site as nested random effects [39], and were fit by restricted maximum likelihood.

Both models included the following inputs as fixed effects, selected in advance based on their availability in the ABCD dataset and their relevance as factors influencing schizophrenia or psychotic-like experiences: ASD diagnosis, family history of psychosis, trauma index, executive function, processing speed, working memory, age, sex, race, ethnicity, and income-to-needs ratio. We entered variables using a simultaneous forced-entry strategy [40], verified model stability using variance inflation factors to rule out collinearity. We evaluated model significance via Satterthwaite's approximation, and assessed model fit using Nakagawa's R^2 [41].

For both models we represented categorical inputs using dummy coding, with ASD diagnosis, family history of psychosis, sex, and ethnicity coded based on presence/absence, and race coded using the most common race (white) as the reference level. We transformed continuous inputs (i.e., trauma index, age, income-to-needs ratio, and measures of executive function, processing speed, or working memory) by dividing by two standard deviations, while leaving binary inputs untransformed. This scaling method has been recommended [42, 43] for situations where models include a mixture of continuous and binary inputs, because it allows regression coefficients to be directly compared when assessing relative effect sizes. This is because the difference between two standard-deviation changes for a continuous variable represents the change from a very low (~2nd percentile) to a very high (~98th percentile) value. Such a change is comparable to the difference between the two conditions (0 or 1) of a binary variable [42].

After obtaining results from the linear model, we conducted sensitivity analyses to test their robustness to five key analytic variations. First, we removed all observations containing outliers, which we identified within continuous variables using Tukey's interquartile range method, a conservative approach that defines an outlier as any value $< Q_1 - 1.5 \times IQR$ or $> Q_3 + 1.5 \times IQR$, where Q_1 is the lower quartile, IQR is the interquartile range, and Q_3 is the upper quartile [44]. Second, we restricted our analysis to households with only one child participating in ABCD. Third, we re-coded trauma index score as a binary variable. Fourth, we re-expressed our dependent variable logarithmically using the $\ln(x + 1)$ transformation. Finally, we used PQ-BC total score rather than distress score as our dependent variable.

As an additional exploratory analysis related to hypothesis 1, we looked for group differences in mean item-level PQ-BC distress scores between participants with and without ASD. We conducted multiple univariate analysis of variance (ANOVA) tests, again accounting for multiple testing via the Benjamini-Hochberg method.

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To compare executive function, working memory, and processing speed among ASD children with psychotic-like experiences, ASD children without psychotic-like experiences, and children with psychotic-like experiences but not ASD (hypothesis 2), we derived three groups (hereafter referred to as ASD+/PLS+, ASD+/PLS−, and ASD−/PLS+), again using the PQ-BC distress score cutoff of ≥ 2 standard deviations above the mean to represent the presence of likely significant psychotic-like experiences. We tested for differences in demographics and clinical characteristics across the three groups using Fisher's exact test (for categorical variables) and one-way ANOVA (for continuous variables), and carried out post-hoc pairwise tests using Benjamini-Hochberg corrected Fisher's test and Tukey's range test respectively. After confirming homogeneity of variance across groups using Levene's test, we estimated a linear regression model for each measure, with group membership (coded with ASD+/PLS− as the reference group) and relevant demographic factors as predictors.

Last, to investigate the validity of our ASD ascertainment, we estimated a forced-entry logistic regression model with parent-reported ASD as the outcome. Sex, history of speech delay, maternal age, paternal age, race, ethnicity, age, and income-to-needs ratio were inputs. Given the limited number of ASD cases in our sample, we did not use a multilevel model here. Instead, we used generalized estimating equations to adjust for family unit [45], and did not adjust for ABCD recruitment site.

All analyses used an *a priori* significance threshold of $\alpha = 0.05$.

Software and data

We conducted analyses in R 3.5.1 [46], and have shared scripts to reproduce our results at https://github.com/amandeepjutla/2019-abcd-asd.

The ABCD dataset is available to interested researchers through the NIMH Data Archive (https://nda.nih.gov/). We used ABCD data release 2.0.1, which can be found at http://dx.doi.org/10.15154/1504041.

We obtained annual poverty threshold data for 2016, 2017, and 2018 from the US Census Bureau (https://www.census.gov/).

Results

Sample characteristics

As shown in Table 1, the mean age of our sample's 9,127 participants was 9.91 years. 52.33% of participants were male. Mean income-to-needs ratio was 4.51. Mean number of reported traumatic experiences (i.e., trauma index score) was 0.52. 10.48% of participants had a parent-reported family history of psychosis. Regarding race, 67.74% of participants were white, 12.98% black, and 19.27% "other." 18.70% of participants were of Latinx ethnicity.

Mean PQ-BC total and distress scores were 2.56 and 3.50 respectively. 4.65% of participants had a PQ-BC distress score ≥ the 2 standard deviations above the mean threshold (which

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meant a score above 18). 1.65% of participants (n = 151) had a parent-reported ASD diagnosis.

Participants with ASD differed from those without it in several ways. They had higher PQ-BC total scores, $t(153.00) = -3.95$, $p = 1.30 \times 10^{-3}$ and higher distress scores, $t(152.82) = -3.19$, $p = 7.89 \times 10^{-3}$ (Figure S1).

Their executive function was relatively impaired, $t(154.14) = 2.27$, $p = 0.04$, as were processing speed, $t(154.66) = 2.44$, $p = 0.04$, and working memory, $t(154.04) = 3.12$, $p = 0.01$ (Figure S2). They had older fathers, $t(154.82) = -2.29$, $p = 0.04$ and were more likely to be male, $\chi^2 = 72.86$, $p = 4.87 \times 10^{-17}$) or to have a history of speech delay, $\chi^2 = 200.90$, $p = 9.29 \times 10^{-45}$.

Hypothesis 1: ASD diagnosis as a predictor of psychotic-like experiences

Linear model: ASD as predictor of continuous PQ-BC distress score—In the linear model (Table 2), ASD had a strong positive effect on PQ-BC distress score, with ASD youth having scores 2.47 points higher on average than non-ASD youth ($p = 2.24 \times 10^{-5}$).

This absolute effect size was at least as strong as those of several other predictors in the model, including the positive predictor black race, which increased scores (relative to white race) by an average of 1.27 points ($p = 1.36 \times 10^{-6}$), the positive predictor family history of psychosis, which increased PQ-BC distress scores by 1.05 points on average ($p = 2.61 \times 10^{-5}$), the positive predictor Latinx ethnicity, which increased scores by an average of 0.99 points, ($p = 2.61 \times 10^{-5}$), the negative predictor income-to-needs ratio, for which an increase of two standard deviations decreased PQ-BC distress scores by an average of 1.23 points ($p = 2.47 \times 10^{-12}$), and the negative predictor working memory, for which a two-standard deviation increase decreased PQ-BC distress scores by an average of 1.12 points ($p = 1.48 \times 10^{-12}$).

The effect of ASD was also larger than the positive predictor trauma, for which an increase in trauma index score by two standard deviations raised PQ-BC scores by 0.54 points ($p = 2.99 \times 10^{-4}$) and the negative predictor age, for which an increse in two standard deviations reduced PQ-BC scores by an average of 0.75 points ($p = 5.69 \times 10^{-7}$).

Sex, “other” race, executive functioning, and processing speed were not significant predictors in this model.

Model fit was acceptable, with R^2 of 0.31. VIFs for all model parameters were between 1.01 and 1.24, suggesting minimal collinearity.

Logistic model: ASD as predictor of PQ-BC score above a threshold—The logistic model, in which we regressed against PQ-BC distress score ≥ 2 standard deviations above the mean (Table 3) illustrates ASD’s effect size in concrete terms. ASD predicted a PQ-BC score above this threshold (odds ratio (OR) 3.18, 95% CI 1.78 – 5.69, $p = 9.45 \times 10^{-5}$) with an effect at least as strong as those of Latinx ethnicity (OR 1.69, 95% CI 1.26 – 2.27, $p = 4.39 \times 10^{-4}$), family history of psychosis (OR 1.68, 95% CI 1.25 – 2.25, $p = 5.54 \times 10^{-4}$), black relative to white race (OR 1.57, 95% CI 1.15 – 2.15, $p = 4.68 \times$

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10^{-3}), income-to-needs ratio (OR 0.49, 95% CI 0.38 – 0.64, $p = 1.38 \times 10^{-7}$), and working memory (OR 0.51, 95% CI 0.41 – 0.64, $p = 3.28 \times 10^{-8}$). The effect of ASD was also stronger than that of age (OR 0.76, 95% CI 0.61 – 0.94, $p = 0.01$). Sex, "other" race, trauma index score, executive functioning, and processing speed were not significant predictors in this model.

Model fit was again acceptable, with R^2 of 0.33, and parameter VIFs between 1.01 and 1.28 again suggesting minimal collinearity.

Exploratory analysis: group differences in mean item-level PQ-BC distress scores—The results of univariate ANOVAs comparing mean item-level PQ-BC distress scores between participants with and without ASD are provided in Table S2. After Benjamini-Hochberg correction, individuals with ASD scored higher than those without on eleven of the PQ-BC's 21 items.

Hypothesis 2: Differences in neurocognitive performance among sub-groups

ASD+/PLS+ (n = 18), ASD+/PLS− (n = 133) and ASD−/PLS+ (n = 406) groups differed in terms of age, sex, race, ethnicity, income-to-needs, maternal age, paternal age, and history of speech delay, with most differences driven by the contrast between ASD+/PLS− and ASD−/PLS+ (Table S3). Linear regression models adjusting for these factors (Table S4) showed no significant effect of group membership in predicting performance along any of the three NIH Toolbox cognitive measures we had selected.

Robustness of findings

ASD ascertainment—As our ascertainment of ASD was based on parent report, and not on gold-standard diagnosis by a clinician, our analysis assumed that parent-reported ASD was a reasonably accurate proxy for "confirmed" ASD.

To examine this assumption, we estimated a logistic regression model with parent-reported ASD as the outcome and a series of predictors chosen based on their having a previously-described association with ASD and their availability in the ABCD dataset: male sex, history of speech delay, paternal age, and maternal age[4]. We also included race, ethnicity, age, and income-to-needs as covariates. Our results, shown in Table S5, indicate that the predictors of parent-reported ASD in the ABCD cohort are consistent with known predictors of ASD in the general population, with history of speech delay (OR 6.09, 95% CI 4.34 – 8.53, $p < 2 \times 10^{-16}$), male sex (OR 4.48, 95% CI 2.77 – 7.25, $p = 1.07 \times 10^{-9}$) and paternal age (OR 1.64, 95% CI 1.02 – 2.64, $p = 0.04$) reaching statistical significance. We consider these results an indication that our use of parent-reported ASD in this study is reasonable.

Sensitivity analyses—Out of our n = 9,127 sample, we identified 245 observations containing outlier values for trauma score, 3 for income-to-needs, 393 for NIH Toolbox card sort, 78 for NIH Toolbox list comprehension, and 157 for NIH Toolbox pattern recognition. After removing all observations containing any outliers, our total sample size decreased to 8,291. In this smaller, more homogenous sample, ASD continued to be a robust predictor,

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and was again at least as strong as black (relative to white) race, Latinx ethnicity, or family history of psychosis.

The effect of ASD continued to be at least as strong as these predictors when our analysis was restricted to households with only one child participating in ASD, when we re-coded trauma history from a scalar index to a binary presence/absence variable, when we logarithmically transformed PQ-BC distress score, and when we used PQ-BC total score rather than distress score as our dependent variable.

Discussion

Our finding that ASD diagnosis is associated with predicts psychotic-like experiences in youth is consistent with literature suggesting that rates of SCZ and psychosis are greater in adults with ASD than in the general population [14, 15]. It also adds new information in suggesting that the magnitude of ASD as a risk factor for psychotic-like experiences is significant even when compared to other established SCZ risk factors, such as family history and lower income-to-needs ratio.

Although it is possible that ASD is acting as a proxy for another SCZ risk factor we have not considered, we consider this unlikely, as it is unclear what this factor would be. In contrast, black race and Latinx ethnicity, which in our results also appeared to predict psychotic-like experiences, could have been proxies for other known SCZ/psychosis risk factors not included in our models, such as urbanicity, an ethnic density effect, or first- or second-generation immigration status [47].

Our results therefore may have implications for both clinicians working with CHR and early psychosis populations and clinicians working with ASD youth. Clinicians working with the CHR population might consider finding ways to connect with those working with the ASD population to ensure that a referral pipeline is in place. Clinicians who work with the ASD population, in turn, may benefit from incorporating psychosis screens into their assessments, and referring to CHR assessment clinics when indicated.

Findings also are of import for researchers interested in the nosology of ASD and psychotic disorders. Our exploratory finding that ASD youth had higher mean distress scores on 11 of the PQ-BC's 21 items requires independent replication, but has interesting implications.

However, although some of these items may indicate individual psychotic-like pheomena of particular importance in the ASD population, it is important to note that the PQ-BC instrument was not designed with the ASD population in mind. Several PQ-BC items ask about how sensory experiences, communication difficulties, or how the respondent perceives the beliefs of others, and may therefore index the sensory hypersensitivity, special or unusual interests, and communication difficulties that are common in ASD [48] rather than emerging psychosis. This highlights the difficulty of identifying psychotic experiences in ASD. It also indicates the need for adapted assessment instruments that capture the unique phenomenology of psychosis in this population, and lead to better understanding of how ASD with and without psychotic-like experiences may differ.

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In addition to focusing on the symptoms most relevant to ASD patients, a psychosis instrument adapted for this population could incorporate other dimensions likely to be at least as important as symptom presence vs. absence. Level of conviction in psychotic-like symptoms might be one. Another might be the trajectory of such symptoms, including their onset and frequency. The PQ-BC does not necessarily capture this, but this longitudinal information may be of particular importance with the ASD population, in which a deteriorating or worsening symptom trajectory by middle childhood is unusual[5], and could potentially be a sign of emerging psychosis.

We were not able to identify a difference in cognitive profile among individuals with both reported ASD and psychotic-like experiences as compared with individuals who had only one or the other. This may in part due to our sample size, which was relatively small, particularly considering the numerous factors our models took into account, as well as the theory-agnostic nature of our exploratory analysis: we did not have specific predictions about cognition.

Although the ABCD cohort is large, only 151 participants had reported ASD, and of those, 18 also had psychotic-like experiences. Future studies that combine data collected from multiple large cohorts might have the power to detect subtle differences along cognitive dimensions. In the future, studies might also explore aspects of social cognition, language, and sensory functioning to better dissociate these groups.

We acknowledge that our study has some important limitations. Our method of ASD ascertainment – parent report of an ASD diagnosis – is less robust than a gold-standard diagnosis might have been. However, evidence suggests that parent-reported ASD is often accurate. In one study of 118 youth with parent-reported ASD enrolled in the nationwide Interactive Autism Network registry, parents were able to provide records confirming an ASD diagnosis in 116 (98.31%) cases [49]. In a similar study of enrollees in the Autism Spectrum Database – UK study, records substantiated parent-reported ASD in 142 of 156 (91.03%) cases [50]. Our finding that predictors of parent-reported ASD in the ABCD cohort are similar to known predictors of ASD lends further support to the idea that parent report is a meaningful indicator. Notably, however, even though our binary parent-report indicator served as a reasonable proxy for ASD diagnosis, it did not give us continuous data about ASD severity, either overall or at the level of individual traits. Research diagnoses and/or ASD-specific measures providing such information would have been useful, had they been available. Future research implementing such measures may be able to make inferences about subgroups within ASD who are most at risk of psychotic-like experiences.

A relatively high proportion of our sample (10.48%) reported a family history of psychosis. We attribute this to the rather broad way that “family history of psychosis” was defined in our dataset: as hallucinations or delusions in any blood relative. Our finding that ASD diagnosis predicts psychotic-like experiences at least as strongly as a family history of psychosis should therefore be interpreted as preliminary. Ideally, future work examining the question will be able to do so in a population where a family history of psychosis is defined more narrowly, such as by specific diagnosis of a psychotic disorder in a first-degree relative.

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Although ABCD is not an ASD-focused study, it is notable that even in this dataset, collected without an intention to examine ASD as a risk factor for psychotic-like experiences, we nevertheless found a strong relationship. In our view, this speaks to the robustness of this association. It also supports results from registry studies that similarly were not designed with an eye towards recruiting participants with ASD or psychotic symptoms [51, 52].

The ABCD cohort is relatively young, and most work examining convergence between ASD and schizophrenia has been conducted with older groups who have formal diagnoses. This limits the generalizability of our findings. However, our identification of an association between ASD and psychotic-like experiences well before the psychosis prodrome typically appears raises intriguing possibilities for future research.

Although previous studies have explored the association between ASD and psychotic-like experiences in middle childhood or adolescence [53–57], ours is, to our knowledge, the first to examine this association within a large normative community sample of typically-developing young children.

As the ABCD cohort ages, and as longitudinal data are collected, we hope to delineate how ASD relates to trajectories of psychotic-like experiences over time, leading to a more robust understanding of how, when, and why ASD and SCZ converge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

Dr. Veenstra-VanderWeele has consulted or served on an advisory board for Roche Pharmaceuticals, Novartis, and SynapDx; has received research funding from Roche Pharmaceuticals, Novartis, SynapDx, Seaside Therapeutics, and Forest; and has received an editorial stipend from Springer and Wiley. The remaining authors report no biomedical financial interests or potential conflicts of interest.

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Table 1

Characteristics of study participants across ASD and non-ASD groups

Variable	Full sample (n = 9127)	No ASD (n = 8976)	ASD (n = 151)	*p*
Continuous	***M (SD)***	***M (SD)***	***M (SD)***	***t*-test**
Age (in years)	9.91 (0.62)	9.91 (0.62)	10.00 (0.61)	0.14
PQ-BC total score	**2.56 (3.52)**	**2.53 (3.49)**	**4.00 (4.54)**	$\mathbf{1.30 \times 10^{-3}}$ **
PQ-BC distress score	**3.50 (7.31)**	**3.46 (7.26)**	**5.99 (9.72)**	$\mathbf{7.89 \times 10^{-3}}$ **
Income-to-needs ratio	4.51 (2.88)	4.51 (2.88)	4.33 (3.03)	0.53
Trauma index score	0.52 (1.08)	0.52 (1.09)	0.57 (0.78)	0.50
NIH TB Card Sort (executive function)	**97.38 (15.26)**	**97.43 (15.22)**	**94.29 (16.86)**	**0.04**
NIH TB Pattern Comparison (processing speed)	**94.18 (21.97)**	**94.25 (21.95)**	**89.66 (22.93)**	**0.04**
NIH TB List Sorting (working memory)	**101.57 (14.69)**	**101.64 (14.65)**	**97.44 (16.43)**	**0.01**
NIH TB Picture Vocabulary (language)	108.13 (16.79)	108.13 (16.77)	107.87 (18.25)	0.86
Maternal age in years at birth	29.73 (6.05)	29.72 (6.04)	30.44 (6.34)	0.23
Paternal age in years at birth	**31.98 (6.90)**	**31.95 (6.89)**	**33.28 (7.08)**	**0.04**
Categorical	**Count (%)**	**Count (%)**	**Count (%)**	χ^2
Male sex	**4778 (52.33)**	**4647 (51.75)**	**131 (86.75)**	$\mathbf{4.87 \times 10^{-17}}$ ***
White race	6183 (67.74)	6084 (67.76)	102 (67.55)	0.96
Black race	1185 (12.98)	1166 (12.99)	19 (12.58)	0.96
“Other” race	1759 (19.27)	1729 (19.26)	30 (19.87)	0.96
Latinx ethnicity	1707 (18.70)	1686 (18.78)	22 (14.57)	0.44
Family history of psychosis	957 (10.48)	937 (10.44)	20 (13.25)	0.46
History of speech delay	**1535 (16.81)**	**1445 (16.10)**	**90 (59.60)**	$\mathbf{9.29 \times 10^{-45}}$ ***

Note: *M* = mean; *SD* = standard deviation; *p*-values are Benjamini-Hochberg corrected.

*: $p < 0.05$

**: $p < 0.01$

***: $p < 0.001$

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Table 2

Predictors of continuous PQ-BC distress score

Predictor	β	95% CI		*SE*	*t*	*p*
		Lower	Upper			
ASD	**2.47**	**1.33**	**3.61**	**0.58**	**4.24**	**2.24×10^{-5}** ***
Black race	**1.27**	**0.75**	**1.78**	**0.26**	**4.84**	**1.36×10^{-6}** ***
Family history of psychosis	**1.05**	**0.56**	**1.54**	**0.25**	**4.21**	**2.61×10^{-5}** ***
Latinx ethnicity	**0.99**	**0.53**	**1.45**	**0.24**	**4.21**	**2.61×10^{-5}** ***
Trauma index score	**0.54**	**0.25**	**0.84**	**0.15**	**3.62**	**2.99×10^{-4}** ***
"Other" race	0.38	−0.03	0.78	0.21	1.81	0.07
Male sex	0.13	−0.17	0.42	0.15	0.86	0.39
NIH TB Pattern Comparison (processing speed)	−0.24	−0.56	0.08	0.16	−1.45	0.15
NIH TB Card Sort (executive function)	−0.25	−0.57	0.07	0.17	−1.51	0.13
Age	**−0.75**	**−1.05**	**−0.46**	**0.15**	**−5.01**	**5.69×10^{-7}** ***
NIH TB List Sorting (working memory)	**−1.12**	**−1.43**	**−0.81**	**0.16**	**−7.09**	**1.48×10^{-12}** ***
Income-to-needs ratio	**−1.23**	**−1.57**	**−0.89**	**0.18**	**−7.02**	**2.47×10^{-12}** ***
(Intercept)	2.87	2.24	3.50	0.32	8.91	1.35×10^{-9} ***

Note: 95% CI = 95% Wald confidence interval; *p*-values estimated via Satterthwaite's approximation.

*: $p < 0.05$

**: $p < 0.01$

***: $p < 0.001$

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Table 3

Predictors of PQ-BC distress score above 2 SD cutoff

Predictor	β	95% CI		*SE*	*z*	*p*
		Lower	Upper			
ASD	**3.18**	**1.78**	**5.69**	**0.94**	**3.90**	**9.45×10^{-5}** ***
Latinx ethnicity	**1.69**	**1.26**	**2.27**	**0.25**	**3.52**	**4.39×10^{-4}** ***
Family history of psychosis	**1.68**	**1.25**	**2.25**	**0.25**	**3.45**	**5.54×10^{-4}** ***
Black race	**1.57**	**1.15**	**2.15**	**0.25**	**2.83**	**4.68×10^{-3}** **
"Other" race	1.27	0.96	1.66	0.25	1.70	0.09
Trauma index score	1.19	1.00	1.43	0.11	1.92	0.06
NIH TB Card Sort (executive function)	0.96	0.75	1.23	0.12	−0.30	0.77
Male sex	0.96	0.78	1.19	0.10	−0.33	0.74
NIH TB Pattern Comparison (processing speed)	0.88	0.70	1.10	0.10	−1.11	0.27
Age	**0.76**	**0.61**	**0.94**	**0.08**	**−2.51**	**0.01** *
NIH TB List Sorting (working memory)	**0.51**	**0.41**	**0.65**	**0.06**	**−5.53**	**3.28×10^{-8}** ***
Income-to-needs ratio	**0.49**	**0.38**	**0.64**	**0.07**	**−5.27**	**1.38×10^{-7}** ***
(Intercept)	0.02	0.01	0.03	< 0.01	−16.49	4.13×10^{-61} ***

Note: 95% CI = 95% Wald confidence interval; *p*-values estimated via Satterthwaite's approximation.

*: $p < 0.05$

**: $p < 0.01$

***: $p < 0.001$