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Original Article

Impact of puberty timing, status and oestradiol on psychotic experiences in the context of exposomic and genomic vulnerability to schizophrenia in female adolescents: longitudinal ABCD study

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Background

During puberty, sex-specific processes shape distinct mental health outcomes. However, research on puberty and psychosis has been limited, and the findings are conflicting.

Aims

To explore how puberty status and timing and oestradiol levels influence psychotic experiences and whether they interact with genetic and exposomic vulnerabilities to schizophrenia in female adolescents.

Method

We analysed data from female participants in the Adolescent Brain Cognitive Development Study at baseline (n = 5673) and two annual follow-up assessments. Psychotic experiences were assessed using the Prodromal Psychosis Scale and puberty status with the Pubertal Development Scale. Age at menarche and salivary oestradiol concentration were recorded. Exposomic vulnerability to schizophrenia (ES-SCZ) and polygenic risk score for schizophrenia (PRS-SCZ) were calculated. Longitudinal mixed logistic regression models were used to test associations of psychotic experiences with hormone levels and puberty status. Age of menarche was analysed using second follow-up data.

Results

Earlier menarche (odds ratio 0.68, 95% CI: 0.59 to 0.78) and higher oestradiol concentration (odds ratio = 1.08, 95% CI: 1.01 to 1.16) were associated with greater likelihood of psychotic experiences, as were mid-pubertal (odds ratio 1.41, 95% CI: 1.18 to 1.69) and late to post-pubertal (odds ratio 2.23, 95% CI: 1.74 to 2.86) compared with pre-pubertal stage. ES-SCZ and PRS-SCZ were associated with greater likelihood of psychotic experiences. No significant interactions of puberty factors with ES-SCZ or PRS-SCZ were detected.

Conclusions

Physical and hormonal puberty factors have critical roles in development of psychosis. The absence of interaction effects could be attributed to the age range of the cohort. Further research during follow-ups is essential.

Keywords

Puberty and menarche; oestrogen; environment; genetics; psychosis.

Despite extensive research efforts, the patho-aetiology of psychosis spectrum disorders (PSD) remains poorly understood. A significant challenge stems from the broad range of clinical presentations within PSD. Notably, sex differences appear to contribute to this heterogeneity, as evidenced by dissimilarities between men and women in terms of the onset, progression, prognosis and postulated aetiology of PSD.[1,2]

Sex/gender differences in mental health trajectories during puberty

Many of the differences become apparent during sensitive developmental phases such as puberty. During this period, sex-specific (biological) and gender-specific (social and/or cultural) processes occur that have a central role in the emergence of distinct symptom profiles. Boys seem to exhibit greater externalising issues, especially at the ages of 6 to 11 years.[3] On the other hand, pre-pubertal girls and boys exhibit similarities in internalising problems, with disparities becoming apparent during and after puberty. Particularly from the age of 12 years, girls manifest more internalising symptoms such as depression compared with boys.[3,4] These differences may be at least partly be attributed to increased vulnerability in girls during this period.[4] Similarly, PSD tends to surface during adolescence and young adulthood, predominantly in men,[5] and clinical presentation is often more severe in men.[2] Therefore, exploration of the underlying neurobiology during maturation may lead to opportunities for intervention.

The role of puberty, early menarche and oestrogen in the development of psychosis spectrum disorders

Extensive research has established a link between early puberty and elevated externalising and internalising psychopathology in both males and females.[6] By contrast, there has been limited research to explore the relationship with PSD, with some studies indicating that early menarche (age at first period) may be associated with fewer negative symptoms, improved functioning and later onset in female patients with schizophrenia.[7–11] A recent study using UK Biobank data identified 619 phenotypes associated with genetic risk for early menarche. Notably, it identified a positive association with variables related to depression and a negative association with distress stemming from psychotic experiences.[12] Early menarche may mark

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vulnerability to psychopathologies such as depression and anxiety, while potentially offering protection against PSD, particularly in the context of oestrogen and neural maturation.[13,14] The 'oestrogen hypothesis' suggests that oestrogens, especially oestradiol, protect females against PSD. Levels of oestradiol, one of three oestrogens, increase during female maturation.[15] This may modify mechanisms that are potentially linked to PSD, including mitochondrial function, dopamine activity and stress-related systems.[16] Moreover, menstrual phases with higher oestradiol levels are linked to reduced symptoms of PSD,[17] whereas menopause (with decreased oestradiol levels) is linked to increased incidence of PSD in females.[18] Preliminary research suggests that oestradiol treatment may improve symptoms in male and female PSD patients.[16] However, limited results are available on the effects of oestradiol and puberty timing on psychotic experiences in children and adolescents.

The role of genomic and exposomic factors in the development of psychosis spectrum disorders

PSD has a complex aetiology, shaped by the genome and exposome (the environmental exposures an individual encounters over their lifetime).[19] Multiple genes constitute genomic liability, and various environmental factors, including childhood adversity and cannabis use, contribute to exposomic liability.[19,20] We have previously shown in a case–control study that the interplay between genomic and exposomic liabilities significantly amplifies the risk of developing schizophrenia,[19] as well as demonstrating that it increased the risk of experiencing significantly distressing psychotic experiences among child and adolescent participants in the Adolescent Brain Cognitive Development (ABCD) Study.[21] Another ABCD cohort study found that early puberty, combined with heightened environmental risk represented by a latent factor, was linked to increased rule-breaking behaviours in both males and females, as well as greater depressive symptoms in females.[22] These findings demonstrate the importance of considering genomic and exposomic factors to understand psychosis development during puberty.

Study objectives and approach

In the present study, we investigated the impact of puberty on psychosis expression in female adolescents of the ABCD Study. To comprehensively understand puberty factors and triangulate our findings, we examined puberty status, timing and hormone levels, focusing on variables specific to females. Furthermore, as an explorative secondary aim, we investigated whether these processes might vary in the context of exposomic and genomic risk of schizophrenia.

Method

Participants

Data were extracted from the 5.1 release (DOI: 10.15154/z563-zd24) of the ABCD Study, encompassing assessments from 1 September 2016 to 15 January 2022. This ongoing longitudinal study in the USA consists of 11 868 children who were initially 9 to 10 years old at baseline. The recruitment process spanned 21 sites, employing a multi-stage probability sampling method to establish a school sample characterised by demographic diversity.[23] The data collection was approved by the centralised institutional review board (IRB) at the University of California San Diego and local research site institutional review boards, and data access was facilitated by the National Institute of Mental Health National Data Archive. Written informed consent was obtained from participating parents and/or caregivers, along with assent from the youth.

The sample for this analysis was restricted to female participants who had completed the evaluation of psychotic experiences at least once across the three annual assessment points (i.e. baseline, first follow-up and second follow-up assessments). Individuals using hormonal contraception were excluded from analyses involving oestradiol ($n = 24$). In addition, as polygenic risk score performance varies across different populations owing to an imbalance favouring European ancestry,[24] only participants of European descent with high-quality genotyping data were included in the genetic analyses, consistent with prior research.[21,25]

Measurements

Distressing psychotic experiences

The Prodromal Questionnaire–Brief Child Version, which has been previously validated for a school-age population,[26] was used to assess psychotic experiences at baseline and during follow-up assessments. Psychotic experiences, such as unusual thought content and perceptual abnormalities within the past month, were evaluated using a 21-item scale. Participants indicated the level of distress they experienced associated with the psychotic experiences on a five-point Likert scale (1 = Not very bothered; 2 = Slightly bothered; 3 = Moderately bothered; 4 = Very much bothered; 5 = Extremely bothered). In the current study, a binary variable indicating significantly distressing psychotic experiences was created to assess a clinically relevant manifestation of psychotic experiences, in line with previous reports in this data-set.[21] Psychotic experiences were considered to be present if participants endorsed at least one psychotic experience accompanied by significant psychological distress, with a scoring threshold of ≥ 3 of the five points.

Perceived pubertal status and age at menarche

We used caregiver-rated measures for perceived puberty status and age at menarche, as caregiver ratings are considered more accurate than adolescent self-reports. At each assessment, puberty stages and, if applicable, age at menarche were recorded.

To evaluate perceived puberty status, we employed the Pubertal Development Scale,[27] with ratings provided by both the primary caregiver and the adolescent participant. To assess puberty status, five questions were used to inquire about growth spurt, body hair, skin, breast development and menarche. The physical markers were rated on a four-point Likert scale (1 = has not begun yet, 2 = barely begun, 3 = definitely begun, 4 = seems complete). Menarche was assessed first with a yes/no response, followed by a question to determine the age. Following previous research, we used a pubertal category score.[27] The scores for body hair growth and breast development were summed, and menarche was used to categorise as follows: pre-pubertal, score = 2 and no menarche; early pubertal, score = 3 and no menarche; mid-pubertal, score ≥ 3 and no menarche; late pubertal, score ≤ 7 and menarche; post-pubertal, score = 8 and menarche.[27] Given the young age of the cohort, there were very few individuals in the post-pubertal stage. Therefore, we combined the late and post-pubertal categories for the current analyses.

Age at menarche was evaluated separately to assess the timing of puberty. Implausible responses (e.g. 111) were treated as missing. When multiple reports were available across the three assessment points, we used the earliest recorded assessment. In cases of incomplete caregiver reports on age at menarche, adolescent self-reports were used as a supplement ($n = 126$). For analyses involving age at menarche, we included only individuals who had experienced their first period before the second follow-up assessment, and we standardised available data for these analyses.

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Hormone measures

Salivary samples were obtained to measure oestradiol concentrations at baseline and each subsequent follow-up assessment. Comprehensive information on the collection process and sample preparation is available in an earlier report.[28] In short, saliva samples were collected by research assistants using the passive drool method. Participants were instructed to refrain from eating, chewing gum or drinking for 30 min before collection and not to have major meals 60 min before collection. After collection, saliva samples were directly cooled on ice and then sent to Salimetrics.[28] To avoid multiple freeze–thaw cycles, samples were assayed in duplicate within 1 day.

In the pre-processing steps, we adhered to the procedures outlined in the previous report.[29] Only participants who provided a valid saliva sample were considered for hormonal analyses. We excluded participants if there was a discrepancy between their recorded salivary sex and sex reported at birth. In addition, any measures that were affected by hormone quality issues or fell outside the sensitivity limits of the assay were excluded (see ref. 29 for details). When two replicates were available, the mean value was used. Otherwise, the single value was used. Hormone data were standardised for each time point separately.

Following established procedures within the ABCD Study[30] and to address inconsistencies in time assessments, we recoded measures as missing under the following conditions: when the start time of data collection occurred before the wake-up time, when the end time of collection occurred before the start time, or when the freeze time preceded the end time of collection. If caregivers or participants reported that the participants were using hormonal contraceptives, they were excluded from the hormonal analyses. To ensure alignment with the cohort's protocol and recommendations,[30] we restricted sample collection start times to between 07:00 and 19:00.

Exposome score for schizophrenia (ES-SCZ)

The ES-SCZ was computed based on a previous report.[31] This score has previously been used in the ABCD Study.[21] Nine environmental factors (emotional neglect, physical neglect, emotional abuse, physical abuse, sexual abuse, cannabis use, winter birth, hearing impairment and bullying) at baseline and two follow-up assessments were extracted from the ABCD Study data-set. More information on these exposures can be found in the Supplementary Material available at https://doi.org/10.1192/bjp.2025.36 and in a previous report.[21] Binary variables (0 = absent; 1 = present) indicating lifetime exposure for each environmental factor were generated as detailed in the Supplementary Material. An aggregated weighted score was calculated by summing the nine exposures multiplied by their weighted risks (log odds) for schizophrenia.[31]

Polygenic risk score for schizophrenia (PRS-SCZ)

PRS-SCZ was constructed for participants who passed genetic and sample quality control. For comprehensive quality control steps and principal component analysis related to ancestry, please refer to the Supplementary Material. We generated PRS-SCZ using data from the most recent schizophrenia genome-wide association study (GWAS; European subsample) based on 53 386 cases and 77,258 controls,[32] applying a Bayesian framework method that utilised continuous shrinkage on single-nucleotide polymorphism effect sizes. This method is robust to varying genetic architectures, provides substantial computational advantages and enables multivariate modelling of local linkage disequilibrium patterns.[33] We used the 1000 Genomes Project European Sample (https://github.com/getian107/PRScs) as a disequilibrium reference panel. To compute posterior effect sizes, we used the default settings (Supplementary Material). After calculation of posterior effect sizes, PRS-SCZ was calculated using the '–score' function and the SUM modifier in PLINK1.9.[34] After quality control, 742 011 variants were used in the PRS-SCZ calculation. PRS-SCZ data from a subsample of 2775 European females were used and PRS-SCZ was standardised.

Statistical analysis

All analyses in the current study were performed using Stata (release 18).[35] We applied separate longitudinal mixed logistic regression models with oestradiol concentration (baseline: $n = 5163$) or puberty status (baseline: $n = 5456$) as the independent variable and psychotic experiences as the dependent variable, using three assessment points: baseline and two annual follow-up assessments. To account for multiple testing in the longitudinal analyses, Bonferroni correction was applied ($0.05/2 = 0.025$). Age at menarche was analysed cross-sectionally in individuals who had reached menarche ($n = 2947$) at the second follow-up, with psychotic experiences at the second follow-up serving as the outcome variable. Missing values for the covariates can be found in Supplementary Table 2.

All models included random intercepts for site and family membership. The longitudinal analyses also accounted for individual assessments to manage multiple assessments per participant and further incorporated a random slope for assessment points. To investigate the effects of puberty factors within the context of environmental and genetic vulnerability to schizophrenia, we tested for multiplicative interactions with ES-SCZ and PRS-SCZ, respectively.

In alignment with previous literature, the models were adjusted for two sets of covariates: (1) age; and (2) age, family income, parental education, body mass index and ethnicity (except for genetic analyses, which were limited to a European subsample; for details, see the Supplementary Material). Hormonal analyses included additional methodological adjustments (wake-up time on collection day, start time of collection, duration of collection, and time from collection to freezing) and physiological adjustments (caffeine intake and engagement in vigorous physical exercise within the past 12 h; yes/no). Genetic analyses were adjusted for ten principal components.

Results

In this study, there were 5673 participants with data for baseline assessment, and 5348 and 5203 for 1-year and 2-year follow-up assessments, respectively. Table 1 presents sample characteristics at different time points, Supplementary Table 1 details the covariates and Supplementary Table 2 provides information on missing values.

The cross-sectional analyses revealed that earlier age at menarche was significantly associated with a greater likelihood of reporting psychotic experiences at the second follow-up assessment (model 1: odds ratio 0.68, 95% CI: 0.59 to 0.78, $P < 0.001$; model 2: odds ratio 0.77, 95% CI: 0.67 to 0.88, $P < 0.001$). The longitudinal analyses indicated that increased standardised oestradiol concentration was associated with increased likelihood of psychotic experiences (model 1: odds ratio 1.08, 95% CI: 1.01 to 1.16, $P = 0.020$). The association was trend-significant ($P = 0.096$) in model 2 (Table 2).

According to the longitudinal analyses of puberty status, being in later puberty stages (compared with the pre-pubertal reference group) was associated with increased likelihood of experiencing psychotic experiences. Specifically, individuals in the mid-pubertal (model 1: odds ratio 1.41, 95% CI: 1.18 to 1.69, $P < 0.001$) and the

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Table 1 Sample characteristics at different time points

Variables	Baseline 5673	First follow-up 5348	Second follow-up 5203
Psychotic experiences, *n*	1531 (27%)	1102 (21%)	939 (18%)
Puberty stage, *n*			
Pre-pubertal	1676 (31%)	755 (15%)	185 (4%)
Early pubertal	1279 (23%)	891 (18%)	413 (9%)
Mid-pubertal	2353 (43%)	2753 (54%)	2196 (45%)
Late pubertal or post-pubertal	148 (3%)	684 (13%)	2048 (42%)
Age in years at menarche; mean (s.d.)[a]	NA	NA	11.10 (0.89)
Oestradiol in pg/mL, unstandardised; mean (s.d.)	1.04 (0.50)	1.01 (0.51)	1.08 (0.56)
ES-SCZ; mean (s.d.)	2.32 (0.58)	2.46 (0.69)	2.55 (0.74)

ES-SCZ, exposome score for schizophrenia; NA, not applicable.
a. Restricted to individuals with age ≥ age at menarche at the second follow-up assessment.

Table 2 Main effects of puberty factors and vulnerability to schizophrenia on psychotic experiences

	Model 1 (adjusted for age)			Model 2 (adjusted for age, body mass index, family income, parental education and ethnicity)		
Variables	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Puberty factors						
Oestradiol[a]	1.08	1.01–1.16	**0.020**	1.06	0.99–1.14	0.096
Age in years at menarche (cross-sectional[b])	0.68	0.59–0.78	**<0.001**	0.77	0.67–0.88	**<0.001**
Puberty status						
Pre-pubertal (reference)	NA	NA	NA	NA	NA	NA
Early pubertal	1.17	0.96–1.41	0.114	1.04	0.85–1.27	0.733
Mid-pubertal	1.41	1.18–1.69	**<0.001**	1.08	0.89–1.31	0.461
Late pubertal or post-pubertal	2.23	1.74–2.86	**<0.001**	1.44	1.09–1.90	**0.010**
Genomic and exposomic risk						
ES-SCZ (cross-sectional[b])	1.61	1.39–1.85	**<0.001**	1.55	1.34–1.79	**<0.001**
ES-SCZ (longitudinal)	1.86	1.69–2.05	**<0.001**	1.72	1.56–1.91	**<0.001**
PRS-SCZ[c] (cross-sectional[b])	1.32	1.05–1.66	**0.017**	1.27	0.99–1.64	0.060
PRS-SCZ[c] (longitudinal)	1.36	1.18–1.58	**<0.001**	1.33	1.15–1.54	**<0.001**

Bold text indicates statistically significant results. ES-SCZ, exposome score for schizophrenia; PRS, polygenic risk score for schizophrenia; NA, not applicable.
a. Additionally adjusted for salivary collection covariates.
b. This analysis was conducted at the second follow-up assessment to align with the analysis of age at menarche.
c. Genetic analyses were conducted within the European subsample and additionally adjusted for ten principal components.

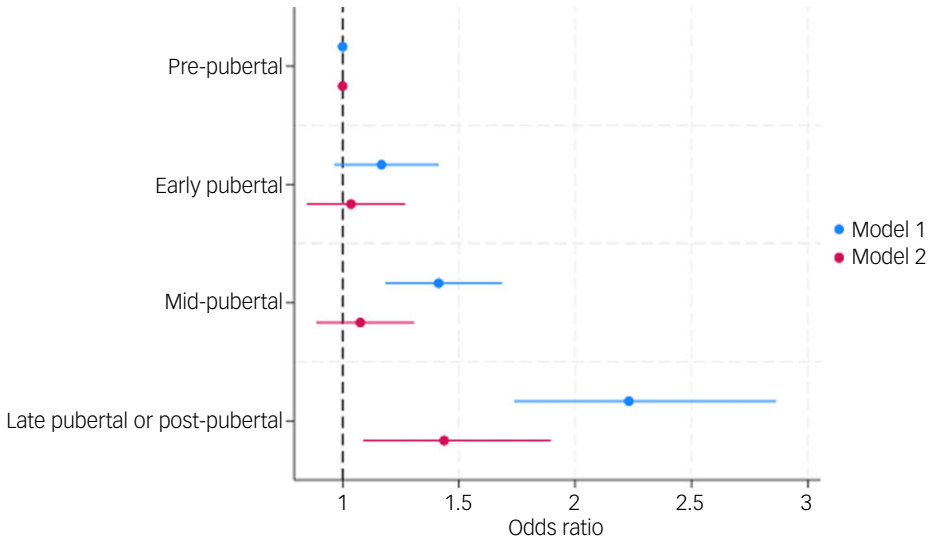

Fig. 1 Effects of perceived puberty status on psychotic experiences. Model 1: adjusted for age; model 2: adjusted for age, body mass index, family income, parental education and ethnicity.

late or post-pubertal stages (model 1: odds ratio 2.23, 95% CI: 1.74 to 2.86, $P < 0.001$) had more psychotic experiences. The difference between the pre-pubertal and early pubertal stages was not statistically significant (model 1: odds ratio 1.17, 95% CI: 0.96 to 1.41, $P = 0.114$). Follow-up contrast analyses further indicated differences between the early pubertal and mid-pubertal stages (model 1: $\chi^2(1) = 5.31$, $P = 0.021$), the early pubertal and late or post-pubertal stages (model 1: $\chi^2(1) = 31.31$, $P < 0.001$) and the

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Table 3 Interaction effects of puberty factors and vulnerability to schizophrenia on psychotic experiences

	Model 1 (adjusted for age)			Model 2 (adjusted for age, body mass index, family income, parental education and ethnicity)		
Variables	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Interaction with ES-SCZ						
Age at menarche × ES-SCZ (cross-sectional[a])	1.04	0.91–1.20	0.562	1.01	0.88–1.17	0.891
Oestradiol × ES-SCZ[b]	1.07	0.98–1.18	0.144	1.07	0.97–1.18	0.169
Puberty status × ES-SCZ						
Pre-pubertal (reference)	NA	NA	NA	NA	NA	NA
Early pubertal	1.00	0.74–1.35	0.979	0.97	0.71–1.33	0.842
Mid-pubertal	1.00	0.77–1.30	0.979	0.92	0.70–1.21	0.551
Late pubertal or post-pubertal	0.94	0.70–1.26	0.680	0.89	0.65–1.22	0.474
Interaction with PRS-SCZ						
Age at menarche × PRS-SCZ[c] (cross-sectional[a])	0.87	0.70–1.09	0.227	0.91	0.72–1.14	0.405
Oestradiol × PRS-SCZ[b,c]	1.02	0.91–1.14	0.736	1.01	0.90–1.13	0.858
Puberty status × PRS-SCZ[c]						
Pre-pubertal (reference)	NA	NA	NA	NA	NA	NA
Early pubertal	0.90	0.68–1.18	0.429	0.93	0.70–1.22	0.588
Mid-pubertal	1.02	0.80–1.30	0.868	0.99	0.77–1.26	0.906
Late pubertal/Post-pubertal	1.02	0.73–1.43	0.914	0.99	0.70–1.39	0.933

ES-SCZ, exposome score for schizophrenia; PRS-SCZ: polygenic risk score for schizophrenia; NA, not applicable.
a. This analysis was conducted at the second follow-up assessment to align with the analysis of age at menarche.
b. Additionally adjusted for salivary collection covariates.
c. Genetic analyses were conducted within the European subsample and additionally adjusted for ten principal components.

mid-pubertal and late or post-pubertal stages (model 1: $\chi^2(1) = 26.92$, $P < 0.001$).

Results for model 2 were similar (Fig. 1 and Table 2); however, the difference between the pre-pubertal (reference group) and mid-pubertal stages was no longer significant. Follow-up contrast analyses further indicated differences between the early pubertal and late or post-pubertal stages (model 2: $\chi^2(1) = 6.73$, $P = 0.010$), as well as between the mid-pubertal and late or post-pubertal stages (model 2: $\chi^2(1) = 9.32$, $P = 0.002$). The difference between the early pubertal and mid-pubertal stages was no longer significant (model 2: $\chi^2(1) = 0.18$, $P = 0.670$).

ES-SCZ was significantly associated with psychotic experiences in the cross-sectional analyses (model 1: odds ratio 1.61, 95% CI: 1.39 to 1.85, $P < 0.001$) and longitudinal analyses (model 1: odds ratio 1.86, 95% CI: 1.69 to 2.05, $P < 0.001$). The results converged with those of model 2 (Table 2). Furthermore, PRS-SCZ was significantly associated with psychotic experiences in the cross-sectional analyses (model 1: odds ratio 1.32, 95% CI: 1.05 to 1.66, $P = 0.017$) and the longitudinal analyses (model 1: odds ratio 1.36, 95% CI: 1.18 to 1.58; $P < 0.001$). The results for model 2 were similar; however, the cross-sectional analyses using model 2 showed a trend-significant association ($P = 0.060$, Table 2). There were no statistically significant interactions of ES-SCZ or PRS-SCZ with puberty factors (Table 3).

Discussion

To the best of our knowledge, this study represents the first comprehensive exploration of the impact of puberty factors (timing, perceived status and oestradiol concentration) on psychotic experiences in a female adolescent general population, particularly within the context of exposomic and genomic susceptibility to schizophrenia. Earlier age at menarche and higher oestradiol concentration were associated with a greater likelihood of psychotic experiences. Furthermore, being in a later perceived puberty stage was associated with psychotic experiences. Both increased genetic and environmental vulnerability to schizophrenia were associated with the likelihood of psychotic experiences. However, we found no interactions between puberty factors and exposomic or genomic risk for schizophrenia with respect to the effects of these factors on psychosis.

The finding of the present study that earlier age at menarche was associated with an increased likelihood of experiencing psychotic experiences during adolescence aligns with studies linking early puberty to internalising and externalising symptoms.[6] However, there is also some evidence that early menarche may be protective against severe outcomes in patients with PSD, although the relationship remains inconclusive in the literature.[7-12] Notably, most previous studies have involved small sample sizes and primarily focused on patients and older individuals. The relationship between puberty timing and psychosis may differ in younger individuals from the general population compared with adults with severe clinical conditions. Although early puberty might represent a transdiagnostic risk factor for various mental health issues during adolescence, it could potentially still be protective in patients with PSD, especially when it is linked to oestradiol concentration. It is also plausible that as time progresses, immediate sociobiological effects diminish, making way for more enduring neurobiological modifications. Furthermore, some studies suggest that both early and late puberty may be associated with increased risk of psychosis in the adult general population.[36] The current sample comprised relatively young individuals, with a maximum age of 14 at the second follow-up assessment. Furthermore, only a subsample had undergone menarche by the second follow-up or had information on age at menarche at this assessment point. Consequently, a comprehensive follow-up that includes individuals with later age at menarche is necessary.

The current findings indicate that higher oestradiol concentrations are associated with a greater likelihood of experiencing psychotic experiences. This may indicate that higher oestradiol concentrations are not universally protective against psychosis across the lifespan. This divergence from the oestrogen hypothesis, in combination with the finding on age at menarche, could be attributed to the complex nature of puberty, in which factors have both immediate- and long-term effects, influencing neurobiological

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mechanisms that may be activated later in life. Notably, a recent ABCD study[13] demonstrated an association between menarche status (present versus not present) at baseline and first follow-up and the incidence of psychotic experiences. Individuals who were post-menarche at both time points exhibited the highest likelihood of psychotic experiences, followed by those transitioning from pre- to post-menarche and, finally, individuals who were pre-menarche at both time points. That study also reported that heightened hippocampal connectivity, which has previously been linked to increased oestradiol exposure and neurological protection in high-risk individuals,[14] was associated with fewer psychotic experiences only in those who remained pre-menarche at both time points. These findings, combined with ours, raise important questions about when high oestradiol concentration indicates vulnerability or a protective effect and how the timing and status of puberty affect the individual.

The current study also found that being in a later stage of perceived puberty, as opposed to the pre-pubertal phase, was associated with more reports of psychotic experiences, indicating a specific vulnerability during the later stages. These findings align with research showing that puberty is a critical vulnerability period during which many mental health problems emerge. Notably, although being in a later stage of puberty increased the risk of psychotic experiences in this sample, studies have suggested that older age is generally associated with a reduced risk of such experiences. Younger individuals report psychotic experiences more frequently, with a decline in prevalence observed from childhood through adolescence and into adulthood.[37,38] Although experiencing psychotic experiences is linked to the development of PSD, these experiences may not independently indicate a risk of later PSD in many individuals. Therefore, future studies should aim to understand how multiple factors – such as the timing of puberty and the occurrence of psychotic experiences during different puberty stages – affect the development of more severe clinical outcomes later in life. Notably, the age at which first psychotic experiences occur may also interact with puberty factors to affect severe outcomes, adding further complexity to this relationship.

The effects of sex (biological) and gender (sociocultural) on mental health during puberty are intricately intertwined. In addition to biological changes, researchers have theorised that the effects of puberty on internalising and externalising problems in girls could be attributed to different psychological mechanisms.[39] For instance, developmental readiness suggests that individuals are not prepared for changes during puberty. Maturational deviance posits that early or late developers diverge from the typical developmental timeline, which can lead to adverse social reactions. For instance, research suggests that teachers may have lower academic expectations of girls displaying early secondary sex characteristics.[40] In the current study, we investigated both visible physical developmental changes, which may provoke sociocultural reactions, and hormonal levels, which are more non-visual biological changes. This is crucial, as a recent ABCD study found that although hormone levels and perceived physical markers of puberty showed moderate correlations, they represented distinct aspects of development.[29] Another crucial aspect is brain development during puberty, which can be influenced by hormonal fluctuations, although the mechanisms underlying this influence are not fully understood. Future research should explore how puberty factors relate to PSD symptoms through brain adaptations.

This study confirms that exposomic and genomic risk factors for schizophrenia influence psychotic experiences in female general-population adolescents. These findings support previous research on the critical roles of environmental and genetic risk factors across the psychosis spectrum.[21] However, no interactions were found between genetic or environmental vulnerability to schizophrenia and puberty factors. These findings should be interpreted cautiously owing to the limited sample size for these analyses and the young age of participants. Previous studies[22] have indicated an interaction between environmental risk and puberty with respect to effects on mental health problems, underscoring the multifactorial nature of such problems. Future follow-up analyses will be needed as more clinically relevant phenotypes emerge. Although current GWAS evidence indicates that sex-specific PRS-SCZ is unlikely to differ significantly from general PRS-SCZ,[32] future advances in this field may offer valuable insights. In addition, an important area for research would be to explore how sex-specific vulnerabilities influence help-seeking behaviour of those at risk of psychosis.

This study represents a comprehensive evaluation of the role of puberty factors in psychotic experiences in female adolescents. Nonetheless, there are several limitations to consider. First, the young age of the participants may have limited the findings on interaction effects, as many individuals had not yet completed all stages of puberty or provided information on age at menarche. It is possible that these effects will become more evident as participants age and more severe clinical phenotypes emerge. Likewise, the analyses involving age at menarche were restricted to individuals who had experienced menarche before the second follow-up assessment; therefore, they could have overlooked different effects that might emerge among those with a later age at menarche. Furthermore, individuals with later menarche may not have reached advanced puberty in this cohort; this could have affected associations between puberty stages and psychotic experiences. However, significant differences among pre-menarche stages (pre- versus mid-pubertal, early versus mid-pubertal) suggest that pubertal changes may influence psychotic experiences risk beyond menarche status. Second, the small sample size, particularly concerning individuals with information on age at menarche, follow-up assessments and genetic data, might have led to low statistical power for interaction effects. Third, following prior research,[21] we limited genetic analyses to the European subpopulation to optimise PRS-SCZ performance with ancestry-matched GWAS data. This improves precision for the European group but limits generalisability to those of non-European ancestries. Future studies should adopt approaches that include diverse ancestry groups to address these limitations. Fourth, the ABCD Study solely focused on salivary measures of the free form of oestradiol in females, constraining our exploration of the broader oestrogenic landscape. Research on the connection between oestrogen and PSD has predominantly focused on oestradiol during reproductive years, and certain protective effects have been attributed to this form of oestrogen. A previous ABCD study linked cognitive functioning to hormone profiles, including testosterone, dehydroepiandrosterone and oestradiol. Given the importance of cognition in PSD, this is a valuable approach that could also be applied to psychosis in future studies. Fifth, various factors, such as other hormones (e.g. cortisol), daily hormonal fluctuations and menstrual cyclicity may influence hormone levels. We aligned our methodology with previous covariate approaches[28,30] and used available variables. However, future studies could benefit from exploring additional factors that may affect oestradiol concentrations and should aim to gain deeper insights into the relationship between puberty factors and psychosis, particularly in the context of more severe outcomes.

Finally, the findings of the current study regarding the important influence of puberty on the risk of psychosis expression during adolescence emphasise the need for comprehensive follow-up research that examines both the immediate- and long-term impacts of puberty on mental health outcomes across diverse populations. It is crucial for such research to explore male-specific aspects of puberty to gain a more complete understanding of sex-specific effects.

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Supplementary material

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Author contributions

L.-K.P. conceptualised the study and its design, performed data analyses, interpreted the results and wrote the first draft of the manuscript. T.P. contributed to the analyses by precleaning the data, reviewed the content and provided final approval for publication. A.A.-M. prepared the genetic data for analyses, reviewed the content and provided final approval for publication. B.D.L. prepared the genetic data for analyses, reviewed the content and provided final approval for publication. B.P.F.R. contributed to the acquisition of the data, reviewed the content and provided final approval for publication. S.G. contributed to the acquisition of funding and data, development of the study design, and drafting and reviewing the manuscript, as well as providing final approval.

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Declaration of interest

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