

Environmental Risk Factors and Psychotic-like Experiences in Children Aged 9–10

Nicole R. Karcher, PhD, Jason Schiffman, PhD, Deanna M. Barch, PhD

Objective: Research implicates environmental risk factors, including correlates of urbanicity, deprivation, and environmental toxins, in psychotic-like experiences (PLEs). The current study examined associations between several types of environmental risk factors and PLEs in school-age children, whether these associations were specific to PLEs or generalized to other psychopathology, and examined possible neural mechanisms for significant associations.

Method: The current study used cross-sectional data from 10,328 children 9–10 years old from the Adolescent Brain Cognitive Development (ABCD) Study. Hierarchical linear models examined associations between PLEs and geocoded environmental risk factors and whether associations generalized to internalizing/externalizing symptoms. Mediation models examined evidence of structural magnetic resonance imaging abnormalities (eg, intracranial volume) potentially mediating associations between PLEs and environmental risk factors.

Results: Specific types of environmental risk factors, namely, measures of urbanicity (eg, drug offense exposure, less perception of neighborhood safety), deprivation (eg, overall deprivation, poverty rate), and lead exposure risk, were associated with PLEs. These associations showed evidence of stronger associations with PLEs than internalizing/externalizing symptoms (especially overall deprivation, poverty, drug offense exposure, and lead exposure risk). There was evidence that brain volume mediated between 11% and 25% of associations of poverty, perception of neighborhood safety, and lead exposure risk with PLEs.

Conclusion: Although in the context of cross-sectional analyses, this evidence is consistent with neural measures partially mediating the association between PLEs and environmental exposures. This study also replicated and extended recent findings of associations between PLEs and environmental exposures, finding evidence for specific associations with correlates of urbanicity, deprivation, and lead exposure risk.

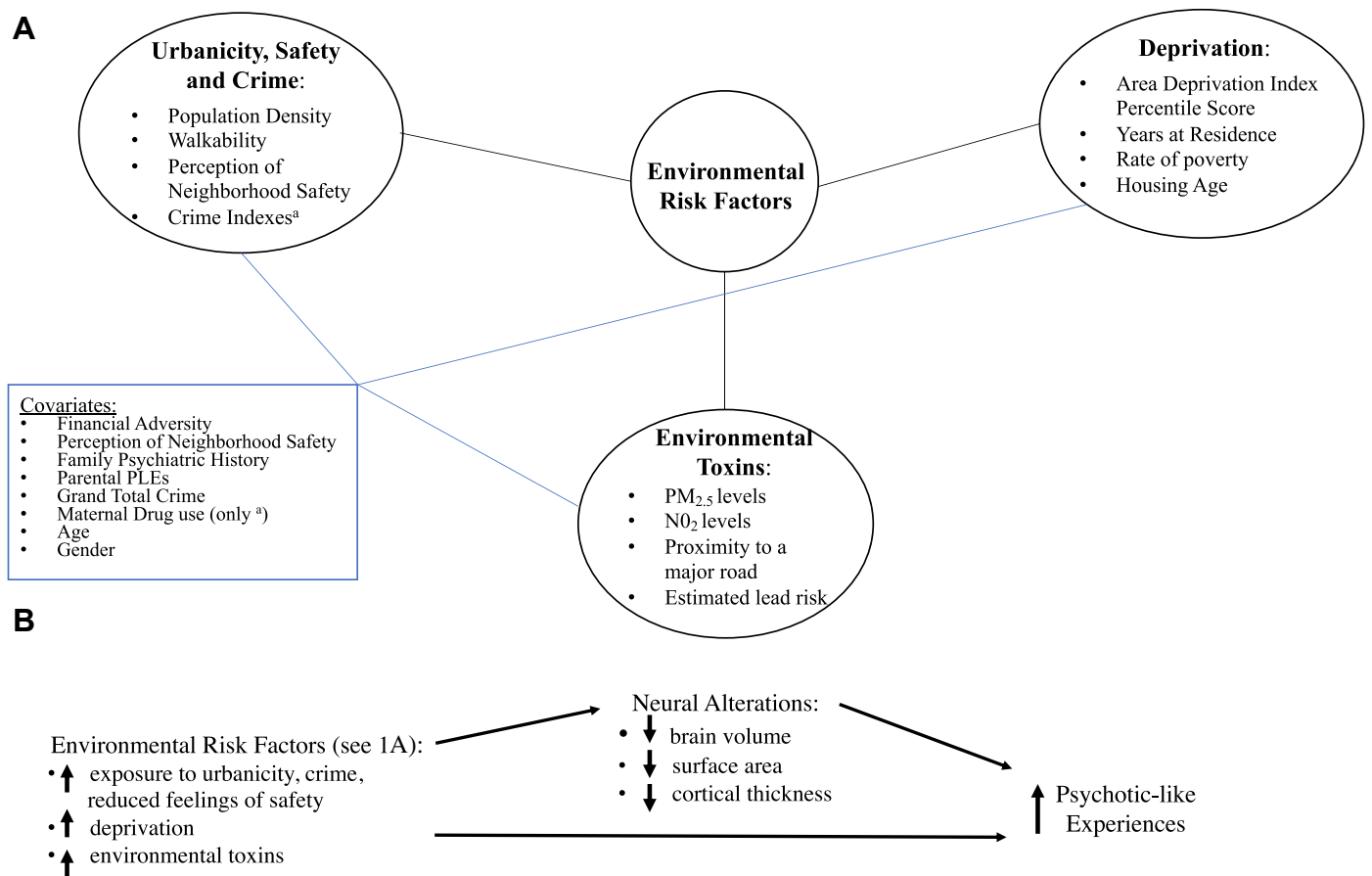
Key words: deprivation, lead exposure, MRI, psychotic-like experiences, urbanicity

J Am Acad Child Adolesc Psychiatry 2021;60(4):490–500. 

Research investigating associations between environmental characteristics and psychosis¹ indicates exposure to urban environments is associated with two- to threefold increased psychosis risk.² However, only recently has research examined associations between environmental risk factors and earlier markers of psychosis risk, including associations with psychotic-like experiences (PLEs).³ PLEs, or nonclinical schizophrenia spectrum symptoms (eg, perceptual abnormalities, mild delusional thoughts), in childhood are associated with greater odds of developing psychiatric disorders, including psychotic disorders, during adulthood.⁴ The current study examined associations between these environmental factors and PLEs in school-age children.

Few studies have examined which specific environmental factors, including urbanicity (eg, population density, crime rates),⁵ toxins (including air pollution),³ and increased poverty/deprivation,⁶ are associated with psychosis risk when accounting for confounding factors, including

financial adversity and psychiatric family history (Figure 1).³ A wealth of evidence suggests that exposure to socio-environmental adversity, including deprivation (eg, low income, employment, education), is associated with increased rates of psychosis.⁷ Research has also found evidence for associations of environmental toxins and pollutants (eg, particulate matter and nitrogen dioxide) with markers of psychosis risk,⁸ though research also implicates these pollutants in other psychiatric problems, including internalizing and externalizing symptoms.⁹ However, a commentary on prior research³ suggested that the association between pollutants and PLEs may be at least partially attributable to lead exposure,¹⁰ consistent with other previous work.¹¹ One reason to suspect exposure to toxins may contribute to associations between environmental risk factors and psychosis is that exposure to air pollution or lead may result in increased oxidative stress and/or systemic inflammation, which have been suggested as causal factors in psychosis development.¹² Furthermore, the authors of a

FIGURE 1 Illustration of the Specific Environmental Factors and Covariates Examined and the Hypothesized Mediation Model

Note: (A) Illustration of the types of environmental risk factors, including urbanicity, crime, and safety; deprivation; and environmental toxins. The figure also details the covariates used in analyses with each of these types of environmental risk factors. (B) Illustration of the hypothesized model whereby structural neural alterations mediate the relationship between environmental risk factors and psychotic-like experiences. NO₂ = nitrogen dioxide; PLEs = psychotic-like experiences; PM_{2.5} = particulate matter with inhalable particles with diameters generally ≤ 2.5 μ m.

^aMaternal drug use was only included as a covariate in the crime index models.

recent study suggested that air pollution may increase risk for PLEs by directly influencing brain structure or function owing to increased inflammation or stress.³

The idea that environmental factors may be associated with increased PLEs through a specific influence on brain development is consistent with research linking reductions in volume, surface area, and cortical thickness to psychosis spectrum symptoms.^{13,14} Furthermore, research indicates that especially deprivation¹⁵ and exposure to environmental toxins^{16,17} are associated with a host of structural abnormalities, including global volumetric reductions and altered cortical thickness. However, there is less research regarding the interrelationships between environmental risk factors, structural abnormalities, and markers of psychosis risk. There is evidence that urban exposure is associated with reduced gray matter volume in male patients with psychosis,¹⁸ although another study found urbanicity did not influence the association between genetic risk for psychosis

and cortical thickness.¹⁹ To our knowledge, no studies have explicitly examined whether there is evidence consistent with structural brain measures that mediate associations between specific environmental risk factors and PLEs, as was examined in the current study (Figure 1).

The current study examined associations between PLEs and environmental risk factors using cross-sectional data from children 9–10 years old in the Adolescent Brain Cognitive Development (ABCD) Study. This age range provides several important advantages, including providing evidence that early exposure to toxins and deprivation may have an influence on prepubertal neurodevelopment related to PLEs.²⁰ We examined whether, as expected, PLEs were associated with exposure to specific types of environmental risk factors, including urbanicity (population density and crime exposure), deprivation (including neighborhood adversity), and toxins. Furthermore, given that environmental risk factors are also associated with other psychiatric

difficulties (eg, internalizing/externalizing symptoms),²¹ we also examined evidence of specificity of associations with environmental risk factors. Lastly, we examined possible mechanisms for significant associations, specifically whether there is evidence consistent with the hypotheses that structural brain metrics (eg, volume, surface area, cortical thickness) mediate associations between environmental risk factors and PLEs. Research indicates that preadolescence is associated with ongoing brain changes, including increases in both gray and white matter preceding the postadolescent decreases in cortical gray matter.²² Additionally, research indicates that environmental risk factors are associated with reductions in brain structure and function.¹⁵ It was therefore expected that environmental risk factors would be associated with global reductions in brain volume, surface area, and thickness.^{15–17} Further, as PLEs in general are associated with reduced global volume, surface area, and cortical thickness,^{13,14} we hypothesized that we would find evidence consistent with reduced brain volume, surface area, and cortical thickness mediating the associations between environmental risk factors and PLEs.

METHOD

Participants

A sample of 11,875 children was obtained from the ABCD Study (Data Release 2.0.1), a large-scale study tracking children 9–10 years old recruited from 21 research sites across the United States.²³ Potential subjects were excluded from participating in the ABCD Study for the following reasons: child not fluent in English; magnetic resonance imaging (MRI) contraindication (eg, irremovable ferromagnetic implants or dental appliances, claustrophobia, pregnant); major neurological disorder; gestational age less than 28 weeks or birth weight less than 1,200 g; history of traumatic brain injury; or a current diagnosis of schizophrenia, autism spectrum disorder (moderate, severe), mental retardation/intellectual disability, or alcohol/substance use disorder.

ABCD Study data were accessed from the National Institutes of Mental Health Data Archive (see Acknowledgments). All measures were collected at the ABCD Study baseline assessment wave. Participants were removed from analyses owing to missing data ($n = 1,546$) (Table S1, available online). The final sample size was 10,328 children (47.4% female; 53.2% White, 20.1% Hispanic, 14.0% African American, 2.1% Asian, and 10.6% other race/ethnicity).

Measures

Symptom Measures. Child participants completed the Prodromal Questionnaire–Brief Child Version (PQ-BC), a 21-item self-report questionnaire previously validated for use with school-age children using the ABCD Study

sample.²⁴ Consistent with this previous research,²⁴ distress scores were calculated as the total number of endorsed questions weighted by level of distress (ie, 0 = no, 1 = yes [but no distress], 2–6 = yes [1+ score on distress scale]). Parental PLEs were assessed as in previous research²⁴ using the summation of parent's responses to 4 questions from the Achenbach Adult Self-Report.²⁵ Internalizing symptoms were examined using the validated and computerized Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS) for *DSM-5*²⁶ using summations of child-rated current depression and generalized anxiety disorder symptoms and parent-rated Child Behavior Checklist (CBCL) internalizing measure *t* scores.²⁵ We also examined the child's externalizing symptoms using the parent-rated CBCL externalizing measure *t* scores.²⁵

Family history of psychiatric disorder was assessed using the parent-rated Family History Assessment Module Screener²⁷ and scored as the proportion of family members (ie, the participant's mother; father; or maternal grandmother, grandfather, uncles, aunts) endorsing a history of psychosis, depression, mania, suicidality, previous hospitalization, or professional help for mental health issues.³ Financial adversity was measured as the summation of endorsement of 7 parent-rated questions of financial difficulties from a demographic questionnaire. This measure included the following questions:

1. Needed food but could not afford to buy it or could not afford to go out to get it?
2. Were without telephone service because you could not afford it?
3. Did not pay the full amount of the rent or mortgage because you could not afford it?
4. Were evicted from your home for not paying the rent or mortgage?
5. Had services turned off by the gas or electric company or the oil company would not deliver oil because payments were not made?
6. Had someone who needed to see a doctor or go to the hospital but did not go because you could not afford it?
7. Had someone who needed a dentist but could not go because you could not afford it?

Environmental Risk Factors. A number of environmental risk factors were retrieved based on the child's primary address coordinates (Figure 1A; see Table S2, available online, for correlations between environmental risk factors).

1. Urbanicity, safety, and crime. Based on current residential address at baseline, population density, a

neighborhood walkability index, parent-rated perception of neighborhood safety, and crime exposure estimates were examined. Population density was calculated based on estimates from the National Aeronautics and Space Administration Socioeconomic Data and Applications Center, calculated based on the 2010 census tracts and adjusted to United Nations estimates of national-level population counts. A neighborhood walkability index was created based on data obtained from the Environmental Protection Agency (<https://www.epa.gov/smartgrowth/smart-location-mapping#walkability>) and 2010 census tract estimates. Perception of neighborhood safety was calculated as a summation of 3 parent-rated questions (ie, “I feel safe walking in my neighborhood, day or night”; “Violence is not a problem in my neighborhood”; “My neighborhood is safe from crime”); each was rated on a scale from 1 to 5 (1 = strongly disagree, 5 = strongly agree). Next, crime exposure information was obtained from the Uniform Crime Report from the Federal Bureau of Investigation, compiled by the Inter-university Consortium for Political and Social Research,²⁸ averaged from 2010–2012 to create stable county-level estimates. Crime exposure estimates included grand total offenses, total violent offenses, total drug offenses, and total driving under the influence offenses.

2. Deprivation. Overall deprivation was defined as the Area Deprivation Index (ADI) national percentile scores for the current residential address at baseline, calculated from the 2011–2015 American Community Survey 5-year summary (see Table S5, available online, for ADI sub-scores).²⁹ We also examined the proportion of individuals living in poverty (–125% of poverty level), average age of the home within the area, and number of years at current residence.
3. Environmental toxins. Based on current residential address at baseline, estimates of air pollution exposure and lead exposure were examined. Estimates of air pollution, including nitrogen dioxide levels (primarily obtained from car emissions), were obtained from the National Aeronautics and Space Administration Socioeconomic Data and Applications Center, based on satellite reports averaged over 3 years (2010–2012) with a resolution of 100 km². In addition, a 2016 annual average of daily particulate matter 2.5 (consisting of inhalable particles, with diameters generally $\leq 2.5 \mu\text{m}$) was created at 1-km² spatial resolution.³⁰ Estimates of lead exposure risk were obtained by first geocoding the participant’s address at the census tract level and then calculating risk scores based on data obtained from vox.com (<https://www.vox.com/a/lead->

exposure-risk-map). Estimated lead exposure risk scores (1–10, 10 being the most at risk) were calculated using proportion of individuals living in poverty and average age of the home (see Deprivation section above).

Structural MRI Measures. For the current study, structural MRI measures included volume,³¹ area,³² and cortical thickness.³³ All children underwent MRI on a 3T scanner-Prisma (Siemens Healthineers, Munich, Germany), Discovery MR750 (GE Healthcare, Chicago, Illinois), or Achieva dStream or Ingenia CX (Philips Healthcare, Andover, Massachusetts)- with a 32-channel head coil and completed T1-weighted and T2-weighted structural scans (1-mm isotropic). Structural neuroimaging processing was completed using FreeSurfer version 5.3.0 through standardized processing pipelines.³⁴ Participants who did not pass FreeSurfer Quality Control measure (ie, at least one T1 scan that passed all quality control metrics) were excluded from analyses (n = 69). Cortical reconstruction and volumetric segmentation was performed by the ABCD Study Data Acquisition and Integration Core using the FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). This preprocessing includes removal of nonbrain tissue using a hybrid watershed/surface deformation procedure,³⁵ automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray/white matter boundary, automated topology correction, and surface deformation following intensity gradients.³³ Images were registered to an atlas, which was based on individual cortical folding patterns to match cortical geometry across subjects. The cerebral cortex was parcellated into 34 regions per hemisphere based on the gyral and sulcal structure. The subcortical white matter and deep gray matter volumetric structures were segmented into 22 regions.³⁶

For the current study, we specifically examined the following global structural MRI metrics (see Supplement 1, available online, for analyses with each of the parcellated cortical and subcortical Desikan regions): intracranial volume, total cortical brain volume, total subcortical gray matter volume, total surface area, total cortical thickness, and hippocampal volume, owing to the wealth of research linking hippocampal volume to both environmental risk factors and PLEs.^{15,37}

Statistical Analyses

The analyses used hierarchical linear models, with all multiple comparisons false discovery rate corrected across 15 models. We employed false discovery rate as opposed to more conservative approaches (eg, Bonferroni) as a way to

TABLE 1 Associations Between Environmental Risk Factors and Psychotic-like Experiences^a

Risk factor	β	Lower 95% CI	Upper 95% CI	SE	t^b	FDR-corrected p	R^2
Urbanicity, crime, and safety							
Population density	.006	−0.016	0.028	0.011	0.516	.61	.019
Walkability	−.010	−0.034	0.015	0.012	−0.804	.52	.019
Perception of neighborhood safety	−.054	0.033	0.075	0.011	5.084	< .001	.019
Crime exposure indexes							
Grand total offenses exposure	.048	−0.006	0.103	0.027	1.783	.15	.019
Adult violent offenses exposure	−.092	−0.270	0.086	0.090	−1.021	.41	.018
Total drug offenses exposure	.227	0.057	0.402	0.086	2.648	.02	.022
DUI offenses exposure	−.118	−0.289	0.052	0.085	−1.389	.27	.018
Deprivation							
Overall deprivation (ADI percentile score)	.146	0.121	0.172	0.013	11.214	< .001	.034
Years at residence	−.056	−0.076	−0.036	0.010	−5.491	< .001	.021
Rate of poverty	.075	0.051	0.098	0.012	6.269	< .001	.024
Housing age	−.007	−0.030	0.017	0.012	−0.573	.61	.019
Environmental toxins							
2016 PM _{2.5} levels	.021	−0.012	0.053	0.016	1.254	.31	.020
NO ₂ levels	−.036	−0.081	0.009	0.022	−1.603	.19	.019
Proximity to a major road	−.005	−0.025	0.015	0.010	−0.525	.61	.019
Lead exposure risk	.029	0.006	0.053	0.012	2.467	.03	.019

Note: Boldface type indicates significant estimates. ADI = Area Deprivation Index; DUI = driving under the influence; FDR = false discovery rate; NO₂ = nitrogen dioxide; PM_{2.5} = particulate matter with inhalable particles with diameters generally ≤ 2.5 μm .

^aModels examining significant environmental risk factors (ie, risk factors in bold) remained significant even when including both child-rated internalizing and parent-rated internalizing and externalizing symptoms, FDR-corrected p s < .05.

^bTwo-tailed.

effectively balance the risk of both type I and type II error in this relatively large sample. All analyses were conducted in R lme4 package³⁸ (multcomp package for multiple comparison analysis³⁹), with family unit and the 21 ABCD Study research sites modeled as random intercepts. We included covariates consistent with previous analyses (Figure 1A).³ For imaging analyses, covariates also included scanner type and average motion rating. Results are expressed as standardized estimates (β s) with 95% bootstrapped (5,000 iterations) CIs.

Hierarchical linear models examined the association between PLEs and each of the environmental risk factors (Figure 1A). Owing to significant skew and zero inflation of PLEs and child-rated internalizing symptoms, negative binomials were also conducted, with results remaining consistent. We also examined whether associations between PLEs and environmental risk factors exhibited specificity or whether these variables were also (or even more strongly) associated with internalizing/externalizing symptoms. Differences between correlations were examined using Meng's z -test procedures.⁴⁰ Lastly, we performed hierarchical mediation analyses using the lavaan package in R⁴¹ to examine evidence for structural MRI abnormalities

potentially mediating associations between PLEs and significant environmental risk factors.

RESULTS

Associations Between PLEs and Environmental Risk Factors

Urbanicity, Safety, and Crime. Even when accounting for covariates (Table 1 and Figure 1A; see Table S3, available online, for associations with individual PQ-BC items and Table S4, available online, for associations with covariates; see Supplement 1, available online, for analyses only containing Caucasian participants), greater total drug offense exposure ($R^2 = .022$) and less perception of neighborhood safety ($R^2 = .019$) were associated with greater PLEs.

Deprivation. Greater overall deprivation as assessed by ADI percentile score ($R^2 = .034$), rate of poverty ($R^2 = .024$), and fewer years at residence ($R^2 = .021$) was associated with greater PLEs (see Table S5, available online, for specific ADI subscore associations with PLEs), even when accounting for covariates (Table 1 and Figure 1A).

Environmental Toxins. When accounting for covariates (Table 1 and Figure 1A), only increased lead exposure risk

TABLE 2 Associations Between Environmental Risk Factors With Both Internalizing and Externalizing Symptoms When Including Psychotic-like Experiences in Models

Risk Factor	Child-rated internalizing symptoms			Parent-rated internalizing symptoms			Parent-rated externalizing symptoms		
	β	t^a	FDR-corrected p	β	t^a	FDR-corrected p	β	t^a	FDR-corrected p
Urbanicity									
Population density	.001	0.370	.83	.005	1.584	.24	.003	1.063	.70
Walkability	.004	0.978	.73	.000	-0.043	.99	0.002	0.464	.88
Perception of neighborhood safety	-.002	-0.282	.83	-.041	-4.780	< .001	-.035	-4.271	< .001
Crime exposure indexes									
Grand total offenses exposure	.000	-0.201	.84	-.006	-2.708	.06	-.002	-1.072	.70
Adult violent offenses exposure	-.001	-1.271	.73	.000	-0.586	.73	.000	-0.283	.88
Total drug offenses exposure	.000	-0.819	.73	-.001	-1.386	.26	.000	-0.694	.75
DUI offenses exposure	-.001	-0.949	.73	.000	-0.202	.95	.000	0.284	.88
Deprivation									
Overall deprivation (ADI percentile score)	.007	1.846	.47	-.006	-1.224	.31	.005	1.243	.70
Years at residence	-.005	-1.013	.73	-.012	-1.918	.15	-.025	-4.436	< .001
Rate of poverty	.008	1.738	.47	-.014	-2.545	.06	-.004	-0.724	.75
Housing age	-.001	-0.295	.83	-.010	-1.877	.15	-.004	-0.935	.72
Environmental toxins									
2016 PM _{2.5} levels	.001	0.489	.82	.002	0.493	.76	-.001	-0.175	.92
NO ₂ levels	.001	0.669	.78	-.003	-1.864	.15	-.003	-2.059	.22
Proximity to a major road	.003	0.589	.79	.008	1.460	.26	.000	-0.049	.96
Estimated lead risk	.003	0.790	.73	-.012	-2.420	.07	-.004	-0.879	.72

Note: Boldface type indicates significant estimate. ADI = Area Deprivation Index; DUI = driving under the influence; FDR = false discovery rate; NO₂ = nitrogen dioxide; PM_{2.5} = particulate matter with inhalable particles with diameters generally $\leq 2.5 \mu\text{m}$.
^aTwo-tailed.

($R^2 = .019$) was significantly associated with increased PLEs.

Specificity of Associations Between PLEs and Environmental Risk Factors

We also examined whether associations between PLEs and environmental risk factors were specific to PLEs or whether

these variables were also associated with internalizing/externalizing symptoms. When including PLEs in the model (Table 2; see Supplement 1, available online, for additional results), both parent-rated internalizing and externalizing symptoms were significantly associated with less perception of neighborhood safety. In addition, parent-rated externalizing symptoms were significantly associated

TABLE 3 Associations Between Structural MRI Metrics and Psychotic-like Experiences

MRI metric	β	Lower CI	Upper CI	SE	t^a	FDR-corrected p
ICV	-.028	-0.045	-0.011	0.009	-3.196	.002
Total subcortical gray volume	-.034	-0.052	-0.015	0.009	-3.569	< .001
Total cortical volume	-.042	-0.060	-0.023	0.009	-4.409	< .001
Total cortical thickness	-.035	-0.053	-0.017	0.009	-3.739	< .001
Total surface area	-.019	-0.035	-0.003	0.008	-2.300	.03
Total hippocampal volume	-.015	-0.032	0.003	0.009	-1.641	.10

Note: FDR = false discovery rate; ICV = intracranial volume; MRI = magnetic resonance imaging.
^aTwo-tailed.

TABLE 4 Associations Between Structural MRI Metrics and Environmental Risk Factors

Risk factor	ICV			Subcortical gray volume			Total volume			Total surface area			Average cortical thickness		
	β	t^a	<i>p</i>	β	t^a	<i>p</i>	β	t^a	<i>p</i>	β	t^a	<i>p</i>	β	t^a	<i>p</i>
Urbanicity, crime, and safety	.076	7.695	<.001	.091	8.508	<.001	.106	9.935	<.001	.091	8.685	<.001	.041	4.483	<.001
Perception of neighborhood safety	-.344	-4.456	<.001	-.247	-2.995	<.001	-.392	-4.608	<.001	-.355	-4.307	<.001	-.099	-1.373	.17
Total drug offenses exposure	-.148	-12.097	<.001	-.163	-12.460	<.001	-.199	-15.053	<.001	-.161	-12.374	<.001	-.088	-7.858	<.001
Deprivation															
Overall deprivation (ADI percentile score)	.047	4.892	<.001	.036	3.451	<.001	.065	6.295	<.001	.046	4.546	<.001	.044	4.925	<.001
Years at residence	-.111	-10.104	<.001	-.121	-10.185	<.001	-.148	-12.417	<.001	-.126	-10.764	<.001	-.055	-5.418	<.001
Rate of poverty															
Environmental toxins															
Lead exposure risk	-.051	-4.587	<.001	-.059	-4.937	<.001	-.068	-5.629	<.001	-.061	-5.129	<.001	-.021	-2.059	.047

Note: ADI = Area Deprivation Index; FDR = false discovery rate; ICV = intracranial volume; MRI = magnetic resonance imaging.
^aTwo-tailed.

with fewer years at residence. Internalizing and externalizing symptoms were not significantly associated with the other risk factors, including total drug offense exposure, overall deprivation, rate of poverty, and lead exposure risk. Importantly, PLEs remained significantly associated with all aforementioned environmental risk factor correlates even when including internalizing and externalizing symptoms in the model.

Next, we examined whether PLEs showed significantly stronger associations with environmental risk factors compared with internalizing/externalizing symptoms. In comparison to internalizing/externalizing symptoms, PLEs showed significantly stronger associations with total drug offense exposure ($Z_s > 10.12, ps < .001$), greater deprivation ($Z_s > 6.04, ps < .001$), and rate of poverty ($Z_s > 3.10, ps < .001$). Also, PLEs showed significantly stronger associations with fewer years at residence than internalizing symptoms ($Z_s > -2.31, ps < .05$; externalizing symptoms: $Z = -0.90, p = .18$), PLEs showed significantly stronger associations with perception of neighborhood safety than child-rated internalizing symptoms ($Z = 2.01, p < .05$; parent-rated symptoms: $Z_s < -0.69, ps > .25$), and PLEs showed significantly stronger associations with lead exposure risk than parent-rated internalizing and externalizing symptoms ($Z_s > 3.02, p < .005$; child-rated symptoms: $Z = 1.50, p = .07$).

Associations Between PLEs, Environmental Risk Factors, and Structural Abnormalities

All of the structural MRI variables (ie, intracranial volume, total subcortical gray volume, total cortical volume, total cortical thickness, total surface area, and total hippocampal volume) were significantly associated with PLEs (Table 3) except for hippocampal volume. Furthermore, these structural MRI variables were also associated with all of the environmental risk factors that were significantly associated with PLEs (Table 4), including perception of neighborhood safety, all deprivation indices, and lead exposure risk. The exception was that total drug offense exposure was not significantly associated with cortical thickness.

We next examined evidence for these structural MRI variables mediating the association between environmental risk factors and PLEs. There was evidence that cortical volume partially mediated the association between deprivation as measured by rate of poverty (and to a lesser extent, overall deprivation; see Table S6, available online) and PLEs (indirect effect [path ab] bias-corrected 95% CI, 0.004–0.01; proportion mediated = 16.42%) (note similar evidence of mediation was found for the other volume indices; see Table S6, available online). There was evidence that total cortical volume also partially mediated the relationship between perception of neighborhood safety (an index of

urbanicity, safety, and crime) and PLEs (indirect effect [path ab] bias-corrected 95% CI, 0.004–0.008; proportion mediated = 16.33%) (note similar evidence of mediation was found for the other volume indices; see Table S6, available online). There was also evidence that cortical volume mediated the association between lead exposure risk and PLEs (indirect effect [path ab] bias-corrected 95% CI, 0.004–0.01; proportion mediated = 29.17%) (note evidence of mediation was found for each of the other structural indices; see Table S6, available online). The other environmental risk factors (eg, drug offense exposure, years at residence), either did not show significant evidence of mediation (ie, drug offense exposure) or the proportion mediated by the structural MRI variables was <10% (Table S6; see Tables S7–S10, available online, for results with individual Desikan regions).

DISCUSSION

Overall, the current study moves forward our understanding of the nature of associations between PLEs and environmental risk factors and makes first steps in understanding the possible neural mechanisms contributing to the association between both deprivation and urbanicity and PLEs. As expected, PLEs were associated with several specific types of environmental risk factors, namely, measures of urbanicity (ie, drug offense exposure, less perception of neighborhood safety), deprivation (including overall deprivation, rate of poverty, fewer years at residence), and lead exposure risk. These associations showed evidence of being more strongly associated with PLEs compared with internalizing or externalizing symptoms, especially for overall deprivation, poverty, and lead exposure risk (see Supplement 1, available online, for additional analyses). Both PLEs and environmental risk factors were generally associated with reduced global brain structural metrics, including reduced volume and surface area. Further, there was some evidence consistent with brain volume partially mediating the association between deprivation (ie, both rate of poverty and overall deprivation), perceptions of neighborhood safety, and lead exposure risk with PLEs.

In terms of associations between PLEs and specific environmental risk factors, consistent with the majority of previous work, we found that deprivation and poverty were associated with PLEs.⁴² In addition, fewer years at residence, which may be associated with greater residential mobility during childhood, was associated with increased PLEs.⁴³ Consistent with previous research,⁵ we also found an association between increased exposure to crime, specifically drug offense exposure, and PLEs. This association

may be attributable to several factors, including increased stress.⁴⁴ Lastly, while the current study failed to replicate recent findings of an association between air pollution and increased PLEs,³ we found an association between PLEs and lead exposure risk. This finding is consistent with previous work,¹¹ including a recent commentary on the previous pollution findings suggesting that such results might reflect lead exposure.¹⁰ Lead exposure risk may be a proxy for unsafe environmental conditions leading to stress and thereby leading to PLEs, or lead exposure may be associated with PLEs in a negative cascade, whereby increased exposure leads to increased inflammation, leading to a host of negative outcomes (eg, cognitive impairments, distress) and then increased PLEs.^{11,45} Notably, associations with environmental risk factors were not specific to PLEs measuring suspiciousness (Table S3, available online). The current study helps to clarify that associations between PLEs with these environmental risk factors remain even when accounting for covariates (Figure 1A). However, further work is needed to specify exact mechanistic pathways.

Importantly, the current study found evidence that associations between environmental risk factors and PLEs exist over and above other markers of psychopathology. First, only PLEs, and not internalizing/externalizing symptoms, were significantly associated with increased drug offense exposure and increased lead exposure risk, indicating perhaps a unique association with PLEs. Furthermore, there was greater evidence for an association between PLEs with deprivation and poverty than internalizing/externalizing symptoms. This may indicate that poverty is associated with psychopathology in a graded fashion, wherein greater deprivation is more strongly associated with more severe forms of psychopathology (eg, increased PLEs). Overall, the current study provides evidence that PLEs are more strongly associated with several environmental risk factor metrics, although other environmental risk factors (eg, fewer years at residence, perception of neighborhood safety) were not clearly more strongly associated with PLEs than internalizing/externalizing symptoms and therefore may represent more general associations with psychopathology.

The current study was the first study to examine cross-sectional evidence that structural neural indexes (eg, volume, area, thickness) mediate associations between environmental risk factors and PLEs. Reduced volume (with the exception of hippocampal volume not being significantly associated with PLEs) and area metrics were significantly associated with both increased PLEs and increased environmental risk factors. The current study also found PLEs were associated with several structural neural metrics (see

Supplement 1, available online, for regional structural MRI analyses) located in regions implicated in resting-state functional connectivity networks associated with PLEs in our prior research using the ABCD Study,⁴⁶ perhaps indicating that subtle neural alterations in higher-order cognitive regions may be possible mechanisms underlying PLEs. Such findings are also consistent with prior research finding that exposure to urbanicity, deprivation, and environmental toxins can have a detrimental effect on the developing brain in preadolescence,¹⁵ which may have implications for the critical pruning processes occurring during adolescence.²² Importantly, the results potentially indicate that global structural brain metrics, and especially volume, may partially mediate associations between deprivation (ie, rate of poverty, overall deprivation, and to a lesser extent, years at residence) with PLEs. This supports the theory that one pathway by which deprivation is associated with increased psychosis risk is through neural impairments.⁴⁷ Interestingly, we found evidence consistent with brain volume partially mediating the association between reduced perceptions of neighborhood safety and PLEs. Perception of neighborhood safety may be a proxy for perceived stress associated with living in that neighborhood, which would be entirely consistent with previous findings regarding interrelationships between chronic stress, volume, and psychosis.⁴⁸ We also found evidence consistent with lead risk exposure mediating the association between reduced cortical volume and increased PLEs (and perhaps particularly middle temporal volume; see Supplement 1, available online), in line with previous research.¹⁷ Overall, these mediation findings are potentially consistent with the notion that underlying pathophysiology in conjunction with exposure to negative environments (eg, urbanicity, poverty, toxins) may further exacerbate neurobiological impairments, leading to increased risk for psychosis spectrum symptoms, but longitudinal work is needed to generate further evidence.

The current study has a number of limitations. The fact that all measures were collected at the ABCD Study baseline assessment limits the conclusions that can be drawn from the current study. It is possible that structural abnormalities were present before any environmental risk exposure. Along these lines, we were not able to examine exposure before age 9. Future research should conduct longitudinal analyses to further clarify these associations. Next, we do not have information about the degree of each individual's exposure to environmental risk factors (eg, amount of exposure to drug offenses, exact degree of lead exposure), which again limits the conclusions that can be drawn from these analyses, and future research is required to examine dose-response associations. Third, self-report of PLEs was not followed up with a clinical interview, although research indicates that self-

reported PLEs, even those not confirmed with clinical interview, are still clinically relevant and associated with higher rates of psychopathology.⁴⁹ Fourth, associations with other self-reports were in the small to moderate range (β s \leq .23), as is expected given the nonclinical sample and has been previously found with PLEs in the ABCD Study sample.²⁴ Fifth, a number of participants (n = 1,546) had missing data and therefore were not included in analyses. These participants significantly differed from the included participants on a number of measures, including demographics and PLEs. However, when including participants with partial data (eg, data for some environmental risk factors but not others), results remained consistent. Lastly, we did not include race/ethnicity as a covariate, owing to the all too frequent confounding of minority status with other relevant factors involved in the current study (eg, deprivation, increased exposure to offenses, reduced access to resources).⁵⁰ Future research should disentangle associations between these environmental risk factors and race/ethnicity.

The current research makes an important contribution to understanding the nature of associations between environmental risk factors and PLEs, including significant associations with exposure to drug offenses, perception of neighborhood safety, overall deprivation, poverty, number of years at residence, and lead exposure risk. Furthermore, there is some evidence that several of the associations, especially with poverty, overall deprivation, total drug offense exposure, and lead exposure risk, were more strongly associated with PLEs than other psychopathology. Lastly, we found evidence consistent with the possibility that structural brain metrics partially mediated associations between deprivation, neighborhood safety, and lead exposure risk with PLEs, which may have important clinical implications. Future clinical interventions and public health policies to reduce exposure to deprivation, correlates of urbanicity (ie, reduced perception of neighborhood safety, increased exposure to drug offenses), and environmental toxins will be important for reducing negative effects of exposure on psychosis risk.

Accepted July 9, 2020.

Dr. Karcher is with Washington University School of Medicine, St. Louis, Missouri. Dr. Schiffman is with University of Maryland, Baltimore County, and the University of California, Irvine. Dr. Barch is with Washington University in St. Louis, Missouri.

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (<https://abcdstudy.org>), held in the National Institute of Mental Health Data Archive. This is a multisite, longitudinal study designed to recruit more than 10,000 children aged 9–10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, U24DA041147, U01DA041093,

and U01DA041025. A full list of supporters is available at <https://abcdstudy.org/federal-partners.html>. A listing of participating sites and a complete listing of study investigators can be found at https://abcdstudy.org/Consortium_Members.pdf. ABCD Study consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD Study consortium investigators.

The ABCD Study data repository grows and changes over time. The ABCD Study data used in this report came from <https://dx.doi.org/10.15154/1503209>.

This work was supported by National Institute on Drug Abuse grant U01 DA041120 (D.M.B.), NIH grant MH014677 (N.R.K.) and grants R01-MH112612 and R34-MH110506 (J.S.), and the Behavioral Health Administration, Maryland Department of Health and Mental Hygiene, through the Center for Excellence on Early Intervention for Serious Mental Illness OPASS 14-13717G/M00B4400214 (J.S.).

Author Contributions

Conceptualization: Karcher

Data curation: Karcher

Formal analysis: Karcher

Investigation: Karcher

Methodology: Karcher

Supervision: Barch

Visualization: Karcher

Writing – original draft: Karcher

Writing – review and editing: Karcher, Schiffman, Barch

ORCID

Nicole R. Karcher, PhD: <https://orcid.org/0000-0001-5887-5529>

Jason E. Schiffman, PhD: <https://orcid.org/0000-0002-1363-4497>

Deanna M. Barch, PhD: <https://orcid.org/0000-0003-1693-8506>

The authors are grateful to Wesley Thompson, PhD, of the University of California San Diego, for his valuable and constructive suggestions during the revision of this research work. They also thank the families participating in the ABCD Study.

Disclosure: Drs. Karcher, Schiffman, and Barch have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Nicole R. Karcher, PhD, Department of Psychiatry, One Brookings Drive, Campus Box 1125, Washington University, St. Louis, MO 63130; e-mail: nkarcher@wustl.edu

0890-8567/\$36.00/©2020 American Academy of Child and Adolescent Psychiatry

<https://doi.org/10.1016/j.jaac.2020.07.003>

REFERENCES

- Faris REL, Dunham HW. *Mental Disorders in Urban Areas: An Ecological Study of Schizophrenia and Other Psychoses*. Chicago, IL: University of Chicago Press; 1939.
- Fan CC, McGrath JJ, Appadurai V, *et al*. Spatial fine-mapping for gene-by-environment effects identifies risk hot spots for schizophrenia. *Nat Commun*. 2018;9:5296.
- Newbury JB, Arseneault L, Beevers S, *et al*. Association of air pollution exposure with psychotic experiences during adolescence. *JAMA Psychiatry*. 2019;76:614-623.
- Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch Gen Psychiatry*. 2000;57:1053-1058.
- Newbury J, Arseneault L, Caspi A, Moffitt TE, Odgers CL, Fisher HL. Why are children in urban neighborhoods at increased risk for psychotic symptoms? Findings from a UK Longitudinal Cohort Study. *Schizophr Bull*. 2016;42:1372-1383.
- Kirkbride JB, Jones PB, Ullrich S, Coid JW. Social deprivation, inequality, and the neighborhood-level incidence of psychotic syndromes in East London. *Schizophr Bull*. 2014;40:169-180.
- Fett AJ, Lemmers-Jansen ILJ, Krabbendam L. Psychosis and urbanicity: a review of the recent literature from epidemiology to neurourbanism. *Curr Opin Psychiatry*. 2019;32:232-241.
- Khan A, Plana-Ripoll O, Antonsen S, *et al*. Environmental pollution is associated with increased risk of psychiatric disorders in the US and Denmark. *PLoS Biol*. 2019;17:e3000353.
- Perera FP, Tang D, Wang S, *et al*. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6-7 years. *Environ Health Perspect*. 2012;120:921-926.
- Fuller-Thomson E, Munro A P. Lead exposure as a confounding factor in the association of air pollution exposure and psychotic experiences. *JAMA Psychiatry*. 2019;76:1095-1096.
- Reuben A, Schaefer JD, Moffitt TE, *et al*. Association of childhood lead exposure with adult personality traits and lifelong mental health. *JAMA Psychiatry*. 2019;76:418-425.
- Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. *Biol Psychiatry*. 2013;74:400-409.
- Drakesmith M, Dutt A, Fonville L, *et al*. Volumetric, relaxometric and diffusometric correlates of psychotic experiences in a non-clinical sample of young adults. *Neuroimage Clin*. 2016;12:550-558.
- van Erp TGM, Walton E, Hibar DP, *et al*. Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biol Psychiatry*. 2018;84:644-654.
- Johnson SB, Riis JL, Noble KG. State of the Art Review: Poverty and the developing brain. *Pediatrics*. 2016;137:e20153075.
- de Prado Bert P, Mercader EMH, Pujol J, Sunyer J, Mortamais M. The effects of air pollution on the brain: a review of studies interfacing environmental epidemiology and neuroimaging. *Curr Environ Health Rep*. 2018;5:351-364.
- Marshall AT, Betts S, Kan EC, McConnell R, Lanphear BP, Sowell ER. Association of lead-exposure risk and family income with childhood brain outcomes. *Nat Med*. 2020;26:91-97.
- Frissen A, van Os J, Peeters S, Gronenschild E, Marcelis M. Evidence that reduced gray matter volume in psychotic disorder is associated with exposure to environmental risk factors. *Psychiatry Res Neuroimaging*. 2018;271:100-110.
- Frissen A, van Os J, Habets P, Gronenschild E, Marcelis M. No evidence of association between childhood urban environment and cortical thinning in psychotic disorder. *PLoS One*. 2017;12:e0166651.
- Rees N. Danger in the air: how air pollution may be affecting the brain development of young children around the world. UNICEF; https://www.unicef.org/environment/files/Danger_in_the_Air.pdf. Accessed December 8, 2019.
- Slopen N, Fitzmaurice G, Williams DR, Gilman SE. Poverty, food insecurity, and the behavior for childhood internalizing and externalizing disorders. *J Am Acad Child Adolesc Psychiatry*. 2010;49:444-452.
- Giedd JN, Blumenthal J, Jeffries NO, *et al*. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 1999;2:861-863.
- Barch DM, Albaugh MD, Avenevoli S, *et al*. Demographic, physical and mental health assessments in the Adolescent Brain and Cognitive Development Study: rationale and description. *Dev Cogn Neurosci*. 2018;32:55-66.
- Karcher NR, Barch DM, Avenevoli S, *et al*. Assessment of the Prodromal Questionnaire-Brief Child Version for measurement of self-reported psychoticlike experiences in childhood. *JAMA Psychiatry*. 2018;75:853-861.
- Achenbach TM. *The Achenbach System of Empirically Based Assessment (ASEBA): Development, Findings, Theory and Applications*. Burlington, VT: University of Vermont Research Center for Children, Youth, and Families; 2009.
- Kaufman J, Birmaher B, Brent D, *et al*. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36:980-988.
- Rice JP, Reich T, Bucholz KK, *et al*. Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcohol Clin Exp Res*. 1995;19:1018-1023.
- United States Department of Justice, Office of Justice Programs, Federal Bureau of Investigation. *Uniform Crime Reporting Program Data: County-Level Detailed Arrest and Offense Data, United States, 2010*. Inter-university Consortium for Political and Social Research [distributor]; 2014; <https://doi.org/10.3886/ICPSR33523.v2>.
- Kind AJ, Jencks S, Brock J, *et al*. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. *Ann Intern Med*. 2014;161:765-774.
- Di Q, Kloog I, Koutrakis P, Lyapustin A, Wang Y, Schwartz J. Assessing PM2.5 exposures with high spatiotemporal resolution across the continental United States. *Environ Sci Technol*. 2016;50:4712-4721.
- Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999;9:195-207.
- Chen CH, Gutierrez ED, Thompson W, *et al*. Hierarchical genetic organization of human cortical surface area. *Science*. 2012;335:1634-1636.
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000;97:11050-11055.
- Hagler DJ, Hatton SN, Makowski C, *et al*. Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *Neuroimage*. 2019;202:116091.
- Segonne F, Dale AM, Busa E, *et al*. A hybrid approach to the skull stripping problem in MRI. *Neuroimage*. 2004;22:1060-1075.

36. Desikan RS, Segonne F, Fischl B, *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31:968-980.
37. Nakahara S, Matsumoto M, van Erp TGM. Hippocampal subregion abnormalities in schizophrenia: a systematic review of structural and physiological imaging studies. *Neuropsychopharmacol Rep*. 2018;38:156-166.
38. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67.
39. Hothorn T, Bretz F, Westfall P. Simultaneous inference in general parametric models. *Biom J*. 2008;50:346-363.
40. Meng X-L, Rosenthal R, Rubin DB. Comparing correlated correlation coefficients. *Psychol Bull*. 1992;111:172.
41. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. *J Stat Softw*. 2012; 48:1-36.
42. O'Donoghue B, Roche E, Lane A. Neighbourhood level social deprivation and the risk of psychotic disorders: a systematic review. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51: 941-950.
43. Paksarian D, Eaton WW, Mortensen PB, Pedersen CB. Childhood residential mobility, schizophrenia, and bipolar disorder: a population-based study in Denmark. *Schizophr Bull*. 2015;41:346-354.
44. van Winkel R, Stefanis NC, Myin-Germeys I. Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophr Bull*. 2008;34:1095-1105.
45. Cabrera B, Bioque M, Penades R, *et al.* Cognition and psychopathology in first-episode psychosis: are they related to inflammation? *Psychol Med*. 2016;46: 2133-2144.
46. Karcher NR, O'Brien KJ, Kandala S, Barch DM. Resting-state functional connectivity and psychotic-like experiences in childhood: results from the Adolescent Brain Cognitive Development Study. *Biol Psychiatry*. 2019;86:7-15.
47. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature*. 2010;468: 203-212.
48. Holtzman CW, Trotman HD, Goulding SM, *et al.* Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience*. 2013;249:172-191.
49. Rimvall MK, Gundersen S, Clemmensen L, *et al.* Evidence that self-reported psychotic experiences in children are clinically relevant. *Schizophr Res*. 2019;204: 415-416.
50. Browning CR, Calder CA, Ford JL, Boettner B, Smith AL, Haynie D. Understanding racial differences in exposure to violent areas: integrating survey, smart-phone, and administrative data resources. *Ann Am Acad Pol Soc Sci*. 2017; 669:41-62.