Associations between urban birth or childhood trauma and first-episode schizophrenia mediated by low IQ

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INTRODUCTION

It is estimated that about 70% of the world’s population will live in cities by 2050. China has especially experienced an unprecedented rate of urbanization during the last decades. The proportion of the urban-dwelling population increased from 17.9% in 1978 to 52.6% in 2012. Urbanization was associated with an increased risk of schizophrenia, and even there was a dose-response effect between them. Several replications have been conducted, primarily in Europe. However, one study included a nationally representative general population sample of adults residing in 42 low-income and middle-income countries and found that urbanization could increase the incidence of psychosis in Estonia, but opposite patterns were observed in Mali, Senegal, and the Philippines. However, this study was conducted without considering different patterns of genetic, social, and biological exposures in different countries, so the conclusion might not be reliable. Up to date, only one study found that urbanization was associated with an increased risk of schizophrenia (odds ratio (OR) = 1.44; 95% CI, 1.32 to 1.57) in China. Therefore, it is an open question whether urbanization as a risk of schizophrenia differs between developed and developing countries.

Premorbid Intelligence Quotient (IQ) deficit, especially assessed in late adolescence, is a robust risk factor for the onset of schizophrenia. Previous studies have confirmed that cognitive deficits are emergent in the early stage of neurodevelopment, including childhood and adolescence, before the onset of schizophrenia. Kendler et al. found that the association between lower IQ and schizophrenia may be causal because genetic load for schizophrenia had a much stronger impact on the risk of illness for those with low IQ, rather than the result of shared familial risk factors. Even though IQ is heritable and stable throughout adolescence to old age, it also has a high malleability affected greatly by normal environmental variation, including families, lifespan, and socioeconomic status (SES). In addition, environmental stressors, such as birth complications, substance abuse, urbanization, and childhood trauma, were associated with an increased risk of schizophrenia. However, the potential impact of these environmental stressors on the cognition of schizophrenia has not been fully investigated in patients with schizophrenia.

Increased exposure to environmental stressors caused by urbanization, such as contamination of drinking water, air, and noise, impairs the development of brain structure and function, thus leading to cognition impairment. More access to community resources (e.g., library, playgrounds, and community center), less financial difficulties (e.g., problems meeting basic needs such as food and housing), and less family adversity (e.g., lower father education and poor parental mental health) for children in an urban setting may lead to better neurocognitive development trajectory. Therefore, it is unclear whether urban birth impedes or promotes cognitive development and whether IQ mediates these associations.

Childhood trauma, as adverse experiences in early childhood, including emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, is a well-established risk factor for schizophrenia. Many patients with schizophrenia spectrum disorders have experienced one or more childhood trauma events, and the most frequent subtype of trauma was emotional neglect. A review of childhood trauma and neuroimaging

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studies showed that childhood trauma was associated with decreased gray matter in the prefrontal cortex, alterations of white matter integrity in several fiber bundles (the forceps major, inferior and superior longitudinal fasciculus, and the inferior fronto-occipital fasciculus), and abnormal functional connectivity in individuals with schizophrenia. In addition, a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis was associated with poor neurocognitive function. Thus, we hypothesized that IQ may mediate between childhood trauma and schizophrenia. However, the potential impact of these environmental stressors on the cognition of schizophrenia has not been fully investigated in patients with schizophrenia. In a developing country, the effect of IQ on the relationship between adverse environment exposure and schizophrenia remains unclear. This study aimed to (1) examine whether urban birth and childhood trauma are the risk factors for first-episode schizophrenia (FES) in China and (2) explore the mediating effect of IQ on the relationship between birthplace or childhood trauma and the development of FES.

METHODS
A total of 400 participants were enrolled in this study, including 144 patients with FES and 256 healthy controls (HCs). Patients with schizophrenia were recruited at the ward and out-patients clinic of the Psychiatric Department, West China Hospital, Sichuan University. HCs participants were recruited by poster and word-of-mouth advertisements in Chengdu and surrounding areas. All participants met the following inclusion criteria: (1) age range 16 to 45 years old; (2) Han Chinese; (3) right-handedness; (4) an IQ of 70 or above to exclude mental retardation. The participants (1) received a diagnosis of mental retardation, schizoaffective disorder, or other neurocognitive disorders; (2) suffered from severe head trauma or coma; (3) had an unstable medical condition; (4) were in the period of pregnancy or breastfeeding, were excluded. The diagnosis was assigned to DSM-IV diagnostic criteria according to the Structured Clinical Interview for DSM-IV (SCID) criteria, with SCID-P for patients and SCID-NP for HCs. All participants completed informed consent after a full explanation of the study procedures. Ethical approval for this study was granted by the Ethics Committee of the West China Hospital, Sichuan University.

Clinical measurements
All subjects reported their birthplace (either rural or urban) according to the household register. Immigration status was based on the self-report of whether people moved to another place before 18. Childhood trauma was assessed by a childhood trauma questionnaire (CTQ), a 5-Likert score scale ranging from 25 to 125. A positive and negative syndrome scale (PANSS) was used to evaluate the psychopathology of patients with FES. All assessments were performed by the researchers after unified training.

Assessment of Wechsler Adult Intelligence Scale-Revised
The short version of the Wechsler Adult Intelligence Scale-Revised in China (WAIS-RC) includes 7 subtests, i.e., information, arithmetic, digital symbol coding, digital span, block design, picture completion, and similarities. The total Verbal IQ (VIQ) of scaled scores was obtained as 2(Information + Similarities) + Arithmetic + Digit Span; Total Performance IQ (PIQ) was calculated as 2(Picture Completion + Block Design) + Digit Symbol. The full scale of IQ (FSIQ) estimates was based on the sum scores of VIQ and PIQ. The estimated sums of scaled scores derived from these formulae were converted to IQ scores according to the standard procedure and age-corrected conversion tables in the WAIS-RC manual.

Analysis
T-test or analysis of variance (ANOVA) was carried out for group comparisons. Hierarchical logistic regression analysis was used to examine the associations between birthplace, CTQ, IQ and risk of schizophrenia. In the hierarchical analysis, the following variables were included: step 1 (age + sex + educational attainment); step 2 (variables retained from step 1 + birthplace); step 3 (variables retained from step 2 + CTQ); step 4 (variables retained from step 3 + FSIQ). All analyses above were based on version 15.0 of STATA (College Station, TX: StataCorp LLC). Finally, mediation analysis was carried out to examine whether the mediating effects of IQ could explain the relationship between birthplace/childhood trauma and schizophrenia, with age, sex, body mass index (BMI) and educational attainment as covariates. Mediation analysis was based on version 8.4 of Mplus. Statistical significance was set at P < 0.05. Multiple comparisons were corrected by Bonferroni correction, and P_corrected < 0.05 was used as the significance threshold of correction.

RESULTS
Table 1 shows no difference in age, BMI, birthplace, and immigration status between FES and HCs (P > 0.05). Compared with HCs, education years and FSIQ of patients with FES were lower, and the percentage of males and CTQ of FES were higher.
The primary purpose of this study was to evaluate the relationship between birthplace or childhood trauma, IQ and FES. The current study revealed the rural–urban difference in IQ of patients with schizophrenia. Furthermore, 51.46% of the risk of schizophrenia associated with childhood trauma could be offset by about 52.94% (indirect effect/direct effect) via FSIQ. Total effect of childhood trauma on diagnosis was significant (β = 0.40, 95% CI [0.30, 0.49], P < 0.001), after adjusting for age, sex and educational attainment. The direct effect and indirect effect of childhood trauma on FES were significant (β = 0.31, 95% CI [0.22, 0.39], P < 0.001; β = 0.09, 95% CI [0.05, 0.14], P = 0.001). The association between childhood trauma and FES could be partly explained by FSIQ (proportion explained 22.5%). In total, the estimated model explained 70.5% of the total variance in FES (R² = 0.705).

**DISCUSSION**

The primary purpose of this study was to evaluate the relationship between birthplace or childhood trauma, IQ and FES. The current study revealed the rural–urban difference in IQ of patients with schizophrenia. Furthermore, 51.46% of the risk of schizophrenia associated with urban birth was offset by IQ, and 23.12% of the risk of schizophrenia associated with childhood trauma could be attributable to indirect effects on IQ if these associations were causal.

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**Table 2.** Comparisons of demographic and clinical information between birthplace of rural and urban in FES and HCs.

| Variable                  | FES          | HCs          |
|---------------------------|--------------|--------------|
|                           | Rural (%)    | Urban (%)    | Rural (%)    | Urban (%)    |
| Male sex, n (%)           | 45 (52.33)   | 19 (32.76)*  | 47 (32.87)   | 35 (30.97)   |
| Age (mean, SD)            | 22.35 (5.57) | 23.14 (7.04) | 24.50 (5.76) | 22.71 (4.23)** |
| BMI (mean, SD)            | 20.47 (2.93) | 21.11 (3.70) | 20.62 (2.62) | 21.09 (3.29) |
| Education (years) (mean, SD) | 11.70 (2.60) | 13.40 (2.53)** | 15.75 (2.60) | 15.76 (1.84) |
| CTQ (mean, SD)            | 43.61 (13.21) | 42.86 (13.80) | 32.01 (12.16) | 32.09 (6.83) |
| FSIQ (mean, SD)           | 92.21 (13.40) | 100.34 (13.82)** | 113.71 (11.75) | 121.10 (8.58)** |
| DUP (months) (mean, SD)   | 15.64 (18.86) | 14.47 (20.49) | –          | –          |
| Age of onset (mean, SD)   | 21.46 (5.48) | 22.43 (7.25) | –          | –          |
| GAF (mean, SD)            | 45.96 (11.91) | 50.40 (12.68)* | –          | –          |
| PANSS (mean, SD)          | –            | –            | –          | –          |
| Positive score            | 23.28 (5.98) | 21.23 (6.30)* | –          | –          |
| Negative score            | 23.09 (7.49) | 20.14 (7.66)* | –          | –          |
| General score             | 44.17 (10.02) | 38.32 (10.75)** | –          | –          |
| Total score               | 90.55 (18.79) | 79.68 (20.25)** | –          | –          |

FES, first-episode schizophrenia; HCs, healthy controls; BMI, body mass index; CTQ, childhood trauma questionnaires; FSIQ, full scale of IQ; DUP, duration of untreated psychosis; GAF, global assessment function; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

*P < 0.05; **P < 0.01; ***P < 0.001.
Our results showed general cognitive differences between urban-born and rural-born individuals, consistent with previous studies. Potential possibilities have been proposed to explain the rural-urban gap in cognition. First, low socioeconomic status (SES) based on parental education, occupation, and income, was the most common phenomenon in rural areas, especially in developing countries. SES is associated with declined scores on cognitive and language development and reduced cortical volume and thickness in children. Second, lack of access to community sources (e.g., library, museum, and cultural activities center), lower quality of education (teachers with lower wages and levels of training), and reduced access to preschool education. Third, significantly lower levels or lack of parenting sensitivity and stimulation in rural regions were associated with the poor performance of children. In conclusion, the family environment, community, and school of childhood contribute to the difference in neurocognitive development between urban- and rural-born children.

Our findings suggest that urban birth is associated with an increased risk of schizophrenia after controlled IQ, which is consistent with the previous studies. Previous studies revealed that built environment, environment pollution, social stress related to the urban milieu, and neighborhood characteristics were risk attributes of the urban environments. These risk attributes could illuminate the relationship between urban exposure and schizophrenia. First, design meanings, triggers, symbols, etc., (high-rise buildings, narrow streets with no escape ways, less street planting and gardens, and billboards and flashing lights) of the built urban environment were associated with aberrant brain morphologies and reactivity patterns. Furthermore, exposure to less green space in urban design was associated with a high incidence of psychological stress and schizophrenia. Residential green space was crucial for developing intelligence and behavior in children living in urban areas. Second, environmental pollution (e.g., air pollution, water pollution, and noise pollution) was common in urban areas. Exposure to air pollution, contamination of drinking, and chronic traffic noise in childhood were associated with long-term impairment of the HPA axis, brain structure, and function, which could be a potential neuropsychopathological mechanism of schizophrenia. Third, there was a huge income disparity in modern urban regions. Individuals living in a poverty-stricken area were more likely to suffer from social stressors, crime victimization, and racial discrimination. Indeed, city life-related social stress was associated with increased amygdala activity, and urban upbringing was related to increased pregenual anterior cingulate cortex activity, a critical region for stress regulation, amygdala activity, and neurocognitive processing. Fourth, Kirkbride et al. found that neighborhood characteristics (neighborhood income inequality, absolute deprivation, population density, neighborhood ethnic composition effects, etc.) were associated with the risk of non-affective psychosis. In addition, lack of physical activity and poor diets (low fruit and vegetable intake) were harmful to mental health. Cumulative childhood and adolescence exposure to urban environments was associated with brain structure and function alterations. One study found a significant inverse correlation between urban upbringing and cortical thickness in...
the left dorsolateral PFC, bilateral medial PFC, and the temporal cortex, including the left superior temporal and left para-hippocampal cortex ($p < 0.05$, FWE-corrected)\textsuperscript{58}. Urban exposure was a compound risk factor, including many environmental factors, which may require further study on the role of each element to make better intervention decisions.

Childhood trauma, independent of urban birth, is one of the risk factors for schizophrenia. The potential mechanisms may involve dysfunction of the HPA axis and alterations of neurobiological and epigenetic processes\textsuperscript{39}. Both animal and human studies have confirmed that childhood trauma was related to long-term alterations of the HPA axis, including hyperdopaminergic state and augmented glucocorticoid release, which may affect specific brain regions (such as the hippocampus and the prefrontal cortex), leading to neurocognitive impairment\textsuperscript{60,61}. Childhood trauma is associated with widespread alterations of brain structure and function, including decreased total cerebral gray matter (especially in the prefrontal cortex), decreased white matter integrity in the forceps major, inferior fronto-occipital fasciculus, inferior and superior longitudinal fasciculus, and functional connectivity of the amygdala and the anterior cingulate cortex\textsuperscript{27}. In addition, epigenetic processes, such as DNA methylation and histone modifications, are important for cognition and symptoms in patients with schizophrenia\textsuperscript{62,63}.

In our study, the association between birthplace and schizophrenia was mediated by IQ. A better understanding of cognition may better elucidate the underlying pathological mechanisms of environmental exposure and schizophrenia. IQ with high malleability was susceptible to environmental risk factors. Urban birth individuals were exposed to better education quality and more educational opportunities, as well as pollution, social stress, and bad living habits associated with urbanization. Furthermore, one study found that high IQ significantly reduces the effect of genetic susceptibility on the risk of schizophrenia\textsuperscript{13}. Therefore, the total effect of urban birth on schizophrenia is not significant. In contrast, individuals exposed to deprivation (such as living in a poverty-stricken city area) were more likely to lack educational opportunities and suffer from more social stressors, crime victimization, and racial discrimination, which could impair cognitive development. Thus, urban birth was associated with an increased risk of schizophrenia in people with low IQ.

Additionally, our study found that low IQ partly contributed to the association between childhood trauma and schizophrenia. The adverse impact of childhood trauma on cognition may play a role in the developmental trajectory of schizophrenia, as low IQ is a well-established risk factor for schizophrenia\textsuperscript{13}. This estimation strategy may account for some inconsistent evidence about the association between childhood trauma and schizophrenia in previous studies. Prior studies have focused solely on the main effect of childhood trauma on the increased risk of schizophrenia and have overlooked the possibility of the process via cognition linking them. A multicentric case-control study of first-episode psychosis found that childhood maltreatment was associated with cognition in psychosis and HCs\textsuperscript{65}. However, the correlation is not the same as causation. A possible interpretation is that childhood trauma was associated with neurodevelopment, including alterations of brain structure and function\textsuperscript{27,55,58}, which may be the neuropathological basis of cognitive deficits and the emergence of schizophrenia.

This study has several limitations. First, we did not collect cognitive data on the parents or siblings of the patients. Therefore, the familial liability both for IQ and schizophrenia was not considered. Second, the assessment of IQ used in this study was collected after the onset of illness. Although a previous study found that the IQ of patients with schizophrenia before onset was significantly lower than that of HCs, the effects of duration of untreated psychosis and illness of schizophrenia on IQ could not be excluded. Third, we could not examine the impact of cumulative urban exposure (urban exposure duration or quantified urbanization level) on schizophrenia. Fourth, although we controlled the effect of CTQ and IQ, our study could not prevent individual-level substance abuse, environmental pollutants, and low SES. Finally, the samples in this study were mainly from the Chengdu area of Sichuan province, a relatively developed region in China. The samples cannot well represent the complex characteristics and social and economic level of the Chinese population. Therefore, we cannot conclude that the findings of urbanization increasing the risk of schizophrenia in China are consistent with the results in developed countries.

CONCLUSION

Urban birth and childhood trauma are associated with an increased risk of schizophrenia. Urban birth or childhood trauma may be involved in the onset of FES via a subsequent impact on cognition, which could possibly provide clues to the causal pathway of neurodevelopmental. This research could provide potential intervention targets, particularly in individuals born in urban areas or individuals who experienced childhood trauma, and strategies to promote cognitive development may give rise to protection from FES.

DATA AVAILABILITY

The data that provide the findings of this study are available from the corresponding author upon reasonable request.

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COMPETING INTERESTS

The authors declare no competing interests.

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