

IQ, the Urban Environment, and Their Impact on Future Schizophrenia Risk in Men

Timothea Touloupoulou^{*,1–4}, Marco Picchioni⁵, Preben Bo Mortensen⁶, and Liselotte Petersen⁶

¹Department of Psychology, Bilkent University, Ankara, Turkey; ²Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; ³Department of Psychology, The University of Hong Kong, Hong Kong SAR, China; ⁴The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong SAR, China; ⁵Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; ⁶National Centre for Register-based Research, Aarhus University, Aarhus V, Denmark

*To whom correspondence should be addressed; Department of Psychology, Bilkent University, Bilkent 06800, Ankara, Turkey; Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF, UK; tel: +44-(0)20-7848-0100, fax: +44-(0)20-7848-0287, e-mail: timothea.touloupoulou@kcl.ac.uk

Exposure to an urban environment during early life and low IQ are 2 well-established risk factors for schizophrenia. It is not known, however, how these factors might relate to one another. Data were pooled from the North Jutland regional draft board IQ assessments and the Danish Conscription Registry for men born between 1955 and 1993. Excluding those who were followed up for less than 1 year after the assessment yielded a final cohort of 153 170 men of whom 578 later developed a schizophrenia spectrum disorder. We found significant effects of having an urban birth, and also experiencing an increase in urbanicity before the age of 10 years, on adult schizophrenia risk. The effect of urban birth was independent of IQ. However, there was a significant interaction between childhood changes in urbanization in the first 10 years and IQ level on the future adult schizophrenia risk. In short, those subjects who moved to more or less urban areas before their 10th birthday lost the protective effect of IQ. When thinking about adult schizophrenia risk, the critical time window of childhood sensitivity to changes in urbanization seems to be linked to IQ. Given the prediction that by 2050, over 80% of the developed world's population will live in an urban environment, this represents a major future public health issue.

Key words: IQ/urban birth/urbanicity changes in childhood/population study/future schizophrenia risk

Introduction

The world's urban population is expected to double by 2050.¹ Given the well-established effects of urbanization on schizophrenia risk² with the incidence roughly double in city dwellers³ and evidence of a dose-response effect,⁴ that supports a causative relationship,⁴ urbanicity has significant clinical and public health implications. The urban

effect on schizophrenia is age dependent,⁴ is conditional on neighborhood ethnic composition,⁵ and is moderated by family history.⁶ The effect is robust and remains after all the main schizophrenia confounders, including migration, are considered (reviewed in Kelly et al³).

The age-linked effects of urbanicity, that may have their greatest impact to childhood and adolescence,⁴ leads to speculation that it may be adversely influencing the brain at one or more critical developmental stages.^{7,8} That abnormal early brain development may be relevant to the etiology of schizophrenia is a well-established hypothesis,⁹ though we do not yet understand the mechanism. We wanted to understand whether the disease effects of urban exposure were linked to cognition and specifically to IQ.

Urban exposure perhaps represents a proxy of multiple other risks or processes that are unknown or poorly understood but might include environmental (eg, pollution, noise), biological (eg, infections, vitamin D deficiency), psychological (eg, social defeat, being different, social stress processing), and sociological (eg, social fragmentation, minority status) candidates.¹⁰ New emerging evidence of the neurobiological impact of broadly sociological constructs has suggested that urban upbringing can influence brain morphology downstream,⁷ and neural social stress processing years later.⁸ To date, many of these investigations have tended to implicate emotional, rather than cognitive systems as mediators of the urban effect on the future schizophrenia risk; however, this may be an overly reductionist approach.

Early life deficits in IQ are one of the most consistent findings in schizophrenia research.¹¹ Although individuals' cognitive trajectories can differ,¹² results from prospective childhood and adolescent cohorts converge to suggest that both early deficits, and smaller developmental

gains,¹³ precede the disease. Qualitatively similar deficits are often found in patients' unaffected relatives indicating that transmission of disease vulnerability is expressed cognitively.^{14–16} Genetic modeling suggests shared genetic covariance between cognition and schizophrenia.^{17,18} Furthermore, statistical modeling confirms that these cognitive deficits represent an intermediate process in the disease pathophysiology with etiological and genetic implications.¹⁹ However, we still do not know if and how such deficits might interact with the early environment to influence future risk.

We used a population-based sample of Danish males to address 3 issues. Firstly, to index the role of urbanicity at birth, changes in the degree of urbanicity in childhood, and the effect of IQ on future schizophrenia risk. Urbanicity increases were defined as moving to an area with higher degree of urbanization (eg, moving from a provincial town to the capital) between birth and age 10 years; secondly, we aimed to assess the combined role of urbanicity and IQ on the future adult schizophrenia risk (mutually adjusted analyses); and, finally and uniquely, we aimed to quantify any modifying effect (interaction) between childhood urbanicity change and IQ on the future schizophrenia risk. We hypothesized separate roles for urbanicity, increases in urbanicity, and IQ on that risk. Further, we hypothesized that the impact of these effects would change when mutually adjusted for. Finally, we hypothesized that the relationship between urbanicity at birth and increases in urbanicity in early childhood would vary (interact) with IQ.

Methods

Study Population

The study was based solely on national and administrative registers and followed the relevant national regulations. Approval was provided by the Danish Data Protection Agency. Denmark is a small country with a relatively homogeneous population of 5.3 million. All Danish citizens have a unique personal identification number, which can be used to link information between registers. In this study, we linked each child to their legal parents through the Danish Civil Registration System,²⁰ a register which holds updated information on whether the subject is still alive and in the country. Those records were then linked with information from the Danish Psychiatric Central Register.²¹ That register contains data on all admissions to Danish psychiatric inpatient facilities, and, from 1995 also contains information on psychiatric outpatient appointments. Diagnostic codes used the Danish version of the International Classification of Diseases, 8th revision (ICD-8) in 1969–1993 and the International Classification of Diseases, 10th revision (ICD-10) thereafter. Schizophrenia spectrum disorder (SSD) was identified in cohort members, their parents, and siblings as a hospitalization or outpatient appointment at which a

diagnosis from the schizophrenia spectrum was applied (ICD-8 295.xx, 297.xx, 298.39, 301.83; ICD-10 F2x.xx). Information on parental education and occupation were obtained from the Statistics Denmark registers^{22,23}.

Until 2008 Denmark was divided into 276 municipalities, with each allocated to 1 of 5 hierarchical urbanization categories: capital, capital suburb, provincial city with more than 100 000 inhabitants, provincial town with between 100 000 and 10 000 inhabitants and rural, corresponding to 5220, 845, 470, 180, and 55 people per square kilometer.²⁴ Every subjects' place at birth was defined as the address listed on their birth record and extracted from the Danish Civil Registration System. Changes in urbanicity were identified from the Danish Civil Registration System and defined as either an increase or decrease in urbanization between each subject's birth address and their address aged 10 years. Interim moves were not considered. At the outset, we wanted to cover the whole period of childhood through adolescence to age 18. However, the municipalities' boundaries were redrawn during the time of interest forcing us to arbitrarily restrict changes in urbanicity as outlined above.

Data from draft board examinations on 35 947 men that were conducted in the North Jutland region between the years 1955 and 1984 were available. A second dataset the Danish Conscription Registry contained the results from draft board examinations conducted between the years 2006 and 2010 contained data on a further 140 507 men. The total pooled sample thus included data on 176 454 men who were born between 1955 and 1993. We then restricted the dataset to men born in Denmark, leaving a final cohort of 168 929 men. We "left truncated" the data for 1 year after the date of assessment and so excluded 15 759 men. These men were excluded as their IQ measurement could have been affected by developing psychosis (ie, reverse causality). Patients who were not picked up by in- or outpatient services were not considered. The final cohort included data on 153 170 individuals, of whom 578 were later diagnosed with any SSD (ICD-8 295.xx, 297.xx, 298.39, 301.83; ICD-10 F2x.xx).

Børge Priens

The Børge Priens (BP) test scores are available for all men in Denmark who attended the draft board examination since 1956. Between 10% and 15% of men over the years were exempt from the examination if they were already known to have a medical condition that disqualified them from military service, eg, intellectual disability, asthma, or extreme myopia. The BP test contains 4 subtests each of about 20 items (78 in total) indexing logical, verbal, numerical, and spatial reasoning respectively and is comparable to standard IQ assessments. It correlates 0.82 with full-scale WAIS IQ.^{25,26} The tests are timed and none involve multiple-choice responses. The effect of 1 SD on BP score corresponds to a difference of 10

correct answers. That then corresponds approximately to 15 points on a standard IQ scale centered on 100, with SD = 15.

Statistical Methods

Birth year was categorized into approximately equal sized groups by numbers of surviving subjects at time of draft board examination: 1960–1964, 1965–1969, 1970–1974, 1975–1979, 1980–1984, 1985–1986, 1987, 1988, 1989, 1990, 1991, 1992–1993. Year of assessment was categorized into approximately equal sized groups: 1970–1979, 1980–1989, 1990–1991, 1992–1993, 1994–1995, 1996–1997, 1998–1999, 2000–2003, 2004–2007, 2008–2010. Paternal age at subjects’ birth was categorized as <24, 25–29, 30–34, 35–39, 40–44, and above 45 years, and maternal age as <20, 20–24, 25–29, 30–34, and above 35 years. Highest parental education status when the participants were 18 years of age was categorized into basic, high school, vocational, medium length higher education, and long higher education for mothers and fathers separately. Parental occupation measured at draft board examination was categorized into unemployed, blue collar, self-employed, white collar, manager, and out of the labor market or retired for both parents separately. Second-generation migration status was categorized as follows: both parents Danish born, mother foreign born, father foreign born, or both foreign born.

Incidence rate ratios (IRRs) for schizophrenia were estimated using Cox regression in Stata 12 (Stata).

Analyses were broken down into 3 stages. In stage 1, the IRRs for IQ, urbanicity at birth, and urbanicity change between birth and the age of 10 adjusted for data collection period and birth cohort (period and birth cohort adjusted; [table 2](#)) were calculated. In stage 2, the IRRs for IQ and urbanicity at birth and urbanicity change were included in the same model (mutually adjusted; [table 2](#)); and then further adjusted for the potential confounders: parental age, parental education, parental occupation (social class), familial psychiatric history, and second-generation migrant status (fully adjusted; [table 2](#)). Finally, the main IRR effects of urbanicity at age 10 ([table 3](#)) and the interaction effects between IQ and change in urbanicity between birth and age 10 years ([table 3](#)) were calculated along with further post hoc analyses to test the same effects and interactions but distinctly for populations based on whether their IQ was above or below the mean ([tables 4 and 5](#)).

Results

Subjects’ mean age at draft board examination was 19.4 (SD = 1.0) range 17–32 years, and mean BP score was 41.7 (SD = 10.0). The distribution of participants across the 5 urbanization areas (capital, capital suburbs, provincial cities, provincial towns, and rural) for future patients and nonpatients is shown in [table 1](#). Of these 73.4% of future patients remained in their place of birth, 7.3% moved to a larger city and 19.4% to a smaller city. By comparison, 80.9% of nonpatients remained in their place of birth,

Table 1. Distribution of Exposure and Confounder Variables for Future Patients and Nonpatients

	Distribution in Future Patients, %	Distribution in Nonpatients, %
Exposure variables		
Urbanicity at birth		
Rural area	34.4	37.9
Provincial town	34.4	29.0
Provincial city	16.4	13.6
Capital suburb	5.4	10.6
Capital city	9.3	8.9
Urbanicity at age 10 y		
Larger city than at birth	7.3	5.7
No change from birth	73.4	80.9
Smaller city than at birth	19.4	13.5
Confounder variables		
Low paternal education	32.0	25.7
Low maternal education	50.4	46.9
Father out of work/outside workforce	26.6	14.4
Mother out of work/outside workforce	32.4	19.3
Paternal psychiatric history	4.5	1.3
Maternal psychiatric history	5.0	1.7
Second-generation migrant status		
Both parents Danish born	91.0	90.7
Father foreign born	3.6	3.4
Mother foreign born	3.8	2.9
Both parents foreign born	1.6	2.8
Paternal age at birth, mean years (SD)	30.8 (6.6)	30.9 (5.8)
Maternal age at birth, mean years (SD)	27.2 (5.5)	28.0 (4.8)

5.7% moved to a larger city, and 13.5% to a smaller city (table 1). One possible explanation for the observation that more families are moving to smaller cities is that when children are born into a family, families move to larger premises but in less urban areas. Thirty-two percentage of fathers and 50.4% of mothers of patients with a future SSD had only basic education compared to 25.7% of fathers and 46.9% of mothers for nonpatients (table 1). More future patients had parents outside work (patients: 26.6% of fathers and 32.4% of mothers; nonpatients: 14.4% of fathers and 19.3% of mothers; table 1), and with psychiatric history (patients: 4.5% of fathers and 5.0% of mothers; nonpatients: 1.3% of fathers and 1.7% of mothers of nonpatients; table 1). Mean paternal and maternal age was similar for both future patients and nonpatients (table 1).

Table 2 shows the IRRs of schizophrenia in the study population. IRR estimates are statistically significant unless the CIs include 1. Being born in the capital (IRR: 1.69 [1.20–2.38]) and experiencing an increase in urbanicity before the age of 10 years (IRR: 1.45 [1.05–2.01]) had significant effects on the adult schizophrenia risk. The effect for the latter was statistically insignificant when we adjusted for the confounders in the model (IRR: 1.33 [0.96–1.85]). Each SD increase in IQ was associated with a reduced future risk of schizophrenia (IRR: 0.68 [0.63–0.73]). The estimates changed very little after IQ and the urbanicity measures were included in the same model (IRR: 0.67 [0.62–0.73]) or after the confounders were also adjusted for (IRR: 0.73 [0.67–0.80]).

There was no statistically significant interaction between urbanicity at birth and IQ ($P = .94$) on future schizophrenia risk but there was between changes in urbanicity between birth and age 10 years and IQ ($P = .03$). The IQ effects according to urbanicity at age 10 years are shown in table 3. Overall, the protective effect of higher IQ becomes nonsignificant with any change in urbanicity by age 10.

It is not uncommon in intelligence research to explore whether the nature of any relationship are the same across the full IQ range. Different patterns, if they exist, could be detected across thresholds. We did further post hoc analyses by separating the population on the basis of their IQ into groups above and below the mean. We hypothesized that we would discover that those with higher IQ would prove more resilient indicated by a less steep increase in risk compared to those with IQ below the mean, following any change in urbanization before the age of 10 years. These IQ effects are presented separately in tables 4 and 5 and figure 1. We found that for those with lower IQ, the risk of schizophrenia decreased with increasing IQ (adjusted IRR = 0.59), while the beneficial effect of higher IQ was insignificant for those subjects who moved to a larger city (adjusted IRR = 1.51).

Discussion

Despite the robust evidence of an association between early exposure to an urban environment and IQ independently and schizophrenia, the relationship between them on the adult schizophrenia risk has never been explored before. We addressed prospectively both the effect of childhood urban exposure and the effect of IQ at military conscription on future schizophrenia risk, but also the interplay between these 2 factors and that risk. We found that urban birth and lower IQ were both associated with higher schizophrenia risk, that their contributions were independent of each other, but that changes in urbanicity during childhood interact with IQ to influence the future risk. The last finding points towards factors potentially operating on brain development that overwhelm the protective role of IQ, for some individuals, following urbanicity changes.

Urban birth accounts for a significant proportion of the population risk for schizophrenia. Given the percentage of the population that is currently born in urban

Table 2. IRRs of Schizophrenia in Danish Men

Exposure Variables	Number of Cases	Period and Birth Cohort Adjusted	Mutually Adjusted	Fully Adjusted
IQ score at draft board per SD		0.68 (0.63–0.73)	0.67 (0.62–0.73)	0.73 (0.67–0.80)
Urbanicity at birth				
Rural area	199	1 (ref.)	1 (ref.)	1 (ref.)
Provincial town	199	1.25 (1.02–1.54)	1.27 (1.03–1.57)	1.26 (1.02–1.55)
Provincial city	95	1.15 (0.89–1.50)	1.21 (0.94–1.57)	1.19 (0.91–1.55)
Capital suburb	31	0.92 (0.62–1.36)	0.95 (0.64–1.41)	0.92 (0.62–1.38)
Capital city	54	1.69 (1.20–2.38)	1.80 (1.28–2.54)	1.77 (1.25–2.51)
Urbanicity at age 10 y				
Larger city than at birth	42	1.45 (1.05–2.01)	1.46 (1.06–2.02)	1.33 (0.96–1.85)
No change from birth	424	1 (ref.)	1 (ref.)	1 (ref.)
Smaller city than at birth	112	1.22 (0.96–1.54)	1.22 (0.97–1.54)	1.17 (0.92–1.47)

Note: IRRs with CIs in brackets; IRR estimates are statistically significant unless 1 is present within the CIs. Period and birth cohort adjusted: analyses include either IQ or all 3 urbanicity measures and are adjusted for period and birth cohort; mutually adjusted: IQ and the urbanicity measures are included in the same model; fully adjusted: further adjusted for parental age, parental education, parental occupation (social class), familial psychiatric history, and second-generation migrant status. IRR, incidence rate ratio.

Table 3. Effect of Change in Urbanicity Between Birth and Age 10 y on the IRRs for Schizophrenia Corresponding to Mean IQ and the IQ Effect According to Change in Urbanicity Between Subjects' Birth and Age 10 y (Mutually and Fully Adjusted)

	IRR (CIs)
Urbanicity change between birth and 10 y corresponding to mean IQ	
Larger city than at birth	1.41 (1.01–1.99)
No change from birth	1 (ref.)
Smaller city than at birth	1.24 (0.98–1.58)
IQ according to change in urbanicity from birth to age 10 y	
Larger city than at birth	0.82 (0.62–1.09)
No change from birth	0.69 (0.63–0.76)
Smaller city than at birth	0.87 (0.73–1.04)

Note: IRRs represent the change in risk estimated for each SD increase in IQ (slope). IRR estimates are statistically significant unless they included 1 in the CIs. IRR, incidence rate ratio.

Table 4. Effect of Change in Urbanicity Between Birth and Age 10 y on IRRs Corresponding to Mean IQ

Urbanicity Change Between Birth and Age 10 y Corresponding to Mean IQ	IRR (CIs)
Larger city than at birth	1.05 (0.59–1.86)
No change from birth	1 (ref.)
Smaller city than at birth	1.54 (1.08–2.22)

Note: The IRR estimates are statistically significant unless 1 is within the CIs. IRR, incidence rate ratio.

Table 5. IQ Effect According to Change in Urbanicity Between Birth and 10 y Separately for IQ Below or Above the Mean (Mutually and Fully Adjusted) in Danish Men

IQ According to Urbanicity Change Between Birth and Age 10 y, Separated for Subjects With IQ Above and Below the Mean	IRR (CIs) for Low IQ	IRR (CIs) for High IQ
Larger city than at birth	0.59 (0.39–0.88)	1.51 (0.81–2.82)
No change from birth	0.63 (0.55–0.72)	0.86 (0.68–1.10)
Smaller city than at birth	0.96 (0.70–1.31)	0.75 (0.49–1.16)

Note: IRRs represent the change in risk estimated for each SD increase in IQ (slopes). IRR estimates are statistically significant unless 1 is within the CIs. IRR, incidence rate ratio.

environments, and the projected increases, it represents a huge modifiable risk factor if we can understand the nature of this association better. We found that urban birth contributes significantly to adult schizophrenia risk and that this effect is independent of parental age, parental education, parental occupation, family psychiatric history, and second-generation migrant status. The risk was not explained by IQ, suggesting that the effect of urban birth on future schizophrenia risk is not linked to IQ. The

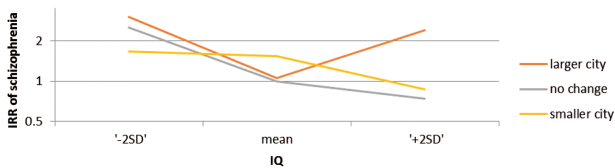


Fig. 1. The IQ effect according to change in urbanicity from birth to age 10 y. IRRs from tables 4 and 5. Gray line goes through IRR = 1 for mean IQ. At +1 SD, the same line goes through IRR = 0.86. Similarly, for red line, IRR = 1.05 at mean IQ. Red line plotted IRR = 1.05 + 1.51 * IQ (SD). IRR, incidence rate ratio.

results were similar for the combined role of urbanicity increases and IQ on the future adult schizophrenia risk. Apart from cognition, another possible mechanism is a social-affective process, mediating the effect of urban birth on the future risk. In line with that hypothesis, childhood urban exposure differentially impacts years later on adult brain systems specifically engaged in social stress, while sparing those supporting cognition.⁸

It may be that childhood urban exposure can accentuate being or feeling different, or standing out, which can then lead to discrimination, marginalization, and social defeat.²⁷ This could then further lead to alterations in, among others, the ability to represent the mental states of others,²⁷ cognitive biases (eg, in reasoning), and salience misattribution, all implicated separately in the genesis and expression of psychosis. A number of models have been proposed that link the biological disturbances that may underlie some of these processes to psychotic experiences. For example, it may be that the assignment of aberrant salience to irrelevant stimuli is a principle mechanism that drives psychosis.^{28,29} According to the theory, the dopamine system, which mediates motivational or incentive salience, is dysregulated in schizophrenia leading to context inappropriate firing and dopamine excess.³⁰ This hyperdopaminergic state contributes to a sense of perceptual awareness that compels the individual to perceive personal significance and attach meaning where none exists, so laying the foundations for delusions. The theory draws from the “incentive salience” hypothesis that was originally used to explain drug addiction.^{31,32} According to that hypothesis, striatal dopamine neurons fire when the expected outcome exceeds that predicted.³³ Thus, dopamine is released when an organism perceives an error in reward prediction. Over time conditioned cues that predict reward elicit the same dopamine response and so the conditioned stimuli acquires positive valence, commanding attention and driving future behavior.³⁴ Several studies have reported an increase in motor speed and/or hemodynamic response, reflecting adaptive or motivational salience, following presentation of conditioned stimuli that are repeatedly associated with reward relative to the presentation of stimuli that do not predict reward.³⁵ This effect is disrupted in schizophrenia and there is evidence

of aberrant activations and responses to nonreward predicting stimuli suggesting that in patients with schizophrenia, abnormally motivational salience to neutral cues develops.^{31,32} Thus, while dopamine in health mediates salience to conditioned cues, in psychosis dopamine dysregulation, possibly secondary to urbanicity stressors like social defeat (eg, children who are born to an urban environment, or who move to a more urban environment in early childhood may experience more adversity, parental divorce, and abuse making them more likely to stand out in their social context), promotes aberrant salience by misassigning incentive salience to irrelevant cues, and thus possibly contributing to hallucinations and delusions.

Cognitive deficits, such as lower IQ, are robustly documented in schizophrenia, predict outcome, and represent targets for treatment.³⁶ Indeed novel statistical modeling has recently suggested that cognitive deficits are an intermediate stage in the pathogenic mechanism linking genes to schizophrenia liability, with about a quarter of the variation in liability accounted for by variation in cognition.¹⁹ That work predicted that some genetic loci for schizophrenia will actually have a greater effect on cognition than on brain structure, providing further support for the concept that cognitive deficits are a core feature of schizophrenia. Here, we found that lower IQ at assessment predicted greater future risk for schizophrenia. That finding is in line with previous work, but the relationship between IQ and childhood changes in urbanicity and the future risk of schizophrenia is novel. Specifically, we found that the protective role of IQ becomes nonsignificant with any changes in urbanicity before the age of 10 years (IRRs: 0.82 [0.62–1.09] and 0.87 [0.73–1.04]; [table 3](#)). We do not know if this finding relates to loss of emotional ties, to social adjustment, or some other process.

By conducting post hoc analyses of the data, we found that moving to a more urban environment before the age of 10 differentially influenced future schizophrenia risk according to the level of adult IQ. Thus, we found that for those with lower IQ, the risk of schizophrenia decreased with increasing IQ (adjusted IRR = 0.59), while the beneficial effect of higher IQ, contrary to our expectations, was insignificant for all subjects including those who moved to a larger (adjusted IRR = 1.51) and smaller (adjusted IRR = 0.75) city before the age of 10 years. This divergence of risk based on IQ was only seen in the context of changes in childhood urbanicity, not urbanicity at birth per se. Thus, based on the precise index of urbanicity used in this study, both separate contributions to risk and interactions between IQ and urbanicity are observed, some of which highlighted loss of the protective IQ effect on risk. We do not know why moving should result in loss of the protective role of IQ in those children with highest IQ. The underlying biological impact of this loss in protection, for example, in terms of emotion regulation, stress sensitivity reduction is very unclear; however, by

improving our understanding of these processes, we will gain new insights into the pathophysiology of the vulnerability to psychosis and the first episode in particular.

In this study, urbanicity change indexed an increase or decrease in the level of urban exposure during a potentially critical phase of brain development between birth and the age of 10. The environmental influences on brain circuit maturation are poorly understood but animal work implies plasticity that can be influenced by environmental stressors.³⁷ In humans, it may be that the peak time of onset of schizophrenia in early adulthood coincides with a time of normal maturation of emotional and cognitive systems, principally in the frontal lobes, some of which lie downstream of other more basic processes that mature earlier. It is likely that our temporal window of urbanicity change captured the impact of urban exposure on a developmentally earlier point in the process.

Strengths of the study include the novelty of the question and that is addressed in a population cohort. The study should be interpreted in light of its limitations. Firstly, we focused on an exclusively male sample, and the extent to which these results can be generalized to females and other populations with different allelic frequencies, environmental exposures, and educational experiences should be born in mind. Secondly, men with an intellectual disability, IQ < 70, were exempted from the draft examination and from military service and thus were not included in this study. While it is normal practice to exclude subjects with intellectual disability from studies on schizophrenia, this could still represent a source of selection bias. Thirdly, the data are restricted to the measures (eg, IQ), timeframe, and the definitions of urbanicity that were available to us from the respective registers. The results could be quite different if any of these factors varied. Perhaps most critically, given our central hypothesis, was the timing of the sampling window for changes in urbanization. For example, if that window failed to correctly capture the developmentally critical periods of childhood and adolescence that are sensitive to that stressor, or where other linked stressors might be active such as drug use in early/mid adolescence, or heightened developmental maturation, for example, of executive functions in later adolescence and early adulthood, then the impact of urbanization could yield different, perhaps even more extreme results. Prospective studies that incorporate these contemporaneous measures and broader time sampling will be crucial. Prospective studies that incorporate contemporaneous measures will be crucial. Fourthly, this is an epidemiological study and so cannot address mechanistic questions. Its results though can be used to inform future experimental studies. Fifthly, we assumed that IQ is a reasonably stable personal trait and that IQ at the age of 18 reflects similar levels of IQ earlier in life. Most studies confirm that this assumption is correct in healthy subjects, but we cannot access this directly in our sample. Many patients with schizophrenia experience a deterioration in IQ from premorbid levels.

To sum up, throughout development, a person's exposure to environmental stressors can influence their future risk for schizophrenia, possibly by altering the trajectory of the developing systems at the time of the exposure.³⁸ Childhood may be a period of heightened sensitivity to certain environmental stressors, like urbanicity. Although the links between urbanicity and cognition with schizophrenia are robust, little is known about the relationship between the 2. The study points towards other mechanisms beyond cognition, possibly emotional, that mediate the impact of urbanicity on schizophrenia risk. It also suggests that when urbanicity changes in early life, the relationship with IQ becomes more complex.

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. UN, DESA. *World Urbanization Prospects, the 2011 Revision: Highlights*. New York, NY: UN, DESA; 2012.
2. Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM. Meta-analysis of the association of urbanicity with schizophrenia. *Schizophr Bull*. 2012;38:1118–1123.
3. Kelly BD, O'Callaghan E, Waddington JL, et al. Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. *Schizophr Res*. 2010;116:75–89.
4. Pedersen CB, Mortensen PB. Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. *Arch Gen Psychiatry*. 2001;58:1039–1046.
5. Boydell J, van Os J, McKenzie K, et al. Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. *BMJ*. 2001;323:1336–1338.
6. van Os J, Rutten BPF, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia Bull*. 2008;34:1066–1082.
7. Haddad L, Schafer A, Streit F, et al. Brain structure correlates of urban upbringing, an environmental risk factor for schizophrenia. *Schizophr Bull*. 2015;41:115–122.
8. Lederbogen F, Kirsch P, Haddad L, et al. City living and urban upbringing affect neural social stress processing in humans. *Nature*. 2011;474:498–501.
9. Weinberger DR, Levitt P. Neurodevelopmental origins of schizophrenia. In: Weinberger DR, Harrison PJ, eds. *Schizophrenia*. 3rd ed. Chichester, UK: Wiley-Blackwell; 2011:393–412.
10. Zammit S, Lewis G, Rasbash J, Dalman C, Gustafsson JE, Allebeck P. Individuals, schools, and neighborhood: a multi-level longitudinal study of variation in incidence of psychotic disorders. *Arch Gen Psychiatry*. 2010;67:914–922.
11. Seidman LJ, Cherkertzian S, Goldstein JM, Agnew-Blais J, Tsuang MT, Buka SL. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England Family Studies. *Psychol Med*. 2013;43:119–131.
12. Reichenberg A, Caspi A, Harrington H, et al. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. *Am J Psychiatry*. 2010;167:160–169.
13. MacCabe JH, Wicks S, Löfving S, et al. Decline in cognitive performance between ages 13 and 18 years and the risk for psychosis in adulthood: a Swedish longitudinal cohort study in males. *JAMA Psychiatry*. 2013;70:261–270.
14. Mark W, Touloupoulou T. Cognitive intermediate phenotype and genetic risk for psychosis. *Curr Opin Neurobiol*. 2016;36:23–30.
15. Touloupoulou T, Mapua-Filbey F, Quraishi S, et al. Cognitive performance in presumed obligate carriers for psychosis. *Br J Psychiatry*. 2005;187:284–285.
16. Zhang R, Picchioni M, Allen P, Touloupoulou T. Working memory in unaffected relatives of patients with schizophrenia: a meta-analysis of functional magnetic resonance imaging studies. *Schizophr Bull*. 2016;42:1068–1077.
17. Touloupoulou T, Goldberg TE, Mesa IR, et al. Impaired intellect and memory: a missing link between genetic risk and schizophrenia? *Arch Gen Psychiatry*. 2010;67:905–913.
18. Touloupoulou T, Picchioni M, Rijdsdijk F, et al. Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. *Arch Gen Psychiatry*. 2007;64:1348–1355.
19. Touloupoulou T, van Haren N, Zhang X, et al. Reciprocal causation models of cognitive vs volumetric cerebral intermediate phenotypes for schizophrenia in a pan-European twin cohort. *Mol Psychiatry*. 2015;20:1386–1396.
20. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39:22–25.
21. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39:54–57.
22. Jensen VM, Rasmussen AW. Danish Education Registers. *Scand J Public Health*. 2011;39:91–94.
23. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health*. 2011;39:95–98.
24. Statistics Denmark. *Befolkningen i Kommunerne*. Copenhagen, Denmark: Statistics Denmark; 1997.
25. Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM. The association between duration of breastfeeding and adult intelligence. *JAMA*. 2002;287:2365–2371.
26. Teasdale TW, Hartmann PV, Pedersen CH, Bertelsen M. The reliability and validity of the Danish Draft Board Cognitive Ability Test: Børge Prien's Prøve. *Scand J Psychol*. 2011;52:126–130.
27. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature*. 2010;468:203–212.
28. Roiser JP, Stephan KE, den Ouden HEM, Barnes TRE, Friston KJ, Joyce EM. Do patients with schizophrenia exhibit aberrant salience? *Psychol Med*. 2009;39:199–209.
29. Miller R. Striatal dopamine in reward and attention: a system for understanding the symptomatology of acute schizophrenia and mania. *Int Rev Neurobiol*. 1993;35:161–278.
30. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res*. 2005;79:59–68.
31. Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. *Schizophr Bull*. 2010;36:472–485.
32. Pankow A, Knobel A, Voss M, Heinz A. Neurobiological correlates of delusion: beyond the salience attribution hypothesis. *Neuropsychobiology*. 2012;66:33–43.
33. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275:1593–1599.

34. Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)*. 2007;191:391–431.
35. Roiser JP, Stephan KE, den Ouden HE, Friston KJ, Joyce EM. Adaptive and aberrant reward prediction signals in the human brain. *Neuroimage*. 2010;50:657–664.
36. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468:187–193.
37. Spinelli S, Chefer S, Suomi SJ, Higley JD, Barr CS, Stein E. Early-life stress induces long-term morphologic changes in primate brain. *Arch Gen Psychiatry*. 2009;66:658–665.
38. Hoftman GD, Lewis DA. Postnatal developmental trajectories of neural circuits in the primate prefrontal cortex: identifying sensitive periods for vulnerability to schizophrenia. *Schizophr Bull*. 2011;37:493–503.