

Evidence of a Dose-Response Relationship Between Urbanicity During Upbringing and Schizophrenia Risk

Carsten Bøcker Pedersen, MSc; Preben Bo Mortensen, DMSc

Background: Many studies have demonstrated that an urban birth or upbringing increases schizophrenia risk, but no studies have been able to distinguish between these effects. The objectives of this study were to discriminate the effect of urbanicity at birth from an effect of urbanicity during upbringing, and to identify particularly vulnerable age periods and a possible dose-response relationship between urbanicity during upbringing and schizophrenia risk.

Methods: Using data from the Danish Civil Registration System, we established a population-based cohort of 1.89 million people, which included information on place of birth, place of residence during upbringing, and the accumulated number of years lived in each category of the 5-level degree of urbanization during upbringing. Schizophrenia in cohort members and mental illness in a parent or sibling were identified by linkage with the Danish Psychiatric Central Register.

Results: Individuals living in a higher degree of urbanization than 5 years earlier had a 1.40-fold (95% confidence interval, 1.28-1.51) increased risk, while individuals living in a lower degree of urbanization than 5 years earlier had a 0.82-fold (95% confidence interval, 0.77-0.88) decreased risk of schizophrenia. For fixed urbanicity at the 15th birthday, risk increased with increasing degree of urbanization at birth. Furthermore, the more years lived in the higher the degree of urbanization, the greater the risk. Individuals who lived their first 15 years in the highest category of the 5-level urbanicity had a 2.75-fold (95% confidence interval, 2.31-3.28) increased risk of schizophrenia.

Conclusion: Continuous, or repeated, exposures during upbringing that occur more frequently in urbanized areas may be responsible for the association between urbanization and schizophrenia risk.

Arch Gen Psychiatry. 2001;58:1039-1046

ALTHOUGH A family history of schizophrenia is the best established risk factor for the disease,¹ it may account for only a small proportion of the population occurrence of schizophrenia.^{2,3} Other factors, such as urbanicity at birth and upbringing, are associated with an increased risk also,²⁻⁴ and causal factors underlying this association may account for a much higher proportion of the population occurrence of the disease. Although the causes of these urban-rural differences are unknown, they have been hypothesized to include, eg, obstetric complications, infections, diet, toxic exposures, household crowding, breastfeeding, social class, and an artifact due to migration.^{5,6}

To reduce the number of possible candidates responsible for this association, the objective of this study was to investigate at what age during upbringing (including birth) children were most vulnerable to urbanicity. However, since ur-

banicity at birth and urbanicity during upbringing are strongly associated, a large study population, including information on place of birth and upbringing, is needed to discriminate the effect of urbanicity at birth from an effect of urbanicity during upbringing, and vice versa.⁷ To our knowledge, studies based on such data have not been published previously. This study uses a large population-based sample of the Danish population, including complete information on all permanent addresses at which cohort members had lived since 1971, to investigate the relative impact of urbanicity at birth and during upbringing. Furthermore, the hypothesis that there is a dose-response relationship between urbanicity during upbringing and schizophrenia risk is investigated.

RESULTS

A total of 8235 persons developed schizophrenia during the 27.1 million person-years of follow-up (**Table 1**). Urbanicity

From the Department of Psychiatric Demography, Institute for Basic Psychiatric Research, Aarhus University Hospital, Risskov, and the National Centre for Register-Based Research, Aarhus University, Aarhus C, Denmark.

PARTICIPANTS AND METHODS

STUDY POPULATION

We used data from the Danish Civil Registration System⁸ to obtain a large and representative set of data on Danish persons, which for all persons included current and historical information on address in Denmark and Greenland and emigrations and immigrations to and from other countries, together with exact dates for changes of residence. All citizens in Denmark are obliged to inform the authorities about any change of permanent address within 5 days. Failure to supply this information will result in the inability to receive a supplementary benefit (eg, unemployment, sickness or disablement benefits, and educational aid from public funds), to go to a day nursery, to go to nursery school, to attend primary and lower secondary school, to obtain free national health care, and to obtain a tax deduction card (required to have paid work). Therefore, it is unlikely that this mandatory information is not reported. This information is complete from January 1, 1971. Our study cohort consists of all persons with known maternal identity who were born in Denmark between January 1, 1956, and December 31, 1983, and who were alive at the 15th birthday (1.89 million persons).

ASSESSMENT OF SCHIZOPHRENIA AND MENTAL ILLNESS IN A PARENT OR SIBLING

The study population and their mothers, fathers, and siblings were linked with the Danish Psychiatric Central Register,⁹ which has been computerized since April 1, 1969. The Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric inpatient facilities and includes data on approximately 450 000 persons and 1.6

million admissions. From 1995 onward, information on outpatient visits to psychiatric departments was included in the register. There are no private psychiatric departments in Denmark. From April 1, 1969, to December 31, 1993, the diagnostic system used was the *International Classification of Diseases, 8th Revision (ICD-8)*,¹⁰ and from January 1, 1994, the diagnostic system used was the *International Classification of Diseases, 10th Revision (ICD-10)*.¹¹ Cohort members were classified as having schizophrenia if they had been admitted to a psychiatric hospital or had been in outpatient care with a diagnosis of the disorder (*ICD-8* code 295 or *ICD-10* code F20). The date of onset was defined as the first day of the first contact (inpatient or outpatient) with a diagnosis of schizophrenia. Parents and siblings were categorized hierarchically with a history of schizophrenia (*ICD-8* code 295 or *ICD-10* code F20), schizophrenialike psychoses (*ICD-8* code 297, 298.39, or 301.83 or *ICD-10* codes F21-F29), or other mental disorders (any *ICD-8* or *ICD-10* diagnosis) if they had been admitted to a psychiatric hospital or had been in outpatient care with one of these diagnoses.

ASSESSMENT OF DEGREE OF URBANIZATION

The 276 municipalities in Denmark were classified according to the degree of urbanization¹²: capital, capital suburb, provincial city with more than 100 000 inhabitants, provincial town with more than 10 000 inhabitants, or rural areas. Denmark is a small homogeneous country with a population of 5.3 million people and a total area of 43 000 km². The capital, capital suburb, provincial city, provincial town, and rural area hold 5220, 845, 470, 180, and 55 people per square kilometer, respectively.¹³ Distances are small in Denmark; most people live within 25 km of a city with more than 30 000 inhabitants, and are even closer to a psychiatric hospital.

at birth is known for all persons, whereas information on urbanicity at a given age depends on the year of birth, as information on place of residence was accessible only from 1971 onward.

CHANGE OF RESIDENCE

The relative risk of schizophrenia increases with increasing age at change of the address or the municipality (**Figure 1**). However, change of address within the same municipality had no influence on schizophrenia risk. Furthermore, the effect of changes of the municipality within the same degree of urbanization increased with increasing age (data not shown). Therefore, the confounding effect of change of residence can be described by changes of the municipality.

We classified change of municipality by 4 variables, counting the number of changes of the municipality from birth to the 5th birthday, from the 5th to the 10th birthday, from the 10th to the 13th birthday, and from the 13th to the 15th birthday (**Table 2**). Compared with persons with no changes of the municipality from the 5th to the 10th birthday, those with one change of the municipality had a relative risk of 1.18. The effect of the number of changes of municipality increased with

increasing age and increasing number of changes. Overall, these 4 variables had a significant effect ($P < .001$), and the model with these 4 variables had a significantly better fit than the model in which the change of municipality was described in 1-year bands (**Figure 1**).

URBANICITY IN 1-YEAR AGE POINTS

Individuals who at birth lived in the capital, the capital suburb, the provincial city, or the provincial town had a relative risk of schizophrenia of 2.24 (95% confidence interval [CI], 1.92-2.61), 1.71 (95% CI, 1.46-2.00), 1.62 (95% CI, 1.36-1.92), and 1.27 (95% CI, 1.10-1.47), respectively, compared with individuals who lived in the rural area (**Figure 2**). This difference remained almost constant for ages from birth to the 15th birthday.

RELATIVE URBANICITY AT SUCCESSIVE AGES

Among those who were born in the capital suburb, those who at the 5th birthday lived in a higher, the same, or a lower degree of urbanization than at birth had a relative risk of schizophrenia of 2.01, 1.82, or 1.55, respectively (**Table 3**, first adjustment), compared with those who at birth and at the 5th birthday lived in the rural area. In

STUDY DESIGN

Using data from the Danish Civil Registration System, for each person in the cohort we obtained information on (1) the degree of urbanization in 1-year age points from birth to the 15th birthday; (2) the number of changes of the address, the municipality, and the degree of urbanization in 1-year age bands from birth to the 15th birthday; and (3) the accumulated number of years each person born in 1971 or later had been living in each degree of urbanization from birth to the 5th birthday, from the 5th to the 10th birthday, and from the 10th to the 15th birthday. The reason we considered change of residence was that initial analyses suggested that to investigate the association between schizophrenia and urbanization we had to control for an increased risk associated with change of residence. Furthermore, to avoid the potential impact of selective migration to cities in the prodromal phase of schizophrenia, only residence during upbringing was considered. By upbringing, we are referring to the period from birth to the 15th birthday. Information on urbanicity at birth, urbanicity during upbringing, and change of residence is independent of the disease status. A total of 1.89 million persons were followed up from their 15th birthday or from April 1, 1970, whichever came later, until the date of onset of schizophrenia, the date of death, the date of emigration, or December 31, 1998, whichever came first.

STATISTICAL ANALYSES

The relative risk of schizophrenia was estimated by log-linear Poisson regression¹⁴ with the GENMOD procedure, using SAS statistical software, version 6.12.¹⁵ All relative risks were adjusted for age and its interaction with sex, calendar year, and history of mental illness in a parent or sibling. Age, calendar year, and history of mental illness in siblings were treated as time-dependent variables,¹⁶ whereas history of

mental illness in a parent was treated as a variable that was independent of time. Age was categorized using the following cut points: 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 35, and 40 years. Calendar year was categorized using the following cut points: 1971, 1976, 1979, 1982, 1985, 1988, 1991, 1993, 1994, 1995, 1996, 1997, and 1998. *P* values were based on findings from the likelihood ratio tests, and 95% confidence limits were calculated by the Wald test.¹⁶ The adjusted-score test¹⁷ suggested that the regression models were not subject to overdispersion. Apart from the reduction in the size of the study population, omission of adjustment for seasonality, maternal and paternal age, and the inclusion of information on permanent address for all cohort members since 1971, the material described is identical to that used in our previous study,³ where we found that the effects of urbanicity at birth and mental illness in a family member were invariant to the diagnostic system and the inclusion of outpatient information.

To evaluate the hypothesis that there is a dose-response relationship between urbanicity during upbringing and schizophrenia risk, we used a statistical model for the accumulated number of years each person had been living in the capital, the capital suburb, the provincial city, and the provincial town. It implies that those who always lived in the rural area during upbringing were chosen as the reference category, and that the effect of these 4 variables measures the effect of exchanging upbringing in the rural area with upbringing in the corresponding degree of urbanization.

By urbanicity at some age point, we refer only to the degree of urbanization at the given age point, whereas by urbanicity during upbringing, we refer to the full sequence of degrees of urbanization of places of residence from birth to the 15th birthday. Furthermore, by a model for urbanicity during upbringing, we refer to a model for the accumulated number of years each person has lived in the capital, the capital suburb, the provincial city, and the provincial town during upbringing.

general, living in a higher degree of urbanization at the 5th birthday than at birth increased risk, while living in a lower degree of urbanization at the 5th birthday than at birth decreased risk. This tendency was not modified by adjustment for change of the municipality (Table 3, second adjustment).

Living in a higher or lower degree of urbanization at the 10th birthday than at the 5th birthday increased risk, but risk was increased more if living in a higher than in a lower degree of urbanization (Table 3, first adjustment). When these estimates were adjusted for the number of changes of the municipality, living in a higher degree of urbanization at the 10th birthday than at the 5th birthday increased risk, while living in a lower degree of urbanization at the 10th birthday than at the 5th birthday decreased risk (Table 3, second adjustment). The same tendency was found when comparing place of residence at the 10th birthday with place of residence at the 15th birthday. Overall, living in a higher degree of urbanization than 5 years earlier increased risk 1.40-fold (95% CI, 1.28-1.51), while living in a lower degree of urbanization than 5 years earlier decreased risk 0.82-fold (95% CI, 0.77-0.88). Furthermore, for fixed urbanicity at birth, risk increases with increasing degree of urbanization at place of residence at the 15th birthday, and for fixed ur-

banicity at the 15th birthday, risk increases with increasing degree of urbanization at place of birth (data not shown).

URBANICITY DURING UPBRINGING

A total of 807 000 people in the cohort were born in 1971 or later and, therefore, these people had accessible information on urbanicity during upbringing. Among them, 1553 persons developed schizophrenia during the 5.6 million person-years at risk (**Table 4**). Compared with those who had always been living in the rural area, those who had always been living in the capital had a relative risk of 2.62. In general, the more years lived in the higher the degree of urbanization, the greater the risk of schizophrenia.

Estimates in the second column of **Table 5** measure the risk per year associated with exchanging residence in the rural area with residence in each degree of urbanization, and estimates in the third column measure the risk associated with exchanging all residence (15 years) in the rural area with residence in each degree of urbanization. The relative risk per 15 years is calculated by raising the relative risk per year to the 15th power, eg, $1.0697^{15} = 2.75$. Compared with those who had al-

Table 1. Distribution of 8235 Cases of Schizophrenia and 27.1 Million Person-years at Risk in a Population-Based Cohort of 1.89 Million Danish People

Variable	No. of Cases	Person-years
Total	8235	27 115 224
Sex		
Male	5462	14 150 781
Female	2773	12 964 444
History		
Maternal		
Schizophrenia	234	86 524
Schizophrenialike psychoses	257	196 298
Other mental disorders	1323	2 067 383
Mother not affected	6421	24 765 019
Paternal		
Schizophrenia	98	45 980
Schizophrenialike psychoses	106	96 483
Other mental disorders	888	1 573 112
Unknown father	640	990 119
Father not affected	6503	24 409 531
Siblings		
Schizophrenia	284	105 515
Schizophrenialike psychoses	115	80 535
Other mental disorders	546	705 134
No affected siblings	7290	26 224 040
Urbanicity		
At birth		
Capital	2594	5 008 126
Capital suburb	793	2 328 013
Provincial city	1073	3 451 055
Provincial town	2375	9 405 666
Rural area	1400	6 922 365
At the 5th birthday		
Capital	559	940 862
Capital suburb	635	1 720 492
Provincial city	449	1 239 834
Provincial town	836	3 220 339
Rural area	822	4 114 556
Other countries	29	80 010
Unknown	6	7909
Unaccessible information	4893	15 775 738
At the 10th birthday		
Capital	913	1 427 445
Capital suburb	1139	2 915 199
Provincial city	660	1 988 951
Provincial town	1416	5 369 404
Rural area	1602	7 224 640
Other countries	47	131 801
Unknown	10	18 555
Unaccessible information	2448	8 039 228
At the 15th birthday		
Capital	1240	2 011 689
Capital suburb	1559	4 017 883
Provincial city	896	2 760 442
Provincial town	2020	7 629 875
Rural area	2453	10 547 958
Other countries	57	126 824
Unknown	10	20 553

ways been living in the rural area during upbringing, those who had always been living in the capital during upbringing had a relative risk of 2.75. According to this model, a person who had been living 7 years in the capital and 8 years in the capital suburb during upbringing had a relative risk of 2.12 ($1.0697^7 \times 1.0355^8$) com-

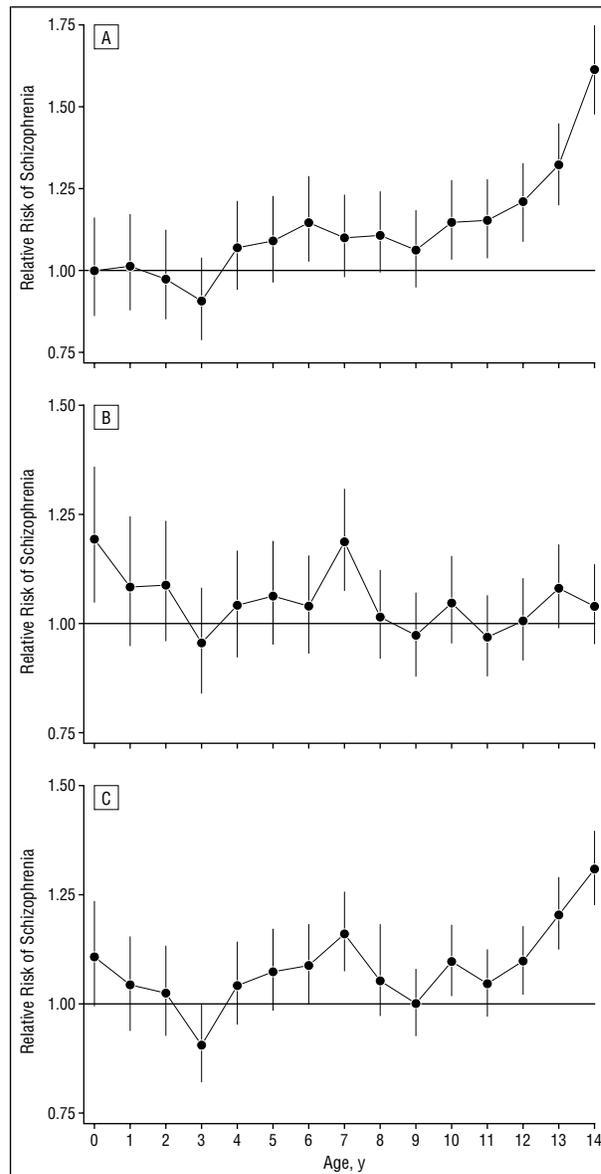


Figure 1. Relative risk of schizophrenia associated with age and change of the municipality (A), the address within the same municipality (B), and the address (C). Those without change of the municipality, the address within the same municipality, or the address are used as the baseline category (relative risk=1.00). Vertical lines indicate 95% confidence intervals. Age 0 indicates the age period from birth to the first birthday, etc. Estimates of relative risks were adjusted for age and its interaction with sex, calendar year, and mental illness in a parent or sibling.

pared with a person who had always been living in the rural area (not accounting for the increased risk associated with change of residence). In general, risk increases with increasing degree of urbanization, and inherent in the log-linear model is that risk increases with increasing number of years lived in each degree of urbanization. The categorical model (Table 4) could be simplified to the log-linear model (Table 5) for urbanicity during upbringing ($P = .63$). In the rest of this article, we use the log-linear model to describe the association between schizophrenia and urbanization. Furthermore, this model had a significantly better fit than any of the models for the modifying effects of urbanicity between the

Table 2. Adjusted Relative Risks According to Number of Changes of Municipality in a Population-Based Cohort of 1.89 Million Danish People*

No. of Changes of Municipality	No. of Cases	Person-years	Relative Risk (95% Confidence Interval)†
From birth to the 5th birthday ($P = .34$)			
0	1004	3 890 119	1.00‡
1	328	1 123 412	0.92 (0.82-1.05)
2	131	376 364	0.97 (0.80-1.16)
≥3	90	217 165	0.91 (0.73-1.13)
From the 5th to the 10th birthday ($P < .001$)			
0	2390	9 119 282	1.00‡
1	601	1 570 244	1.18 (1.07-1.29)
2	216	433 266	1.29 (1.12-1.49)
≥3	135	216 693	1.28 (1.07-1.54)
From the 10th to the 13th birthday ($P < .001$)			
0	4845	17 244 968	1.00‡
1	665	1 455 258	1.16 (1.07-1.26)
2	199	283 956	1.40 (1.21-1.62)
≥3	78	91 815	1.36 (1.08-1.70)
From the 13th to the 15th birthday ($P < .001$)			
0	6324	22 485 003	1.00‡
1	696	1 240 162	1.45 (1.34-1.57)
2	184	217 825	1.79 (1.54-2.08)
≥3	76	55 656	2.49 (1.97-3.13)

*Categories with unaccessible information are not shown.

†Estimates of relative risk were adjusted for age and its interaction with sex, calendar year, urbanicity at birth, mental illness in a parent or sibling, and change of the municipality.

‡Referent.

successive age points of birth, 5th, 10th, and 15th birthday (Table 3).

When urbanicity at birth and urbanicity during upbringing were adjusted mutually, the effect of urbanicity at birth vanished ($P = .80$), while the effect of urbanicity during upbringing was not modified and remained strongly significant ($P < .001$). This means that urbanicity during upbringing explains the effect of urbanicity at birth, ie, urbanicity at birth is a proxy for urbanicity during upbringing. The effect of urbanicity during upbringing did not differ significantly by age at residence ($P = .08$) or sex ($P = .79$) (data not shown), meaning that there was no evidence of age at residence or sex differences in the vulnerability to upbringing in urbanized areas. Furthermore, there were no urban-rural differences in age of onset ($P = .21$).

In any of the models presented herein, the effect of change of municipality remained constant.

COMMENT

Places of residence at nearby ages are strongly associated, meaning that for most people, place of residence at the fifth birthday was identical to place of residence at the fourth and sixth birthday. This correlation impedes the interpretation of the finding of the constant effect of urbanicity according to age (Figure 2). However, suppose children were only vulnerable to urbanicity at the fifth birthday and not to urbanicity at birth or urbanicity at any other age, then the reason many studies (eg, Mortensen and others^{2,3,6}) have found an association between urbanicity at birth and schizophrenia risk is that urbanicity at birth is a proxy for urbanicity at the fifth

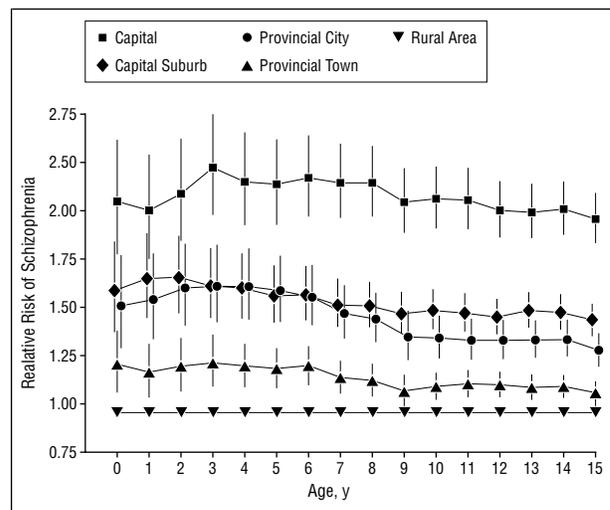


Figure 2. Relative risk of schizophrenia according to urbanicity and age at residence. Urbanicity from birth to the 15th birthday enters separately in these 16 models. Age 0 indicates the time at birth, etc. Vertical lines indicate 95% confidence intervals. To avoid the confidence intervals from overlapping graphically, the age scale for the capital suburb was moved slightly to the left and the age scale for the provincial city was moved slightly to the right. Estimates of relative risks were adjusted for age and its interaction with sex, calendar year of diagnosis, and mental illness in a parent or sibling. Further adjustment for change of the municipality would reduce the effect of urbanicity only slightly.

birthday. Furthermore, because of attenuation caused by misclassification,¹⁸ the effect of this proxy variable would be lower than the effect of urbanicity at the fifth birthday. Therefore, if children were most fragile to urbanicity at some single age point during upbringing, then urbanicity would have a higher effect for this age point

Table 3. Adjusted Relative Risk of Schizophrenia According to Urbanicity in a Population-Based Cohort of 1.89 Million Danish People

Urbanicity	Relative Degree of Urbanization at Place of Residence 5 y Later*								
	Relative Risk (95% Confidence Interval)								
	No. of Cases			First Adjustment†			Second Adjustment‡		
	Higher	Same	Lower	Higher	Same	Lower	Higher	Same	Lower
At birth									
Capital	...	503	430	...	2.75 (2.39-3.17)	2.08 (1.80-2.41)	...	2.53 (2.19-2.92)	1.94 (1.68-2.25)
Capital suburb	22	268	56	2.01 (1.30-3.10)	1.82 (1.55-2.15)	1.55 (1.16-2.06)	1.82 (1.18-2.81)	1.74 (1.48-2.05)	1.44 (1.08-1.92)
Provincial city	9	367	124	1.63 (0.84-3.16)	1.94 (1.67-2.25)	1.46 (1.19-1.80)	1.44 (0.74-2.79)	1.92 (1.65-2.24)	1.41 (1.14-1.73)
Provincial town	117	658	332	2.21 (1.79-2.74)	1.37 (1.20-1.57)	1.20 (1.03-1.40)	2.02 (1.63-2.51)	1.35 (1.18-1.55)	1.17 (1.00-1.37)
Rural area	100	315	...	1.95 (1.56-2.45)	1.00§	...	1.83 (1.46-2.30)	1.00§	...
At the fifth birthday									
Capital	...	434	117	...	2.70 (2.39-3.04)	2.04 (1.67-2.48)	...	2.63 (2.33-2.96)	1.53 (1.22-1.90)
Capital suburb	32	514	84	2.74 (1.92-3.90)	1.72 (1.54-1.93)	2.17 (1.73-2.72)	2.04 (1.41-2.95)	1.67 (1.49-1.87)	1.62 (1.26-2.07)
Provincial city	9	375	62	3.01 (1.56-5.82)	1.79 (1.58-2.03)	2.01 (1.55-2.61)	2.16 (1.11-4.21)	1.84 (1.63-2.09)	1.53 (1.16-2.02)
Provincial town	43	707	85	2.41 (1.77-3.27)	1.28 (1.16-1.42)	1.54 (1.23-1.92)	1.78 (1.29-2.46)	1.30 (1.17-1.45)	1.16 (0.90-1.48)
Rural area	116	704	...	1.92 (1.58-2.34)	1.00§	...	1.45 (1.16-1.81)	1.00§	...
At the 10th birthday									
Capital	...	725	179	...	2.38 (2.17-2.60)	2.61 (2.23-3.05)	...	2.41 (2.20-2.64)	1.93 (1.63-2.28)
Capital suburb	58	955	114	3.14 (2.42-4.09)	1.61 (1.49-1.75)	1.99 (1.64-2.41)	2.26 (1.73-2.96)	1.60 (1.47-1.73)	1.41 (1.16-1.73)
Provincial city	7	582	70	2.40 (1.14-5.04)	1.47 (1.34-1.62)	1.96 (1.54-2.50)	1.70 (0.81-3.59)	1.53 (1.39-1.69)	1.45 (1.13-1.86)
Provincial town	53	1242	115	2.14 (1.63-2.82)	1.16 (1.07-1.25)	1.59 (1.31-1.92)	1.52 (1.14-2.01)	1.18 (1.10-1.28)	1.15 (0.94-1.40)
Rural area	180	1417	...	1.94 (1.66-2.27)	1.00§	...	1.37 (1.16-1.62)	1.00§	...

*Ellipses indicate data not applicable.

†Estimates of relative risk were adjusted for sex and its interaction with age, calendar year, and mental illness in a parent or sibling.

‡Estimates of relative risk were adjusted for all variables in the first adjustment and for change of the municipality.

§Referent.

than for the nearby age points. However, since the effect of urbanicity (Figure 2) does not depend on age at residence, these data show no indication of any ages particularly vulnerable to residence in urbanized areas during upbringing.

The risk associated with 15 years of residence in any urbanicity was greater than the risk associated with living in the same urbanicity as 5 years earlier (Table 3, second adjustment, and Table 5), which in turn was greater than the effect of urbanicity at birth or at some age point (Figure 2). This indicates that the greater the refinement of the modeling of urbanicity, the greater the risk, and that not only urbanicity at birth or at some age point but also the effect of living in the same urbanicity as 5 years earlier are proxies for urbanicity during upbringing. In conclusion, the log-linear model for the accumulated number of years lived in each degree of urbanization during upbringing is the best model describing the association between urbanization and schizophrenia risk. Furthermore, it provides evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk.

The possible etiological factors that might explain our findings remain unknown. However, the finding of a dose-response relationship between schizophrenia risk and urbanicity during upbringing lends support to a causal association. Our findings may suggest that constant, cumulative, or repeated exposures during upbringing occurring more frequently in urbanized areas are responsible for the association between urbanization and schizophrenia risk. The potential explanations for the urban-rural differences shift from factors influencing chil-

dren at or around birth to factors influencing children continuously, or repeatedly, throughout upbringing. Factors such as obstetric complications, prenatal infections, and breastfeeding are, therefore, less likely explanations for these urban-rural differences, although they may well affect risk independently of urbanicity. Also, studies have suggested that household crowding,¹⁹ obstetric complications,²⁰ parental social class,²¹ and prenatal exposure to influenza²² do not explain the urban-rural differences in schizophrenia risk.

When Danish children move from one municipality to another, they usually change school. Therefore, it is interesting that change of municipality had a greater effect on schizophrenia risk than change of address, while change of address within the same municipality had no effect (Figure 1). We can only speculate regarding the underlying causes of these findings; however, they may be related to social maladjustment in preschizophrenic children, the stress of making new friends, and the fact that preschizophrenic children are more anxious in new environments.^{23,24} Life events, such as parental death, parental divorce, or change in social class, are possible but less likely explanations as they are not related to change of the municipality only.

It is extremely unlikely that selective migration or urban-rural differences in the availability of psychiatric services explain the effect of urbanicity at birth; for fixed urbanicity at the 15th birthday, risk increases with increasing degree of urbanization at place of birth, and there was no evidence that age at onset was modified by urbanicity during upbringing, ie, there were no urban-rural differences in the threshold for a psychiat-

Table 4. Distribution of the Number of Cases, the Person-years at Risk, and the Adjusted Relative Risk According to a Categorical Model for the Accumulated Number of Years Lived in Each Degree of Urbanization During Upbringing*

Urbanicity According to the Accumulated Number of Years	No. of Cases	Person-years	Relative Risk (95% Confidence Interval)†	P Value
Capital				
>0 to <5 y	136	314 844	1.34 (1.07-1.68)	<.001
≥5 to <10 y	55	113 206	1.46 (1.07-2.00)	
≥10 to <15 y	89	102 480	2.95 (2.28-3.82)	
Always (15 y)	120	233 972	2.62 (2.12-3.23)	
Capital suburb				
>0 to <5 y	120	275 161	0.97 (0.77-1.21)	
≥5 to <10 y	71	168 721	1.14 (0.86-1.51)	
≥10 to <15 y	107	244 843	1.51 (1.18-1.94)	
Always (15 y)	147	489 353	1.71 (1.40-2.08)	
Provincial city				
>0 to <5 y	70	220 259	1.12 (0.87-1.44)	
≥5 to <10 y	32	102 010	1.08 (0.75-1.55)	
≥10 to <15 y	54	122 771	1.77 (1.33-2.37)	
Always (15 y)	118	415 550	1.69 (1.36-2.09)	
Provincial town				
>0 to <5 y	176	476 356	1.14 (0.95-1.37)	
≥5 to <10 y	91	262 643	1.23 (0.97-1.56)	
≥10 to <15 y	104	339 907	1.32 (1.05-1.65)	
Always (15 y)	239	1 099 021	1.30 (1.09-1.54)	
Rural area				
Always (15 y)	224	1 493 521	1.00‡	
Total	1553	5 607 060

*Categories indicating residence less than 15 years are not mutually exclusive. For example a person who lives 7 years in the capital and 8 in the capital suburb belong to 2 categories (capital: ≥5 to <10 years and capital suburb ≥5 to <10 years). Ellipses indicate data not applicable.

†Estimates of relative risk were adjusted for age and its interaction with sex, calendar year, mental illness in a parent or sibling, and change of the municipality. ‡Referent.

Table 5. Adjusted Relative Risk According to a Log-Linear Model for the Accumulated Number of Years Lived in Each Degree of Urbanization During Upbringing

Urbanicity From Birth to the 15th Birthday	Relative Risk (95% Confidence Interval)*		P Value
	Per Year	Per 15 y†	
Capital	1.0697 (1.0572-1.0824)	2.75 (2.31-3.28)	<.001
Capital suburb	1.0355 (1.0242-1.0469)	1.69 (1.43-1.99)	
Provincial city	1.0363 (1.0232-1.0496)	1.71 (1.41-2.06)	
Provincial town	1.0187 (1.0081-1.0293)	1.32 (1.13-1.54)	
Rural area	1.0000‡	1.00‡	

*Estimates of relative risk were adjusted for age and its interaction with sex, calendar year, mental illness in a parent or sibling, and change of the municipality.

†The relative risk per 15 years is calculated by raising the relative risk per year to the 15th power, eg, $1.0697^{15} = 2.75$.

‡Referent.

ric admission with schizophrenia. Furthermore, services are free and distances are small in Denmark.

The results of the study are based on patients with schizophrenia admitted to a psychiatric hospital or those in outpatient care diagnosed as having schizophrenia. Although not all patients with schizophrenia are admitted to a psychiatric hospital or are in outpatient care during the first episode, many will eventually be admitted or come in for outpatient care and, thus, subsequently will become registered. Furthermore, the classification of degree of urbanization is based on the number of inhabitants in the largest city in the municipality, and is almost certainly a crude proxy variable for the unidentified underlying risk factors and mechanism. If the underlying risk-increasing mechanisms explaining the urban-rural difference can be identified, it is likely that their effects

will be much larger than the association with urbanicity during upbringing we demonstrated.

To our knowledge, this is the first study to directly assess the relative importance of urbanicity at birth and during upbringing. Lewis et al⁴ have shown an association being brought up in urban areas and having schizophrenia later in life, but they did not distinguish this effect from an effect of urban birth. Marcelis et al²⁵ showed that urban residence at onset did not affect schizophrenia risk when controlling for urban birth. However, their results may be biased by the migration of preschizophrenic people before their first hospitalization with schizophrenia. Although our findings must be replicated, they warrant direct tests of the hypothesis that continuous, or repeated, exposures during upbringing that occur more frequently in urban-

ized areas are responsible for the association between urbanization and schizophrenia risk. Candidate risk factors would include infections, diet, and exposure to pollution.

Accepted for publication May 1, 2001.

This study was supported by the Theodore and Vada Stanley Foundation, Bethesda, Md. The National Centre for Register-Based Research is funded by the Danish National Research Foundation, Copenhagen.

Corresponding author and reprints: Carsten Bøcker Pedersen, MSc, National Centre for Register-Based Research, Aarhus University, Taasingegade 1, 8000 Aarhus C, Denmark (e-mail: cbp@ncrr.au.dk).

REFERENCES

1. Gottesman II. *Schizophrenia Genesis: The Origins of Madness*. New York, NY: WH Freeman & Co; 1991.
2. Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, Andersen PK, Melbye M. Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med*. 1999;340:603-608.
3. Pedersen CB, Mortensen PB. Family history, place and season of birth as risk factors for schizophrenia in Denmark: a replication and reanalysis. *Br J Psychiatry*. 2001;179:46-52.
4. Lewis G, David A, Andreasson S, Allebeck P. Schizophrenia and city life. *Lancet*. 1992;340:137-140.
5. Mortensen PB. Urban-rural differences in the risk for schizophrenia. *Int J Ment Health*. 2000;29:101-110.
6. Freeman H. Schizophrenia and city residence. *Br J Psychiatry Suppl*. 1994;164 (suppl 23):39-50.
7. Marcelis M, Navarro-Mateu F, Murray R, Seltén JP, Van Os J. Urbanization and psychosis: a study of 1942-1978 birth cohorts in the Netherlands. *Psychol Med*. 1998;28:871-879.
8. Maling C. The civil registration system in Denmark. *Tech Pap Int Inst Vital Registr Stat*. 1996;66:1-6.
9. Munk-Jørgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull*. 1997;44:82-84.
10. World Health Organization. *Manual of the International Classification of Diseases, 8th Revision (ICD-8)*. Geneva, Switzerland: World Health Organization; 1967.
11. World Health Organization. *International Classification of Diseases, 10th Revision (ICD-10)*. Geneva, Switzerland: World Health Organization; 1992.
12. Statistics Denmark. *Befolkningen i Kommunerne 1. Januar 1997*. Copenhagen, Denmark: Statistics Denmark; 1997.
13. Statistics Denmark. *Statistisk Årbog 1997*. Copenhagen, Denmark: Statistics Denmark; 1997.
14. Breslow NE, Day NE. *Statistical Methods in Cancer Research Volume II: The Design and Analysis of Cohort Studies*. Oxford, England: Oxford University Press; 1987. IARC scientific publication 82.
15. SAS Institute Inc. The GENMOD procedure. In: *SAS/STAT Software: Changes and Enhancements Through Release 6.12*. Cary, NC: SAS Institute Inc; 1997:247-348.
16. Clayton D, Hills M. *Statistical Models in Epidemiology*. New York, NY: Oxford University Press Inc; 1993.
17. Breslow NE. Generalized linear models: checking assumptions and strengthening conclusions. *Statistica Applicata*. 1996;8:23-41.
18. Fuller WA. *Measurement Error Models*. New York, NY: John Wiley & Sons Inc; 1987.
19. Agerbo E, Torrey EF, Mortensen PB. Household crowding and schizophrenia are unrelated in Denmark. *Schizophr Res*. 2001;47:243-246.
20. Eaton WW, Mortensen PB, Frydenberg M. Obstetric factors, urbanization and psychosis. *Schizophr Res*. 2000;43:117-123.
21. Mortensen PB, Agerbo E, Eriksson T, Westergaard-Nielsen N. Parental education and socioeconomic variables as predictors of schizophrenia in the offspring [abstract]. *Schizophr Res*. 2000;41 (special issue):73.
22. Westergaard T, Mortensen PB, Pedersen CB, Wohlfahrt J, Melbye M. Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. *Arch Gen Psychiatry*. 1999;56:993-998.
23. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;344:1398-1402.
24. Done DJ, Crow TJ, Johnstone EC, Sacker A. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *BMJ*. 1994; 309:699-703.
25. Marcelis M, Takei N, van Os J. Urbanization and risk for schizophrenia: does the effect operate before or around the time of illness onset? *Psychol Med*. 1999; 29:1197-1203.