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Urban-Rural Differences in Schizophrenia Risk: Multilevel Survival Analyses of Individual- and Neighborhood-Level Indicators, Urbanicity and Population Density in a Danish National Cohort Study

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Background: **Urban-rural differences in schizophrenia risk have been widely evidenced across Western countries. However, explanation of these differences is lacking. We aimed to identify contextual risk factors for schizophrenia that explain urban-rural differences in schizophrenia risk.** ***Methods:*** **Utilizing Danish population-based registers, we partitioned Denmark into 1885 geographic "neighborhoods" homogeneously sized in terms of population. Information on the entire Danish population from 1981 to 2016 was used to quantify a spectrum of neighborhood-level domains. We subsequently conducted multilevel survival analyses following persons born in Denmark from 1971 to 1982 for the development of schizophrenia allowing for clustering of people within neighborhoods. We used this method to tease apart the effects of individual, specific, and general contextual risk factors for schizophrenia.** ***Results:*** **A significant general contextual effect in schizophrenia risk across neighborhoods was estimated (Medium Incidence Rate Ratio (MRR):1.41; 95% CI:1.35–1.48). Most of the specific contextual factors examined were associated with schizophrenia risk. For instance, neighborhood-level proportion of lone adult households (Incidence Rate Ratios (IRR):1.53; 95% CI:1.44–1.63) had largest risk estimate. Adjustment for all individual-level and specific contextual constructs reduced the IRR for urbanicity from 1.98 (95% CI:1.77–2.22) to 1.30 (95% CI:1.11–1.51).** ***Conclusions:*** **In the largest prospective multilevel survival analyses of schizophrenia risk conducted to date, multiple neighborhood-level characteristics were associated with raised schizophrenia risk, with these contextual factors explaining most of the elevated risk linked with urbanicity. However, the unexplained heterogeneity that was evident in our multilevel models indicates that our understanding of the role of urbanicity in schizophrenia's etiology remains incomplete.**

Key words: schizophrenia/multilevel survival analyses/urbanization/neighborhood-level domains/general contextual effect/specific contextual effect

Introduction

In 1939, Faris and Dunham published their classical ecological study of mental disorders in Chicago.[1] They explored the potential relationship between social organization and the spatial distribution of mental disorders, including schizophrenia. They found that the lower the social organization of the municipality, the higher the incidence rate of schizophrenia. Although considered the first study to identify urban-rural differences in schizophrenia risk, fourteen years earlier Pollock and Nolan

demonstrated urban-rural differences in schizophrenia risk in New York State.[2] This phenomenon fostered numerous studies investigating urban-rural differences per se and studies investigating the impact of neighborhood-level constructs on schizophrenia risk.

People born or raised in urban areas have elevated risks of developing schizophrenia compared to their rural-dwelling counterparts.[3] A meta-analysis found that the risk for schizophrenia linked with residing in a highly urbanized environment was at least twice as high as that associated with living in a very sparsely populated rural environment.[4] Despite differences in methodology and methods to measure urbanization (density of inhabitants,[5] the density of residences,[6–8] city size,[6,9–18] other methods[19,20]) almost all studies have reported significant urban-rural differences in schizophrenia incidence. Urbanization in itself likely does not causally influence the risk of developing schizophrenia; rather it is probably a marker for determinants that are more or less prevalent in urban areas.[12,13,16,17] To date, the search for factors explaining these urban-rural differences have included both methodological issues of migration and selection,[9,21] as well as potential individual-level explanations: sibling composition,[18] maternal and paternal age,[22] parental socioeconomic position,[23] household crowding,[24] family history of mental illness,[12,13] ethnicity,[25–28] toxoplasmosis,[29,30] vitamin D,[31,32] parental substance misuse,[23] parental death,[33] and air pollution.[34] However, none of these factors have consistently explained all urban-rural differences in schizophrenia risk.[12,13,18,21–28,33,34]

There is also robust evidence that social-environmental characteristics of neighborhoods, including social deprivation,[35–39] social disorganization,[39] social fragmentation,[36,39] social marginalization,[39] social capital,[40] residential mobility,[39,41] income inequality,[37] ethnic fragmentation,[38,39] and physical illness[42] are related to distribution of nonaffective psychotic disorders.[35–41,43–49] Studies have also considered ethnic density,[38,43,45] i.e., where the incidence of schizophrenia in ethnic minorities is greater when they compromise a smaller proportion of the local population. While Denmark has access to rich longitudinal population-based registers and have contributed with studies of urban-rural differences in schizophrenia risk, there exist no consistent small area local geography in Denmark, and thus the contribution from Denmark to identify potential social-environmental risk factors for schizophrenia is scarce; with the exceptance of a few studies investigating ethnic density and psychosis.[46,47]

In their national Swedish register-based study, Zammit et al.[48] found that the effect of urbanicity was explained by neighborhood-level covariates including population density, although, the conceptual interchangeability of urbanicity and population density arguably compromises the interpretability of this finding.

We utilized rich interlinked Danish nationwide population-based registers[50] to develop a new homogeneously population-sized geographic division of Denmark, which are hereafter referred to as "data zones". By conducting a novel Danish population-based prospective multilevel survival analysis, we aimed to quantify the degree to which individual-level and neighborhood-level risk factors explain urban-rural differences in schizophrenia risk. Neighborhood-level indicators examined included domains of material deprivation, social fragmentation, social marginalization, and physical illness[39,42,51]

Methods

Since 1968, all Danish residents have been registered in the Danish Civil Registration System,[52] which records personal identification number, gender, date and place of birth, parents' personal identifiers, and continuously updated information on residential address, emigration, death, and disappearance. Unique personal identifiers are used in national registers enabling accurate linkage between registers and between cohort members and their first-degree relatives.

First, we describe the delineation of neighborhoods and neighborhood-level covariates, both of which was based on the entire Danish population, and subsequently, the study population followed for schizophrenia onset using multilevel survival analyses.

Small Area Geography

From 1971 to 2016, Denmark was divided into 2039–2194 parishes.[53] From 1971 to 2006, the country was divided into 270–275 municipalities, and since 2007 it has been divided into 98 municipalities.[53,54] Apart from the longitudinal variation in geographic boundaries, these geographic delineations also vary considerably in population size (Supplementary Methods 1). Both challenges may bias geospatial analyses.[55] Due largely to the availability of the individual-level registers in Denmark, and the lack of a national census, no consistent and homogeneously sized small-area geographic delineation is available in Denmark. Thus, few previous Danish studies have investigated neighborhood-level influences on health.

Delineation of Data Zones

We adopted geographic zone design theory to create a new national small-area delineation.[56,57] We utilized a nationwide database of regularly updated geographic front-door coordinates of residential address for all Danish residents from 1978 onwards[52] combined with a sophisticated automated tessellation clustering procedure to create a homogeneously population-sized small-area division of Denmark. This resulted in 1885 delineated geographic areas, hereafter referred to as "data zones". Data zones were nested within the 98 municipalities. We aimed for a mean data zone size of 2500 residents longitudinally from

1980 to 2016 (Supplementary Methods 1, Supplementary Figure 1). When we applied this delineation scheme nationally, the mean residents per data zone was 2820 people (IQR: 2311 to 3315, SD = 809, range: 768–6495), i.e., corresponding to a coefficient of variation of 28.7%.

Derivation of Neighborhood-Level Indicators/Specific Contextual Covariates

Data zone-level covariates were derived by aggregating individual-level covariates for the entire Danish population. These neighborhood-level indices included material deprivation (low income, short education, not employed, manual work, household overcrowding, no car owned), social fragmentation (lone adult household, residential transience, rented accommodation), social marginalization (violent offender, criminality, foreign-born) and neighborhood-level physical illness. For these factors we calculated the proportion of inhabitants (or households) in each data zone with the characteristic of interest (Supplementary Methods 2); for instance, the proportion of inhabitants in neighborhood convicted for a violent crime. We also calculated age distribution (proportion of residents aged 0–14 years, 15–29 years, 30–49 years, 50–64 years, and 65 age and above), urbanicity, and population density (as described below). These calculations were performed for each data zone annually from 1981 to 2016 using individual-level covariates for the entire Danish population on December 31 each year. We included the neighborhood-level indicators (specific contextual covariates) as data zone-level averages during years 1981–1984 (Supplementary Methods 2).

Delineation of Urbanicity and Population Density

When the causal factor(s) that explain urban-rural differences in incidence are unknown, a universal measure of urbanization cannot easily be conceptualized.[15] We used two competing measures of urbanization; "population density" of the data zone and "urbanicity" categorized in five levels according to the number of inhabitants in the largest city or town in the 270-level municipality.[13] The latter was referred to as "degree of urbanization" in previous Danish studies (e.g.[12,15,16,58]). Although, urbanicity and population density are both neighborhood-level covariates, both have been used as interchangeable proxies for the unknown mechanism driving the urban-rural differences in schizophrenia risk. Supplementary Figures 2A–2S show the geographic distribution of the neighborhood-level indicators examined.

Individual-Level Covariates

Parental sociodemographic indices were obtained from the Integrated Database for Labor Market Research[59]: gross income, highest level of completed education (primary school, high school/vocational training, higher education), and employment status (employed, unemployed, not working for other reasons). Similarly, parents were classified with a history of any secondary care diagnosed mental disorder using the following coding ranges: ICD10: F00–F99, ICD8: 290–315.[60,61] We also included information on maternal and paternal age at cohort member's birth,[22] number of residential changes from the 5th to the 10th birthday,[62] parental Charlson Comorbidity index, parental imprisonment, and parental death. All individual-level covariates were delineated at or shortly before the 10th birthday. Cohort members were classified as having schizophrenia (ICD10: F20; ICD8: 295.x9, excluding 295.79) if they had been admitted to a psychiatric hospital or had received outpatient care with this diagnosis.[63] The date of onset was defined as the first day of the inpatient or outpatient episode during which the diagnosis was first assigned.

Statistical Analyses

People born in Denmark to Danish-born parents[25,64] between 1st January 1972 and 31st December 1981 were followed for onset of schizophrenia. Follow-up was initiated at 10th birthday and was terminated at disease onset, emigration, death, or 31st January 2016, whichever came first. Individual-level variables examined included age, sex, number of residential moves during the past five years, maternal and paternal age at time of cohort member's birth, parental imprisonment, parental Charlson disease, parental death, parental history of mental illness,[61] parental income, parental level of education completed and parental employment status. Age was treated as time-scale. All other variables were analyzed as time-fixed variables measured at initiation of follow-up. Individual-level characteristics were delineated at or shortly before initiation of follow-up, thus ensuring the prospective nature of the study. To avoid potential heterogeneity and/or bias caused by differential effects sizes for foreign migrants and their descendants,[26] by design the study population included people born in Denmark to Danish-born parents.

Data were analyzed using multilevel log-linear Poisson regression models that included both individual- and neighborhood-level variables, data zone as a random intercept,[65] and with the logarithms of the aggregated person-years counts set as an offset variable.[66] This is equivalent to the Cox proportional hazards model, assuming piecewise constant incidence rates[67,68] and allowing for a random intercept for each data zone.[69] Multilevel survival models enable researchers to make valid inferences when examining the effects of both individual- and neighborhood-level predictors of disease risk.[69] All statistical analyses were conducted using R, version 3.5.0. The multilevel Poisson regression model was fitted using Markov Chain Monte Carlo with the *brm* function in the *brms* package (version 2.2.0). We used

five chains with 2500 simulations each with a burn-in of 500 simulations to estimate parameters, i.e., 10 000 simulations in total were generated.

Interpretation of General and Specific Contextual Effects

The contextual influence on disease incidence (or magnitude of clustering) consists of the general contextual effect and the specific contextual effects. The specific contextual effects are the neighborhood-level indicators examined. The general contextual effect estimates effects of neighborhood context on disease incidence without reference to any of the specific neighborhood-level constructs other than the very boundaries defining neighborhoods.[70] In multilevel models, the general contextual effects are random effects, and the specific contextual effects are fixed effects.

The median incidence rate ratio (MRR) quantifies the general contextual effect (degree of clustering) on the incidence rate ratio scale and are thus comparable with individual-level incidence rate ratios. MRRs were estimated following the exact calculation provided in Austin et al,[65] this parameter being the median relative change in the incidence rate of the event when comparing identical individuals from two randomly selected different clusters that are ordered by incidence rate.

Statistical Adjustment Scenarios

Using multilevel survival analyses, we first considered the effect of the individual-level covariates on schizophrenia risk and estimated the general contextual effect across data zones for different individual-level adjustments. The specific contextual effects were estimated in basic adjustment (individual-level age and sex and neighborhood-level age structure) and also in full individual-level adjustment (all individual-level variables examined and neighborhood-level age structure). All estimates of neighborhood-level characteristics were also adjusted for the potential confounding influence of neighborhood-level age structure. We used principal component analyses to generate a combined adjustment for specific neighborhood-level indicators (Supplementary Methods 2). Finally, we estimated the effect of urbanicity and population density with basic and with full individual-level adjustment.

Sensitivity Analyses

As a sensitivity analyses, we repeated the equivalent multilevel survival analyses a) with parish boundaries as the geographic delineators (Supplementary Methods 3, Supplementary Table 2, Supplementary Table 3); b) using schizophrenia and related disorders (ICD10: F20-F29 and eq: ICD8)[60] as the outcome of interest (Supplementary Table 4, Supplementary Table 5); c) using explanatory factor analyses to generate a combined adjustment for all specific neighborhood-level indicators (Supplementary Methods 4, Supplementary Table 6).

Ethics

The Danish Data Protection Agency approved the study, with data access agreed by the Danish Health Data Authority and Statistics Denmark. Because it was based exclusively on registry data, informed consent from cohort members was not required in accordance with Danish legislation.

Results

Among the 579 039 people born in Denmark 1972–1981 by Danish-born parents, a total of 5103 people developed schizophrenia during the 17 191 889 person-years of follow-up 1982–2016; a crude incidence rate of 2.97 per 10 000 person-years at risk.

Associations pertaining to the individual-level risk factors investigated are shown in Table 1, along with descriptive information on number of cases and crude incidence rates per characteristic. For instance, each residential change was associated with a 1.44 (95% CI: 1.38–1.51) fold increased risk of schizophrenia. Most individual-level risk factors were attenuated after adjustment for all other individual-level risk factors examined. For example, the effect of a parental history of any mental disorder was reduced from 3.11 (95% CI: 2.90–3.35) to 2.47 (95% CI: 2.29–2.65). Risk estimates in Table 1 concur with those reported previously in the literature.[22,23,61,71–73]

Table 2 shows the general contextual effect (unexplained heterogeneity) on schizophrenia risk across data zones in different individual-level adjustment scenarios. In the model without covariates, the estimated standard deviation of the random intercept was 0.36 and its estimated standard error was 0.02, which equates to an MRR of 1.41 (95% CI: 1.34–1.47). Further adjustment for individual-level age and sex did not reduce the general contextual effect. When adjusting for all individual-level factors, the MRR was attenuated to 1.32 (95% CI: 1.26–1.39). Further adjustment for neighborhood-level age structure slightly reduced the unexplained heterogeneity between data zones.

Table 3 shows the effects of the array of specific contextual effects investigated. In the basic adjustment models each specific contextual effect was associated with an increased risk of schizophrenia, except for proportion of individuals with low income, proportion of individuals with short education, and proportion of individuals who are manual workers. Each specific contextual effect slightly attenuated the general contextual effect. For instance, a one standard deviation increase in the proportion of households with lone adults increased the incidence rate of schizophrenia 1.53 (95% CI: 1.44–1.63)-fold for all other factors held fixed except data zone and, on the MRR scale, this neighborhood-level indicator

Table 1. Individual-Level Risk Factors for Schizophrenia[a]

Individual-level risk factor	No of cases	Incidence Rate[b]	Basic adjustment[c]	Full individual-level adjustment[d]
			Incidence Rate Ratio (95% CI)	Incidence Rate Ratio (95% CI)
Residential changes[e]				
None	4013	2.73	1.00 (ref)	1.00 (ref)
1 or more	1090	4.42	1.44 (1.38–1.51)	1.26 (1.20–1.32)
Parental history of mental illness				
No	4133	2.58	1.00 (ref)	1.00 (ref)
Any	970	8.23	3.11 (2.90–3.35)	2.47 (2.29–2.65)
Paternal age (years)				
12–19	98	4.21	1.53 (1.25–1.87)	1.06 (0.85–1.32)
20–24	1074	3.27	1.20 (1.11–1.29)	1.06 (0.98–1.16)
25–29	1873	2.69	1.00 (ref)	1.00 (ref)
30–34	1271	2.90	1.07 (1.00–1.14)	1.09 (1.01–1.18)
35–39	479	3.07	1.14 (1.03–1.25)	1.10 (0.99–1.23)
40 and older	308	4.03	1.50 (1.33–1.69)	1.29 (1.12–1.49)
Maternal age (years)				
12–19	445	4.35	1.58 (1.42–1.75)	1.27 (1.13–1.43)
20–24	1747	2.99	1.11 (1.03–1.18)	1.06 (0.99–1.14)
25–29	1774	2.69	1.00 (ref)	1.00 (ref)
30–34	823	2.86	1.05 (0.97–1.14)	0.99 (0.91–1.08)
35–39	268	3.57	1.32 (1.14–1.51)	1.11 (0.96–1.29)
40 and older	46	3.92	1.46 (1.07–1.96)	1.06 (0.76–1.44)
Parental Charlson Comobidity				
Yes	417	3.87	1.31 (1.19–1.44)	1.04 (0.93–1.15)
No	4686	2.91	1.00 (ref)	1.00 (ref)
Parental imprisonment				
Yes	395	6.41	2.17 (1.95–2.39)	1.36 (1.22–1.52)
No	4708	2.84	1.00 (ref)	1.00 (ref)
Parental death				
Yes	177	2.91	2.08 (1.79–2.40)	1.23 (0.87–1.73)
No	4926	6.18	1.00 (ref)	1.00 (ref)
Parental income quartile[f]				
Q1 (lowest)	547	4.83	1.90 (1.73–2.10)	1.34 (1.19–1.50)
Q2	1060	3.27	1.30 (1.20–1.41)	1.21 (1.11–1.31)
Q3	1500	2.80	1.11 (1.04–1.19)	1.10 (1.02–1.18)
Q4 (highest)	1851	2.56	1.00 (ref)	1.00 (ref)
Parental education[f]				
Primary school	527	3.48	1.31 (1.18–1.44)	0.96 (0.86–1.06)
High school/vocational training	2854	2.88	1.06 (0.99–1.13)	0.91 (0.84–0.97)
Short cycle higher education	149	2.40	0.88 (0.74–1.04)	0.84 (0.71–1.00)
Higher education	1222	2.74	1.00 (ref)	1.00 (ref)
Parental employment status[f]				
Outside workforce	169	9.60	3.34 (2.85–3.89)	1.65 (1.39–1.95)
Unemployed	252	7.07	2.52 (2.20–2.84)	1.55 (1.35–1.78)
Employed	4475	2.75	1.00 (ref)	1.00 (ref)

[a] Estimates were based on multilevel survival analyses, neighborhoods are 1885 novel data zones nested in Denmark's 98 municipalities. The 579 039 people born in Denmark 1972–1981 were followed for development of schizophrenia. During the follow-up period from 1982 to 2016, a total of 5103 developed schizophrenia during the 17 191 889 person-years at risk

[b] The incidence rate measure the number of new people who developed schizophrenia per 10,000 person-years at risk.

[c] Estimates were adjusted for age and sex.

[d] Estimates were adjusted for age and sex and all other covariates.

[e] Incidence rate ratio for each residential change from 5th to 10th birthday.

[f] Parental income quartile was delineated as the maximum of maternal and paternal quartiles. Parental educational attainment was delineated as the parent with highest level of completed education. Parental employment status was delineated hierarchically as either parent employed, either parent not employed, and either parent outside workforce. Categories with missing parental socioeconomic position information are not shown.

Table 2. Heterogeneity in Schizophrenia Risk Across Data Zones Adjusting for Individual-Level Risk Factors for Schizophrenia

Adjustment scenario	General contextual effect in schizophrenia risk across data zones, two competing measures[a]	
	Between data zone standard deviation; Random intercept (Standard error of Random Intercept)	Median Incidence Rate Ratio (95% Probability Interval)[b]
None	0.36 (0.02)	1.41 (1.34–1.47)
Basic individual-level adjustment, i.e., age and its interaction with sex	0.36 (0.02)	1.41 (1.35–1.48)
Basic individual-level adjustment, childhood residential transience, parental Charlson, parental death and parental imprisonment	0.33 (0.02)	1.38 (1.31–1.44)
Basic individual-level adjustment, parental age and parental history of mental illness	0.31 (0.03)	1.34 (1.27–1.41)
Basic individual-level adjustment, parental income, parental education and parental employment status	0.34 (0.02)	1.38 (1.31–1.45)
Comprehensive individual-level adjustment, all factors above	0.29 (0.02)	1.32 (1.26–1.39)
Full individual-level adjustment and neighborhood-level age structure	0.27 (0.02)	1.30 (1.24–1.36)

[a] Estimates were based on multilevel survival analyses, neighborhoods are 1885 novel data zones nested in Denmark's 98 municipalities. The 579 039 people born in Denmark 1972–1981 were followed for development of schizophrenia. During the follow-up period from 1982 to 2016, a total of 5103 developed schizophrenia during the 17 191 889 person-years at risk

[b] The Median Incidence Rate Ratio (MRR) quantified the variation between data zones (clusters) by comparing two identical individuals from two randomly chosen data zones. Consider two people with the same covariates chosen randomly from different data zones, the Median Incidence Rate Ratio is the median incidence rate ratio between the person of higher incidence rate and the person of lower incidence rate.

reduced the general contextual effect to 1.27 (95% CI: 1.21–1.34). Further adjustment for all individual-level variables slightly attenuated all risk estimates. Following full individual- and neighborhood-level adjustment statistically significant unexplained heterogeneity remained between data zones (MRR 1.22; 95% CI: 1.14–1.29). The scatterplots presented in Figure 1 reveal the correlation between the neighborhood-level covariates as well as their distributions. Proportion of households without car and proportion of households that rents their home had highest Pearson's correlation coefficient (r = 0.92), while proportion of individuals with a severe physical illness and proportion of individuals convicted with any criminality had lowest absolute correlation coefficient (r = 0.002).

Table 4 shows the associations for the two competing measures of urbanization: urbanicity and population density. The former measured the effect of residence in the most urban environment compared to the most rural environment, whereas the latter measured the effect arising from a one standard deviation increase in the log population density. With full individual-level adjustment, higher population density and higher urbanicity were both associated with elevated schizophrenia risks. Further adjusting for all neighborhood-level indices (Table 3) reduced the effect of both measures of urbanization (Table 4). Further adjusting the two competing measures of urbanization mutually, neighborhood-level population density had marginal significant impact, whereas the relationship with urbanicity remained essentially unchanged.

Sensitivity Analyses

Using parish as the neighborhood boundaries of interest nearly identical results were obtained except neighborhood-level population density was more important than urbanicity (Supplementary Methods 3, Supplementary Tables 2 and 3). Identical results were obtained considering schizophrenia spectrum disorders as the outcome of interest (9288 developed the disorder during 17 140 418 person-year at risk, Supplementary Tables 4 and 5). Identical results were obtained using explanatory factor analyses to generate a combined adjustment for all neighborhood-level constructs (Supplementary Methods 4, Supplementary Table 6).

Discussion

Previous studies have identified consistent but unexplained urban-rural differences in schizophrenia risk.[3,4] Utilizing Denmark's rich interlinked population-based registers,[50] we divided the country into 1885 homogeneously sized data zones, derived a comprehensive spectrum of neighborhood-level characteristics, and used multilevel survival analyses to tease out the effect of neighborhood independently from the characteristics of individuals living in these neighborhoods. We observed unexplained heterogeneity on schizophrenia risk across data zones, which was not explained after adjustment for all measured individual-level covariates. Ten of the thirteen specific neighborhood-level characteristics examined were associated with increased schizophrenia risk. The neighborhood-level associations were attenuated slightly

Table 3. General and Specific Contextual Effects on Schizophrenia Risk

	Basic adjustment[a,b]		Full individual-level adjustment[a,c]	
	Specific contextual effect	General contextual effect	Specific contextual effect	General contextual effect
Neighborhood-level socioeconomic indicator[d]	Incidence Rate Ratio of neighborhood per 1 sd increase	Median Incidence Rate ratio (95% Probability Interval	Incidence Rate Ratio of neighborhood per 1 sd increase	Median Incidence Rate Ratio (95% Probability Interval)
None	-	1.37 (1.31–1.43)		1.30 (1.23–1.36)
Material deprivation				
PI low Income	0.96 (0.92–1.00)	1.36 (1.30–1.42)	0.93 (0.89–0.97)	1.29 (1.22–1.35)
PI short education	0.89 (0.85–0.93)	1.35 (1.29–1.41)	0.87 (0.84–0.91)	1.27 (1.21–1.34)
PI not employed	1.38 (1.28–1.49)	1.33 (1.27–1.39)	1.21 (1.13–1.30)	1.28 (1.22–1.35)
PI manual workers	1.02 (0.98–1.06)	1.37 (1.31–1.43)	0.97 (0.94–1.02)	1.30 (1.23–1.36)
PH overcrowded	1.16 (1.12–1.20)	1.34 (1.27–1.40)	1.11 (1.07–1.15)	1.28 (1.21–1.34)
PH no car owned	1.44 (1.38–1.51)	1.24 (1.16–1.30)	1.32 (1.26–1.38)	1.22 (1.14–1.29)
Social fragmentation				
PH lone adult	1.53 (1.44–1.63)	1.27 (1.21–1.34)	1.36 (1.28–1.45)	1.24 (1.17–1.31)
PH rents home	1.29 (1.25–1.34)	1.26 (1.19–1.32)	1.21 (1.17–1.26)	1.23 (1.16–1.30)
PI residential transience	1.21 (1.16–1.26)	1.32 (1.26–1.38)	1.14 (1.10–1.19)	1.27 (1.21–1.34)
Social marginalization				
PI violent offending	1.21 (1.18–1.25)	1.29 (1.23–1.36)	1.13 (1.10–1.17)	1.26 (1.20–1.33)
PI any criminality	1.15 (1.11–1.19)	1.33 (1.27–1.39)	1.08 (1.05–1.12)	1.28 (1.22–1.35)
PI born abroad	1.22 (1.18–1.26)	1.30 (1.24–1.36)	1.16 (1.12–1.19)	1.26 (1.19–1.32)
Physical illness				
PI Physical illness	1.16 (1.10–1.22)	1.35 (1.29–1.41)	1.12 (1.07–1.18)	1.28 (1.22–1.35)
All area-level indices[e]	–	1.23 (1.16–1.30)	–	1.22 (1.14–1.29)

The specific contextual effects are the neighborhood-level indicators examined. The general contextual effect estimates effects of neighborhood context on disease incidence without reference to any of the specific neighborhood-level constructs other than the very boundaries defining neighborhoods.
PI: Proportion of individuals; PH: Proportion of households
[a] Estimates were based on multilevel survival analyses, neighborhoods are 1885 novel data zones nested in Denmark's 98 municipalities. The 579 039 people born in Denmark 1972–1981 were followed for development of schizophrenia. During the follow-up period from 1982 to 2016, a total of 5103 developed schizophrenia during the 17 191 889 person-years at risk
[b] Estimates were adjusted for individual-level age and its interaction with sex and neighborhood-level age distribution (Basic adjustment).
[c] Estimates were adjusted for Basic adjustment and individual-level residential instability, parental Charlson, parental death, parental imprisonment, parental age, parental history of mental disorders, parental income, parental employment status, and parental education.
[d] Neighborhood-level covariates measure the effect of a one standard deviation increase in the proportion of each covariate. Neighborhood-level covariates were data zone-level averages 1981–1984 (details in Supplementary Methods 2). The effects of each neighborhood-level covariate were modeled separately.
[e] Neighborhood-level covariates were summarized using the first 3 Principal Components of all neighborhood-level covariates (excl. urbanicity and population density). The fixed effect (specific contextual effect) estimate is not comparable to the other neighborhood-level fixed effects and is therefore not shown.

by adjustment for multiple individual-level factors, but the general contextual effect persisted. Finally, following comprehensive individual- and neighborhood-level adjustment, the effects of urbanicity and population density were both greatly attenuated. Further adjusting population density for urbanicity attenuated that relationship marginally around statistical significance, whilst the effect of urbanicity was slightly attenuated. In this large population-based study, multiple neighborhood-level characteristics across a broad array were associated with schizophrenia risk; there was unexplained heterogeneity in schizophrenia risk across data zones, and the effect of urbanicity was attenuated but remained significant.

The most directly comparable published findings thus far have been reported by Zammit et al.[48] who showed that the association with urbanicity was attenuated after adjustment for social fragmentation (immigration, residential mobility, single-parent household) and was eliminated when further adjusted for municipality-level population density. It was based on 203 829 Swedish individuals, 328 of whom were diagnosed with schizophrenia; i.e. a much lower level of statistical power compared to the study that we conducted. Using our data zones with homogenously sized populations, urbanicity tended to be more important than population density. Conversely, using parish boundaries as the geographic delineator, population density tended to be more important than urbanicity (Supplementary Methods 3).[55]

We opted not to generate composite area-level measures of material deprivation[74] or social fragmentation.[75] Instead

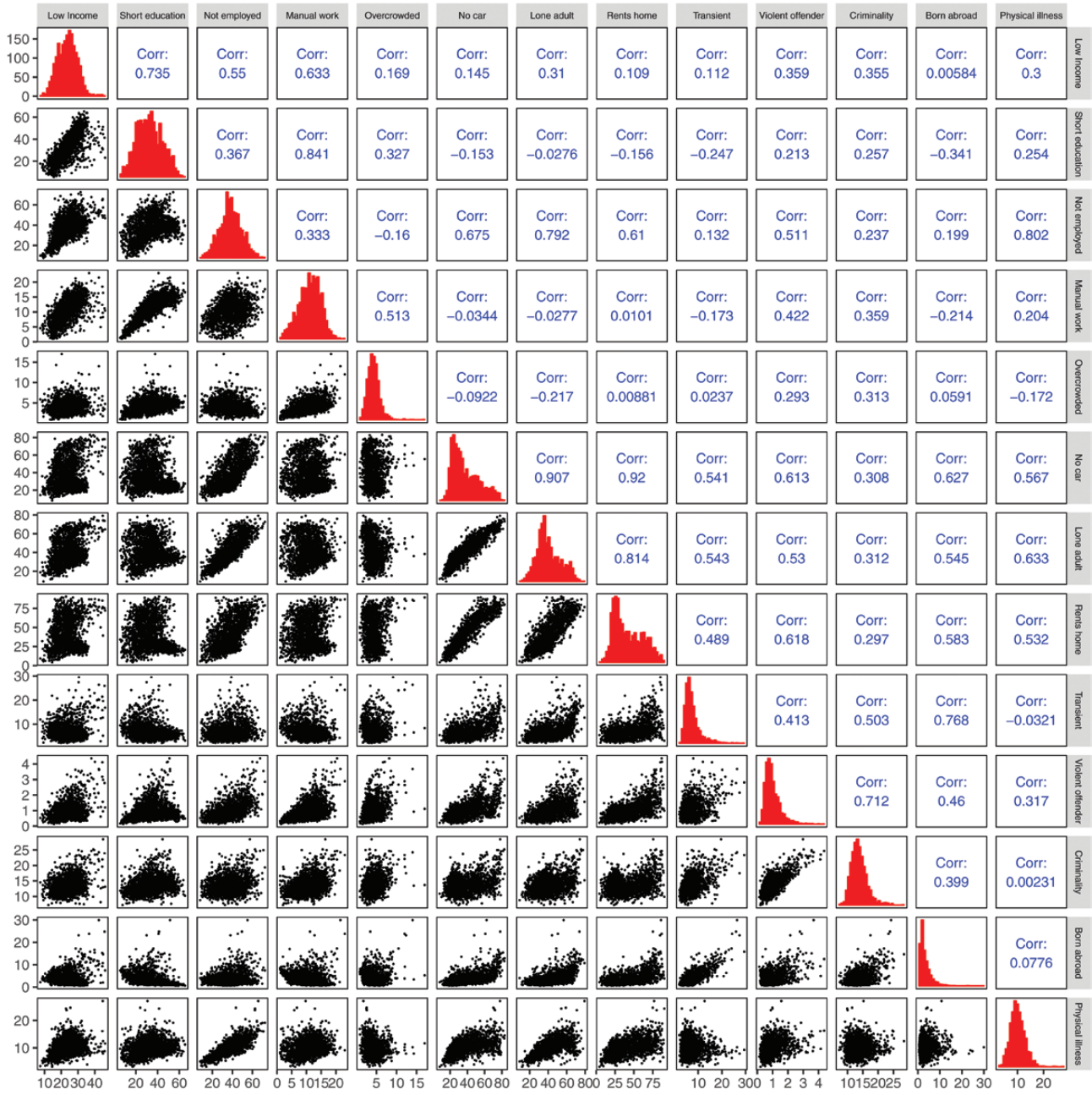

Fig. 1. Scatterplot of neighborhood-level covariates. The scatterplots reveal the correlation between the neighborhood-level covariates across the 1885 data zones as well as their distributions (details in Supplementary Methods 1 and 2, Supplementary Figure 1).

we examined multiple discrete area-level and individual-level indices across a number of sociodemographic and health domains. This constituted a broad array of explanatory variables but, as with any investigation conducted using routinely collected administrative data, we were constrained by the information that was available. Thus, the array of variables examined was not comprehensive, and a considerable degree of residual confounding in the multivariable modeling that we performed is plausible. For instance, following adjustment for all identified individual- and neighborhood-level covariates there remained statistically significant unexplained heterogeneity on schizophrenia risk across neighborhoods. There are numerous unmeasured individual-level genetic and environmental factors as well as area-level contextual factors that could explain this variability.

Among the neighborhood-level indices that we examined, the proportion of households without a car and the proportion of lone adult households were the strongest predictors of schizophrenia risk. Not owning a car has been used extensively in the literature as a proxy for poverty, but older age, living in an urban neighborhood with high quality local public transportation infrastructure, taking a strong political position on environmental

Table 4. Urbanicity, Population Density and Data Zone-Level Heterogeneity by Individual- and Neighborhood-Level Adjustment Scenarios

	Basic adjustment[a,b]		Full individual-level adjustment[a,c]	
	Specific contextual effect	General contextual effect	Specific contextual effect	General contextual effect
Measure of urbanization[d]	Incidence Rate Ratio of neighborhood per 1 sd increase	Median Incidence Rate ratio (95% Probability Interval)	Incidence Rate Ratio of neighborhood per 1 sd increase	Median Incidence Rate Ratio (95% Probability Interval)
No adjustment for neighborhood-level covariates				
Population Density	1.24 (1.20–1.29)	1.30 (1.24–1.36)	1.20 (1.16–1.25)	1.24 (1.17–1.31)
Urbanicity	1.98 (1.77–2.22)	1.29 (1.22–1.35)	1.78 (1.59–1.98)	1.23 (1.16–1.30)
Adjusted for neighborhood-level covariates[e]				
Population Density	1.08 (1.02–1.14)	1.23 (1.15–1.29)	1.08 (1.02–1.15)	1.22 (1.14–1.28)
Urbanicity	1.29 (1.10–1.50)	1.22 (1.15–1.29)	1.30 (1.11–1.51)	1.21 (1.13–1.28)
Adjusted for neighborhood-level covariates[e] and other urbanization proxy				
Population Density	1.06 (0.99–1.12)	1.22 (1.15–1.29)	1.06 (1.00–1.12)	1.21 (1.13–1.28)
Urbanicity	1.24 (1.06–1.45)	1.22 (1.15–1.29)	1.24 (1.06–1.46)	1.21 (1.13–1.28)

[a] Estimates were based on multilevel survival analyses, neighborhoods are 1885 novel data zones nested in Denmark's 98 municipalities. The 579 039 people born in Denmark 1972–1981 were followed for development of schizophrenia. During the follow-up period from 1982 to 2016, a total of 5103 developed schizophrenia during the 17 191 889 person-years at risk
[b] Estimates were adjusted for individual-level age and its interaction with sex and neighborhood-level age distribution (Basic adjustment).
[c] Estimates were adjusted for Basic adjustment and individual-level residential instability, parental Charlson, parental death, parental imprisonment, parental age, parental history of mental disorders, parental income, parental employment status and parental education.
[d] Proxy measure for urbanization. For each data zone, population density was calculated as the number of inhabitants divided by the area, log transformed and thereafter standardized to unit standard deviation. The estimate for urbanicity measure the effect of residence in the most urban environment compared to residence in the most rural environment. It was included as a trend variable scored as Capital 1, capital suburb 0.75, provincial city 0.5, provincial towns 0.25, and rural area 0. Both variables were delineated at initiation of follow-up. Due to the different scales, effect sizes are not directly comparable in size.
[e] Neighborhood-level indicators were summarized using the first 3 Principal Components of all neighborhood-level covariates (excl. urbanicity and population density).

pollution caused by vehicle exhaust fumes, and major life events such as marital break-up can all deter people from owning a car.[76] Conversely, in rural areas, car ownership is often considered a necessity, regardless of socioeconomic status. Thus, indices such as households without a car and those in which single adults live without other residing adults may act as crude markers for other unmeasured complex neighborhood characteristics. Localities, where not owning a car and not living with other adults, are much more common than in the average neighborhood are probably atypical in other influential ways that are unmeasured. Therefore, the observed associations might not be causal. Such variables are also strongly correlated at both area-level and individual-level (Figure 1). Thus, adults living in large cities with high population density are more likely to live in single-occupancy dwellings and not own a car.

Interestingly, studies have reported that the incidence of schizophrenia in ethnic minorities is greater when they compromise a smaller proportion of the population.[43,47,77] In this study including people born in Denmark to Danish-born parents, for each standard deviation increase in the proportion of neighborhood's residents who are foreign-born, schizophrenia risk increased 1.22 fold (Table 3). Thus, in neighborhoods where ethnic minority groups are relatively large in size, this "ethnic density" (or ethnic distinctness) influence may also operate among residents who do not belong to ethnic minorities (people born in Denmark to Danish-born parents in this study). Further studies are needed to investigate the potential generalizability of this novel finding, both in terms of setting and mental health outcome.

In summary, multiple neighborhood-level characteristics across a broad array were associated with schizophrenia risk and collectively these neighborhood-level constructs reduced the effect of urbanicity from 1.98 (95% CI: 1.77–2.22) to 1.30 (95% CI: 1.11–1.51), i.e., contextual factors explained the majority of the urbanicity effect.

Strengths and Limitations

The use of interlinked Danish national registers yielded abundant statistical power and precision for conducting this study. We had access to complete residential address information for all Danish residents. Ascertainment of schizophrenia cases was based on contacts with inpatient and outpatient psychiatric departments and visits to psychiatric emergency care units in a country where barriers to treatment are low, and where treatment is provided through a public healthcare system that is free of charge, and where there is virtually no private mental healthcare provision. Financial factors are thus far less likely to influence pathways to healthcare in Denmark compared to

other nations. Our study is thus representative of the entire population irrespective of recall bias, health status, and socioeconomic position.[18] The prospective nature of this study ensured that all covariates were measured before illness onset. The results of the study are therefore not biased by temporality nor selective migration of people prior to disease onset.[9,21]

In addition, although our results were based on longitudinal prospective survival analyses and have adjusted for some key confounders including history of parental mental illness, urbanicity, and socioeconomic position, as with all observational studies, causality cannot be inferred.[78]

Internationally, this is the largest cohort study to disentangle individual-level and neighborhood-level risk factors on schizophrenia risk. Nationally, it is the first Danish study to utilize a nationwide geographic division of homogeneously sized small area populations on any health outcome. The individual- and area-level measures included in this study may not constitute a comprehensive array of all risk factors. As with all register-based studies, we can only examine the information that's been collected for administrative purposes.

Conclusion

From the largest prospective multilevel survival analyses of schizophrenia risk conducted to date, multiple specific contextual constructs were associated with schizophrenia risk. There, however, remained a substantial level of unexplained heterogeneity in schizophrenia risk across neighborhood boundaries, and the effect of urbanicity was attenuated but remained significant. Although our analyses and findings are novel, we conclude that our understanding of the role of urbanicity in schizophrenia's etiology remains incomplete, and further population-based multilevel modeling studies are needed.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin Open* online.

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Conflict of interests

All authors declare no conflict of interest.

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