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Does Population Density and Neighborhood Deprivation Predict Schizophrenia? A Nationwide Swedish Family-Based Study of 2.4 Million Individuals

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People living in densely populated and socially disorganized areas have higher rates of psychiatric morbidity, but the potential causal status of such factors is uncertain. We used nationwide Swedish longitudinal registry data to identify all children born 1967–1989 (n = 2 361 585), including separate datasets for all cousins (n = 1 715 059) and siblings (n = 1 667 894). The nature of the associations between population density and neighborhood deprivation and individual risk for a schizophrenia diagnosis was investigated while adjusting for unobserved familial risk factors (through cousin and sibling comparisons) and then compared with similar associations for depression. We generated familial pedigree structures using the Multi-Generation Registry and identified study participants with schizophrenia and depression using the National Patient Registry. Fixed-effects logistic regression models were used to study within-family estimates. Population density, measured as ln(population size/km^2), at age 15 predicted subsequent schizophrenia in the population (OR = 1.10; 95% CI: 1.09; 1.11). Unobserved familial risk factors shared by cousins within extended families attenuated the association (1.06; 1.03; 1.10), and the link disappeared entirely within nuclear families (1.02; 0.97; 1.08). Similar results were found for neighborhood deprivation as predictor and for depression as outcome. Sensitivity tests demonstrated that timing and accumulation effects of the exposures (mean scores across birth, ages 1–5, 6–10, and 11–15 years) did not alter the findings. Excess risks of psychiatric morbidity, particularly schizophrenia, in densely populated and socioeconomically deprived Swedish neighborhoods appear, therefore, to result primarily from unobserved familial selection factors. Previous studies may have overemphasized the etiological importance of these environmental factors.

Key words: schizophrenia/urbanization/socioeconomic factors/multilevel models/confounding factors/quasiexperimental designs

Introduction

Large variations in psychiatric morbidity, specifically nonaffective psychotic disorders, across geographic areas within a country was first recognized in the 19th century.[1] Later work suggested that this variation was patterned according to the degree of social disorganization in residential areas.[2] That is, neighborhoods primarily located in densely populated settings[3,4] with high rates of social fragmentation and deprivation appeared to have the highest rates of psychiatric morbidity.[5–7] Importantly, these findings have also been replicated in a number of nationwide studies from Scandinavia,[8–14] where socioeconomic differences across neighborhoods are smaller than in other industrialized countries.[15]

The current understanding of wider environmental influences on schizophrenia, such as population density and neighborhood deprivation, suggests that the disorder onset either is likely triggered by stressors (ie, the stress vulnerability model)[16] or results from long-term exposure to these stressors (ie, the social defeat model),[17] particularly in individuals with genetic liabilities.[18] It remains unclear, however, to what extent these observations reflect social causation processes where an individual's exposure to neighborhood stressors actually causes the illness or selection where high-risk individuals and families with genetic and environmental liabilities are selected into densely populated or socioeconomically deprived areas.

Yet, there are problems with drawing causal inferences from epidemiological studies using observational data. Most notably, prior studies usually failed to control adequately for unmeasured genetic and environmental confounding,[19–21] likely a large problem given nonrandom allocation of families to different residential areas.[22] Consequently, genetically informed designs could help elucidate potential causal mechanisms.[5,23–26] Few studies have been conducted to date, however, and the results are

mixed, mainly due to relatively small and selected samples combined with heterogeneous outcome definitions.[27–29]

In the largest such study to date, we studied the associations between population density and neighborhood deprivation and schizophrenia and depression, respectively. We used longitudinal, Swedish total population data and cousin and sibling comparison models with approximately 2.4 million children born between 1967 and 1989 to assess the relative importance of unobserved familial confounding. We combined neighborhood exposures measured at birth, childhood, and adolescence, with family-based research designs to compare total population effects with those from differentially exposed cousins and siblings.

Methods

Sample

We linked data from numerous Swedish longitudinal, total population registers maintained by Statistics Sweden. Data linkage was possible through a unique 10-digit civic registration ID number assigned to all Swedish citizens at birth and to immigrants upon arrival to the country. Statistics Sweden gave us access to de-identified data after approval from the Regional Research Ethics Committee at Karolinska Institutet.

The following registers were used to generate the database: the Multi-Generation Register linked all index persons to their biological parents and enabled interconnecting biological siblings and cousins; the Small Area Marketing Statistics (SAMS) Register contained annual information on residential area characteristics; the Cause of Death Register provided mortality data; the Migration Register provided migration dates; the Population and Housing Register provided census data on a range of socioeconomic and demographic variables gathered in 1980, 1985, and 1990; the Integrated Database for Labor Market Research provided more comprehensive census data on all individuals 16 years of age and older and registered in Sweden as of December 31 each year since 1990; the National Patient Register supplied data on psychiatric inpatient care since 1973 (ICD-9 and -10) and specialist (non-general practitioner) outpatient care since 2001 (ICD-10); and the National Crime Register supplied detailed information on all criminal convictions in lower general court in Sweden since 1973.

We followed 2 530 788 study participants who were Swedish residents, born 1967–1989, and possible to link to both their biological parents, from their 15th birth date up until December 31, 2009. The median follow-up time was 16.5 years. We used exposure data from the end of the year they turned 15. Participants who had died (n = 23 359), migrated (n = 116 998), or been diagnosed with schizophrenia (n = 72) or depression (n = 1121) before the age of 16 were excluded. Moreover, we removed those who could not be linked to their residential area at the end of the year in which they turned 15 (n = 25 173) or lived in a neighborhood with fewer than 50 inhabitants (n = 2480) at the same time point. The final sample included 2,361,585 individuals, 93.3% of the targeted population. From this sample, we generated 2 additional datasets that included all biological first cousins (n = 1 715059) and full siblings (n = 1 667 894).

Neighborhood Definition

Following other neighborhood studies in Sweden,[11,14] we defined neighborhoods according to Statistics Sweden's SAMS classification system that captures small and internally socioeconomically homogenous residential areas. There are substantial socioeconomic differences across SAMS areas; it has been reported that between 1990 and 2004, the share of means-tested welfare recipients, a common measure of poverty in Sweden,[30] was approximately 29 times higher in the most compared with the least socioeconomically deprived decile.[24]

There are about 9200 SAMS areas with an average population size of approximately 1000 individuals. We discarded areas with a population size of less than 50 (eg, industrial areas, forests) to avoid statistical model convergence issues. The SAMS register annually links individuals with their SAMS area of residence at the end of the year. As such, within-year residential mobility is not captured in this measure.

Population Density and Neighborhood Deprivation

Population density was measured as the natural log of the absolute population size per squared kilometer. Natural log transformations are commonly used to limit the relative influence of the highest exposed observations in a positively skewed distribution.

Other neighborhood-level exposure variables were generated by aggregating data obtained through linkage of all individuals aged 25–64 years in the SAMS register to the annual census records. Prior to 1990, however, censuses were conducted every 5 years. Consequently, we linked individuals recorded in the SAMS register from 1982 to 1989 to the 1980 and 1985 censuses, respectively. In addition, due to the lack of data on the highest attained educational level prior to 1985, we used educational data from 1985 for those recorded in SAMS between 1982 and 1984.

We calculated a standardized omnibus measure of neighborhood deprivation for each SAMS area and year based on 4 items (ie, the proportion of individuals with less than secondary school qualifications, proportion not married, proportion not born in the Nordic countries, and neighborhood crime rate [sum of the number of criminal convictions in the given year divided by the population size]) derived as described above. We compared this measure of neighborhood deprivation with a similar measure[24] using the comprehensive annual censuses (1990–2004) that also included an additional 6 items: median neighborhood income, proportion of

unemployed, welfare recipients, single person/parent households, residential mobility, and violent crime rates. The correlation between these 2 measures was very high (r = .93; 95% CI: 0.93–0.93).

Study participants were linked to the annual population density and neighborhood deprivation scores associated with the area in which they resided. To investigate potential nonlinear associations, we studied the impact of these exposures categorized into quartiles.

Observed Confounders. All statistical models adjusted for sex, birth year (categorized into 5-year intervals), and birth order (categorized as first, second, third, and fourth or more).

Identification of Individuals With Schizophrenia and Depression

To minimize false-positive cases,[31] we defined study participants diagnosed with schizophrenia (ICD-8/9: 295; ICD-10: F20-21) on at least 2 separate occasions as having the disorder. Schizophrenia diagnoses in Swedish patient registries have been validated previously,[32] and we identified 4952 study participants (0.21%) with schizophrenia. Their mean age of onset was 26.3 years (95% CI: 26.1; 26.5).

Depression caseness was defined as having at least 2 hospital discharges of any depressive mood disorder (ICD-9: 296B; ICD-10: F32-F34, F38-F39). We excluded patients with any comorbid schizophrenia and bipolar disorder diagnosed during the study period. To date, no Swedish validation of depression diagnoses in the hospital discharge register exists, but recently a Danish study[33] concluded that single depressive episodes in Denmark's comparable national registries implied high predictive validity for moderate to severe types of depression. While lacking validation studies and attempting to reduce incongruence with the schizophrenia definition, we decided to only include patients with at least 2 separate hospital discharges with depression to minimize the risk of false-positive cases. Using this restrictive definition, we identified 41 372 (1.75%) study participants with depression and a mean age of onset of 27.2 years (95% CI: 27.2; 27.3).

Statistical Analyses

Cousin and sibling correlations for the exposures were estimated using linear mixed-effects models that allowed for varying intercepts across families, the magnitudes of which were expressed as intraclass correlations (ICCs), a measure of similarity between individuals within neighborhoods.[34] We specifically studied cousins and siblings who lived in different neighborhoods at age 15 to increase estimate accuracy.

We assessed general neighborhood influences: the extent that they accounted for the variation in schizophrenia and depression by fitting binomial generalized linear mixed-effects models (GLMMs)[35] to data. To calculate ICCs for the binary outcome variables, we assumed an underlying normal distribution of liabilities.[36] Crude models were fitted on the full population, while the adjusted models specifically studied the effects between siblings who lived in different neighborhoods at age 15. ICCs derived from the crude models will, therefore, measure the degree of similarity among all individuals who live in the same neighborhoods at age 15, while ICCs derived from the adjusted models will measure the degree of similarity among unrelated individuals who live in the same neighborhoods. The relative importance of familial selection factors will be observed as a function of the reduction of the ICC estimates across these models. To accommodate our complex data structure with individuals cross-nested within families and neighborhoods, the adjusted models used the cross-classified GLMM approach.[37]

To describe the impact of population density and neighborhood deprivation on schizophrenia and depression in the total population (Model I), we calculated ORs with corresponding 95% CIs from logistic regression models. We subsequently fitted fixed-effects logistic regression models[38] to the cousin and sibling samples and obtained within-family estimates of the exposures from comparing differentially exposed cousins (Model II) and siblings (Model III). On average, cousins and siblings share 12.5% and 50%, respectively, of their segregating genes, the latter also extensively share childhood environment. Attenuated within-family estimates among cousins and even lower estimates among siblings would consequently be expected if unobserved familial risk factors confounded associations found in the population. Conversely, if total population and within-family estimates were similar in magnitude, this would suggest that familial risk factors did not influence tested associations.

Developmentally Sensitive Periods and Accumulation Effects. Additionally, in a number of subanalyses, we tested for potential bias from ignoring exposure timing and accumulation effects. To maximize statistical power due to the relatively poor availability of exposure data prior to 1982, we studied the following subsamples: exposure at birth (cohorts born in 1968–1989 using county-level data on population density only; n = 2 250 925); mean exposure scores for both population density and neighborhood deprivation between ages 1 and 5 years (cohorts born in 1981–1989, n = 876 607); 6 and 10 years (cohorts born in 1976–1989, n = 1 354 971), and ages 11 and 15 years (cohorts born 1967–1989, n = 1 901 138).

Additional Sensitivity Analyses. To test the stability of estimates obtained in our analyses and to rule out alternative explanations, we conducted various complementary sensitivity analyses and reran Models I and III with alternative model parameterizations on different

outcome definitions and subsamples, First, we adjusted for both time at risk by fitting Cox regression models and the clustering of individuals in different combinations of families and neighborhoods by computing multiway cluster-robust SEs.[39] Second, we tested different categorizations (eg, tertiles and quintiles) of the exposures. Third, we studied the impact of the exposures on individuals who had been diagnosed with schizophrenia or depression only once and those who had been diagnosed solely in inpatient care settings. Last, we studied specific subsamples by excluding females, those of non-Swedish descent, and those who did not live with either parent at age 15 or by including only first-borns and single-child families.

All models were fitted using Stata IC 12.1[40] and MLwiN 2.29.[41]

Results

The 2 361 585 study participants included 1 715 059 first cousins nested within 559 270 extended families, and 1 667 894 full siblings nested within 719 666 nuclear families, and nested within 7388 neighborhoods. A total of 993 820 (58%) cousins and 317 535 (19%) siblings were living in different neighborhoods at age 15. Of these, 8752 cousins and 2327 siblings were also discordant for schizophrenia. Corresponding figures for depression were 82 121 and 18 993. Cousin and sibling ICCs in population density were estimated to .64 and .89, respectively (supplementary table 1). Equivalent estimates for neighborhood deprivation were 0.52 and 0.78, suggesting sufficient variability required in the subsequent within-family analyses. We could only identify 24 287 (1.03%) individuals who were not registered to be living in the same SAMS area as either one of their parents at age 15.

We found substantial differences in outcomes (table 1); siblings shared 49% of the variance in schizophrenia liability, while 21% of the variance in depression liability could be attributed to sibling resemblance. The crude general neighborhood effects were small and substantially attenuated when we adjusted for familial factors; neighborhoods did not significantly explain any remaining variance in schizophrenia (ICC = .006; 95% CI: 0.000; 0.021), but explained about 2% of the variance in depression (ICC = .023; 0.016–0.028).

Table 2 presents descriptive data on observed confounders addressed in this study. Females experienced lower risks of at least 2 schizophrenia diagnoses (OR = 0.52; 0.49–0.56) but higher risks of depression (OR = 1.77; 1.74–1.81). Moreover, we observed a nonlinear association between

Table 1. Crude and Family-Adjusted Neighborhood Intraclass Correlations

Disorder	Crude Neighborhood Model	Nuclear Family-Adjusted Cross-Classified Model	
	Neighborhoods	Neighborhoods	Nuclear families
Schizophrenia	0.041 (0.31; 0.056)	0.006 (0.000; 0.021)	0.487 (0.427; 0.528)
Depression	0.030 (0.027; 0.032)	0.023 (0.016; 0.028)	0.213 (0.184; 0.240)

Note: The estimates reflect the proportion of phenotypic variance that is attributed to neighborhoods and nuclear families.

Table 2. Prevalence and ORs With Corresponding 95% CIs for Sex, Birth Year, and Birth Order Among Individuals Diagnosed With Schizophrenia or Depression in Sweden

		Schizophrenia		Depression	
	Sample Size	Prevalence, %	OR (95% CI)	Prevalence, %	OR (95% CI)
Total	2 361 585	0.21	—	1.75	—
Sex					
Male	1 214 116	0.27	Reference	1.28	Reference
Female	1 147 469	0.14	0.52 (0.49; 0.56)	2.25	1.77 (1.74; 1.81)
Birth order					
1	999 709	0.20	Reference	1.71	Reference
2	859 499	0.20	0.98 (0.92; 1.05)	1.69	0.98 (0.96; 1.01)
3	353 508	0.20	0.96 (0.88; 1.04)	1.85	1.08 (1.05; 1.11)
4+	148 869	0.32	1.57 (1.42; 1.73)	2.16	1.26 (1.22; 1.31)
Birth year					
1967–1969	329 833	0.41	7.54 (6.65; 8.55)	1.65	0.98 (0.95; 1.02)
1970–1974	535 983	0.28	5.22 (4.60; 5.91)	1.69	1.01 (0.98; 1.04)
1975–1979	479 856	0.22	4.01 (3.52; 4.56)	1.80	1.08 (1.04; 1.11)
1980–1984	475 302	0.15	2.84 (2.48; 3.25)	1.94	1.16 (1.13; 1.19)
1985–1989	540 611	0.05	Reference	1.68	Reference

Note: OR, odds ratio; CI, confidence interval.

birth order and the outcomes where only children in the latest birth order category (4+) experienced 59% increased odds of schizophrenia and children in the 2 latest birth order categories experienced 8% and 26% increased odds of depression, respectively, compared with first-borns.

Individuals diagnosed with schizophrenia and depression grew up in more disorganized and densely populated residential areas at age 15 compared with those without a diagnosis (table 3). A percentage increase in the population density score was associated with a 10% increase in the odds of schizophrenia (OR = 1.10; 95% CI = 1.09–1.11) in the total population sample when sex, birth year, and birth order were adjusted for (Model I). However, when we adjusted for unobserved confounders shared by cousins within extended families (Model II), the population estimate of population density on schizophrenia was decreased by over a third (OR = 1.06; 1.03–1.10). Finally, when we adjusted for unobserved familial risk factors shared by siblings within nuclear families (Model III), effects were fully attenuated (OR = 1.02; 0.97–1.08). We observed very similar findings for neighborhood deprivation (table 3), categorical measures of both exposures (table 3) and depression as outcome (table 3).

In the youngest cohort of participants born between 1981 and 1989, we observed that 41% lived in the same neighborhoods as their siblings across the full period (ages 1–15). To account for the mobility across neighborhoods over time, we studied accumulation and timing effects of the exposures across ages 1–5, 6–10, and 11–15 years (table 4). The results did not diverge from our main findings; the observed associations in the population were fully attenuated within nuclear families, thus supporting the conclusion that unobserved familial risk factors were responsible for the observed associations. This pattern of associations was also observed in all of the additional sensitivity tests (supplementary tables 2–5).

Discussion

We performed the largest family-based study to date of the associations between population density and neighborhood deprivation and individual risk of schizophrenia and depression. Consistent with previous research suggesting low general neighborhood effects in total population samples,[13] we found that such effects accounted for merely 2% and 3% of variance in schizophrenia and depression, respectively. When we subsequently estimated family-adjusted general neighborhood effects that additionally accounted for the strong familial correlations in neighborhood residence (eg, 79% of the siblings lived in the same neighborhoods at age 15), we observed that neighborhoods did not account for significant variation in schizophrenia but accounted for about 2% in depression. In addition, we found that sibling similarities explained half of the variance in schizophrenia and a fifth of the variance in depression. In line with systematic reviews and population-based studies examining associations of neighborhood influences on nonaffective psychotic disorders and depression,[3,6,10,13,23] population density and neighborhood deprivation predicted both schizophrenia and depression in the population. However, in subsequent analyses of the same associations, when accounting for unobserved familial risk factors by studying differentially exposed cousins and siblings, we found that effects decreased substantially within extended families (cousin comparisons) and were entirely attenuated within nuclear families (sibling comparisons). Various sensitivity analyses found that these results were stable across

Table 3. ORs With Corresponding 95% CIs for Continuous and Categorical Measures of Population Density and Neighborhood Deprivation at Age 15 on Subsequent Risk for Schizophrenia and Depression Among Those Born in Sweden 1967–1989

	Schizophrenia			Depression		
	Model I	Model II	Model III	Model I	Model II	Model III
Population density						
Continuous measure	1.10 (1.09; 1.11)	1.06 (1.03; 1.10)	1.02 (0.97; 1.08)	1.03 (1.03; 1.04)	1.02 (1.01; 1.03)	1.00 (0.98; 1.02)
Quartile 1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	1.04 (0.95; 1.13)	1.01 (0.83; 1.22)	1.13 (0.80; 1.60)	1.06 (1.03; 1.09)	1.03 (0.97; 1.09)	1.00 (0.90; 1.11)
Quartile 3	1.17 (1.08; 1.27)	1.08 (0.89; 1.31)	1.16 (0.83; 1.63)	1.07 (1.04; 1.10)	1.08 (1.01; 1.14)	1.02 (0.91; 1.13)
Quartile 4 (high)	1.79 (1.66; 1.94)	1.46 (1.21; 1.77)	1.11 (0.78; 1.57)	1.23 (1.20; 1.27)	1.10 (1.03; 1.17)	0.96 (0.86; 1.07)
Neighborhood deprivation						
Continuous measure	1.43 (1.38; 1.49)	1.19 (1.07; 1.33)	1.01 (0.89; 1.16)	1.13 (1.11; 1.14)	1.09 (1.06; 1.13)	0.97 (0.92; 1.02)
Quartile 1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	0.92 (0.84; 1.01)	0.95 (0.80; 1.13)	0.95 (0.77; 1.18)	1.05 (1.02; 1.08)	0.99 (0.94; 1.05)	1.00 (0.93; 1.06)
Quartile 3	1.10 (1.02; 1.20)	1.24 (1.04; 1.48)	1.06 (0.83; 1.36)	1.10 (1.06; 1.13)	1.09 (1.03; 1.15)	1.06 (0.98; 1.14)
Quartile 4 (high)	1.64 (1.52; 1.77)	1.26 (1.06; 1.50)	1.06 (0.83; 1.36)	1.27 (1.23; 1.30)	1.10 (1.04; 1.16)	0.99 (0.91; 1.07)

Note: OR, odds ratio; CI, confidence interval. Model I: Full sample of unrelated children, adjusted for sex, birth order, and birth year. Model II: Within extended families (cousin comparisons), adjusted for sex, birth order, and birth year. Model III: Within nuclear families (sibling comparisons), sex, birth order, and birth year.

Table 4. ORs With Corresponding 95% CIs for Period and Accumulation Effects (Mean Scores) of Population Density and Neighborhood Deprivation

	Schizophrenia		Depression	
	Model I	Model III	Model I	Model III
Population density				
At birth	1.09 (1.07; 1.12)	1.02 (0.90; 1.16)	1.04 (1.03; 1.05)	1.00 (0.95; 1.05)
Ages 1–5	1.16 (1.12; 1.20)	1.15 (0.91; 1.46)	1.04 (1.04; 1.05)	1.01 (0.97; 1.05)
Ages 6–10	1.13 (1.10; 1.15)	1.00 (0.88; 1.13)	1.04 (1.04; 1.05)	0.98 (0.95; 1.01)
Ages 11–15	1.13 (1.11; 1.15)	1.03 (0.95; 1.12)	1.04 (1.04; 1.05)	1.02 (0.99; 1.04)
Neighborhood deprivation				
Ages 1–5	1.29 (1.23; 1.37)	0.84 (0.56; 1.25)	1.07 (1.05; 1.08)	1.03 (0.94; 1.12)
Ages 6–10	1.27 (1.23; 1.32)	0.84 (0.66; 1.08)	1.07 (1.06; 1.08)	1.01 (0.95; 1.08)
Ages 11–15	1.27 (1.24; 1.31)	0.94 (0.79; 1.11)	1.07 (1.06; 1.08)	0.99 (0.94; 1.04)

Note: OR, odds ratio; CI, confidence interval. Model I: Full sample of unrelated children, adjusted for sex, birth order, and birth year. Model III: Within nuclear families (sibling comparisons), adjusted for sex, birth order, and birth year.

sex, ethnicity, birth order, right censoring, nonlinearity, exposure timing, and accumulation effects, as well as alternative definitions of the outcomes.

Overall, our findings support a selection hypothesis; observed ecological risk increases in psychiatric morbidity in densely populated and socioeconomically deprived areas are primarily explained by unobserved familial risk factors. This implies that familial liabilities that explain the onset of schizophrenia and depression in individuals also explain their selection, indirectly via their parents, into densely populated or socioeconomically deprived areas. These findings do not result from insufficient variability in exposures either within families or between neighborhoods.

Prior studies scrutinizing neighborhood influences on mental health problems in the United States using (natural) experimental data have yielded mixed findings,[27–29] likely resulting from the use of relatively small and selected samples and less severe outcome measures. Some authors emphasize the relative importance of socioeconomic characteristics of neighborhoods in the etiology of psychosis,[7] but a recent prediction study excluded neighborhood deprivation measures due to low predictive validity.[42] While the extent to which the results presented here are generalizable to other contexts needs clarification in future research, it should be noted that all nationwide studies investigating the presented associations were conducted in Scandinavia.

Strengths and Weaknesses

The list of strengths includes the application of a longitudinal family-based research design with 2.4 million individuals, born in Sweden from 1967 to 1989. Well-defined and socially homogenous neighborhood definitions were employed, and neighborhood-level characteristics were measured at birth and during childhood and adolescence. The longitudinal nature of the exposures minimized the risk of misclassification and facilitated exploration of potential accumulation effects. Further, assessment of confounding was primarily accomplished through the family-based research design studying differentially exposed cousins and siblings and not with observed family-level confounders correlated with neighborhood-level exposures.

Eight methodological limitations should be noted. First, given that individuals to varying degrees chose their place of residence, estimates of neighborhood exposures are inherently biased due to unobserved individual and familial characteristics being correlated with the neighborhood exposure variables. We counteracted potential risks of such bias in several important ways: neighborhood exposure data were collected only prior to the age of 16 when the individuals' choice is limited (ie, parents make final decisions), and we adjusted for unobserved familial factors explaining parental choices of neighborhoods and included a longitudinal neighborhood exposure measure accounting for movements in and out of multiple neighborhood contexts.[43] If anything, remaining bias after these corrections would drive the estimates away from the null.

Second, while we specifically focused on the smallest and largest definitions of residential areas in Sweden (SAMS areas and counties), we cannot exclude, however unlikely, that other geographical representations of neighborhoods could potentially account for a larger share of the variances in the studied outcomes. Previous neighborhood studies on schizophrenia in Sweden using similar data sets have additionally found negligible effects of both municipalities and primary schools.[13]

Third, our strict approach of increasing the diagnostic precision of the outcome variables by only including patients with at least 2 episodes of schizophrenia and depression could potentially minimize the generalizability of our findings, especially in the case of depression. To

investigate the potential impact of ascertainment bias, we tested a wide range of broader alternative outcome definitions (supplementary table 4) and we failed to observe any meaningful discrepancies from the main findings.

Fourth, in this study we only present results from age 15 (table 3) and by 5-year age bands (ages 1–5, 6–10, and 11–15; table 4). Despite the lack of evidence for any effects consistent with a causal inference in these analyses, it could theoretically be possible that even longer exposure periods (eg, ages 1–15) could yield different results. Unfortunately, our existing data did not have enough statistical power to adequately assess this possibility; while we found no effects that were significantly different from zero, the CIs were too wide and included realistic alternatives, which is why we decided not to present them. Meta-analyses or pooled studies from different large-scale registries may still be warranted to confidently exclude this possibility.

Fifth, although our study have shown that familial effects account for a large proportion of the neighborhoods effects, our design does not address the question whether these familial effects are genetic or shared environmental in origin. Genetic confounding could result from the same genes simultaneously influencing residence in deprived neighborhoods in urban settings as well as later psychiatric morbidity while shared environmental confounding could result from cousins spending longer periods in similar residential environments compared with unrelated individuals before the age 15. Studies with complex quantitative genetic designs will be needed for such endeavors.

Sixth, a common but criticized[21] approach of estimating genetic risk for schizophrenia in nationwide studies has been to adjust for lifetime occurrence in first-degree relatives of study participants. Consistent with previous findings, associations studied by us were only marginally attenuated when we adjusted for genetic risk using this traditional approach (supplementary table 6). Once again, this underlines the importance of considering unobserved familial risk factors in epidemiological studies of psychiatric disorders.

Seventh, inferences from sibling comparison models are contingent upon numerous important assumptions including that siblings share their environment, that exposed siblings do not exert any influence on unexposed siblings, and that differentially exposed siblings are generalizable to the total population.[26,44,45] As expected, we found that differentially exposed siblings were living in more densely populated and deprived neighborhoods than the total population (mean differences: 0.10 [0.10; 0.11] and 0.36 [0.36; 0.37], respectively). Nevertheless, the differences between differentially exposed cousins and the total population were negligible (mean differences: −0.01 [−0.01; −0.01] and −0.08 [−0.07; −0.08], respectively) and the within-extended family results matched the within nuclear family analyses.

Lastly, given that we have reported consistent null findings across a number of different exposure and outcome definitions, one potential concern might be that these findings result from our choice of statistical models. For the general neighborhood effects, we observed a full attenuation in schizophrenia but we only observed a 23% reduction of the effects in depression (table 1). For the specific neighborhood influences, all models, including the sensitivity tests adopting a series of different statistical parameterizations (supplementary table 2), reported null findings (table 3). We would like to emphasize that family fixed-effects models are commonly applied in epidemiology and many related disciplines to investigate whether observed associations are consistent with causal inferences.[25,45]

To summarize, our findings suggest that familial selection factors account for the associations between population density, neighborhood deprivation, and being diagnosed with schizophrenia and that neighborhoods generally account for a very limited share of the phenotypic variance. This was also found for depression. Omission of adequate adjustments for familial confounding may have led previous authors to overemphasize the relative importance of the direct or moderated effects of these wider environmental risk factors. Epidemiological neighborhood studies that rely solely on observed confounders risk obtaining severely biased estimates and should therefore be cautiously interpreted. Future research efforts should be directed toward elucidating the underlying genetic and environmental mechanisms through the continued development of complex intergenerational quantitative genetic models.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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