Individuals, Schools, and Neighborhood

A Multilevel Longitudinal Study of Variation in Incidence of Psychotic Disorders

Stanley Zammit, PhD; Glyn Lewis, PhD; Jon Rasbash, PhD†; Christina Dalman, PhD; Jan-Eric Gustafsson, PhD; Peter Allebeck, PhD

Context: Incidence of schizophrenia and other nonaffective psychoses is greater in urban than rural areas, but the reason is unclear. Few studies have examined whether both individual and neighborhood characteristics can explain this association. Furthermore, as has been shown for ethnicity, the effect of individual characteristics may depend on neighborhood context.

Objectives: To examine (1) whether individual, school, or area characteristics are associated with psychosis and can explain the association with urbanicity and (2) whether effects of individual characteristics on risk of psychosis vary according to school context (reflecting both peer group and neighborhood effects).

Design: Multilevel longitudinal study of all individuals born in Sweden in 1972 and 1977. Diagnoses were identified through linkage with the Swedish National Patient Register until December 31, 2003.

Setting: Population-based.

Participants: A total of 203 829 individuals with data at individual, school, municipality, and county levels.

Main Outcome Measures: Any nonaffective psychosis, including schizophrenia (881 subjects; 0.43% cumulative incidence). For the study of interactions, the outcome was any psychosis (1944 subjects; 0.95% cumulative incidence).

Results: Almost all the variance in risk of nonaffective psychosis was explained by individual-level rather than higher-level variation. An association between urbanicity and nonaffective psychosis was explained by higher-level characteristics, primarily school-level social fragmentation. We observed cross-level interactions between individual- and school-level markers of ethnicity, social fragmentation, and deprivation on risk of developing any psychotic disorder, all with qualitative patterns of interaction.

Conclusions: The association between urbanicity and psychosis appears to be a reflection of increased social fragmentation present within cities. The qualitative interactions observed are consistent with a hypothesis that certain characteristics that define individuals as being different from most other people in their local environment may increase risk of psychosis. These findings have potentially important implications for understanding the etiology of psychotic disorders and for informing social policy.

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Author Affiliations: MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff, Wales (Dr Zammit); Academic Unit of Psychiatry (Drs Zammit and Lewis) and Centre for Multilevel Modelling (Dr Rasbash), University of Bristol, Bristol, England; Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden (Drs Dalman and Allebeck); and Department of Education, University of Göteborg, Göteborg, Sweden (Dr Gustafsson).
†Deceased.

THERE IS SUBSTANTIAL WORLDwide variation in incidence rates of schizophrenia.[1,2] The clearest geographic pattern within this distribution of rates is that urban areas have a higher incidence of schizophrenia than rural areas.[3-6] A similar association with urbanicity has been described for other nonaffective psychoses[7,8] but less consistently so for affective psychoses.[8-12] Furthermore, there is marked variation in rates of these disorders across neighborhoods within cities, although this variation is not described for affective psychoses.[3,13,14]

Possible explanations proposed to explain these findings relate to characteristics of either the individuals who live in cities (compositional effects) or the areas in which they live (contextual effects). Characteristics of individuals that are more common in those living in urban areas and that are associated with increased risk of psychosis include minority ethnic and migrant status,[15] family history,[16] cannabis use,[17] and markers of social and economic adversity, such as growing up in a single-parent household.[18] However, the association with urbanicity has persisted when studies have adjusted for some of these characteristics.[4,7,19,20]

Characteristics of neighborhoods that have been associated with increased risk of psychosis include population and ethnic density, deprivation, and social fragmentation or reduced social capital and cohesion (see reviews[5,21]). Although area characteristics have long been associated with schizophrenia in ecological studies, statistical methods such as multilevel modeling that allow us to tease out the effects of area independently of the characteristics of individuals who live in these areas have been widely accessible only in recent years. Where studies have examined both area and individual effects, and there have been relatively few such studies to date, associations with deprivation seem to have been explained by characteristics of the people living in such areas,[13,22-24] whereas associations with social fragmentation have usually persisted.[13,14,24,25] Almost all studies of area-level exposures to date have used cross-sectional data, and it is possible therefore that any association between area-level variables and psychosis is due to individuals with psychosis changing area after illness onset.

There are 2 other advantages of multilevel-model approaches to studying both area and individual effects simultaneously. The first is that they allow us to estimate the proportion of the variation in incidence of schizophrenia attributable at each level. For most psychiatric disorders, almost all variation seems to be explained by individual effects, and relatively little (less than 5%) is explained by neighborhood characteristics.[26-28] The 2 studies to date that have examined this question for schizophrenia reported much larger variation at the neighborhood level (Aetiology and Ethnicity in Schizophrenia and Other Psychoses [AESOP] study,[13] 26%; 95% confidence interval, 13%-45%; Maastricht study,[14] 12%; 95% confidence interval, 0%-22%). However, although the use of multilevel-model approaches was appropriate in these studies, these are likely to be substantial overestimates of the proportion of variance at the neighborhood level because the statistical methods used for calculation were invalid for the types of model (Poisson) used (although this would not have affected any of the other estimates reported in these studies). A revised estimate of the proportion of variance from the AESOP study is indeed more conservative (neighborhood-level variation, approximately 4%).

The other advantage of using multilevel modeling approaches is that they allow us to study how individual effects vary according to the context where someone lives (cross-level interactions). For example, psychosis risk associated with being of a minority ethnic group appears to be moderated by the proportion of ethnic minority individuals across different neighborhoods.[13,22,29] Area or contextual effects may therefore still be important even though little of the variation in incidence is explained at area levels.

It remains unclear to what extent individual and area effects contribute to variation in incidence of psychosis, and what it is about living in urban areas that explains the increased incidence of schizophrenia compared with more rural areas. The aims of this study were therefore as follows: (1) to examine whether the association between urbanicity and psychosis was explained by either individual sociodemographic characteristics or markers of adversity or by area-level measures of density, ethnicity, deprivation, or social fragmentation; (2) to examine whether area-level characteristics were associated with risk of developing psychosis, independently of individual effects; (3) to examine the proportion of variation in psychosis incidence at individual and area levels; and (4) to examine whether individual effects on risk of psychosis varied according to where individuals lived.

METHODS

SAMPLE

The sample consisted of all individuals born in Sweden in 1972 and 1977 who were resident in Sweden at age 16 years (N = 213 395). Record linkages were performed by means of the unique person identification numbers used in Sweden. Mortality in the cohort was assessed by linkage with the National Cause-of-Death Register. Data on migration and socioeconomic conditions were obtained by linkage with census data, and data were also linked with registers covering occupation and income in parents, available at Statistics Sweden. Linkage with the Multi-Generation Register enabled us to identify parental data. Linkage to the Swedish National School Register was used for identification of schools attended. Diagnoses were identified through linkage with the Swedish National Patient Register up to December 31, 2003. This method recorded about 83% of all psychiatric admissions in 1973. Coverage was 97% from 1974 through 1983, 80% to 95% from 1984 through 1986, and virtually complete since 1987. Twenty-five individuals with onset of psychosis before age 17 years were excluded from the study.

Of those never having been admitted with a psychotic illness before the end of follow-up, 1414 individuals had emigrated, while 1156 had died. Of the remaining sample, 6996 had missing data on school attended or municipality lived in at age 16 years and were also excluded, leaving a sample of 203 829 individuals. Missing data for any of the exposure variables or covariates ranged from 0 to 21 299, and in total 40 908 had missing data for at least 1 of the variables included in the final model (final model n = 169 910).

MEASURES

Outcomes

Our primary outcome, defined a priori to maximize statistical power, was that of clinical diagnoses of all nonaffective psychoses (*International Classification of Diseases, Eighth Revision, Ninth Revision,* and *Tenth Revision* [*ICD-8, ICD-9,* and *ICD-10,* respectively]; *ICD-9* from 1987; *ICD-10* from 1997). This included schizophrenia (*ICD-8* and *ICD-9* code 295 excluding 295.4, 295.5, 295.7; *ICD-10* code F20) and other nonaffective psychoses (*ICD-8* and *ICD-9* codes 295.4, 295.5, 295.7, 297, 298.2-298.9; *ICD-8* code 299; *ICD-10* codes F21-F29). Schizophrenia diagnoses have been shown to have good validity with *DSM* research criteria, although this validity has not been studied for other psychotic diagnoses.[30-32]

Exposures

Data were structured at the following ascending hierarchical levels: individuals (n = 203 829), school year groups at age 16 years (n = 2106), schools (n = 1264), municipalities (n = 284), and counties (n = 24). Fixed effects were examined at the individual level; the level of the school year group, ie, school data for each specific year group (the school level); and the municipality level.

Individual-level variables included sex, having any psychosis in either biological parent, being foreign-born (0, 1, or 2 biological parents born abroad), changing municipalities between ages 8 and 16 years, parental socioeconomic position (unemployed, blue collar, white collar, company owner; highest of rearing parents), parental welfare benefit status, family income (total of income, welfare benefits, and disability pensions for rearing parents), single-parent household, parental education (<9 years, 9-10 years, secondary school, higher education; highest of rearing parents), and school grade achieved at age 16 years (continuous score between 1 [lowest] and 6 [highest]).

School-level variables were derived from averaging individual data. This was done only for schools that had at least 10 children available in that year. School-level variables included foreign-born average (proportion of children with 1 or both parents born abroad; median, 0.15; 90% range, 0.03-0.65), social fragmentation average (proportion of children who migrated into Sweden, moved into a different municipality between ages 8 and 16 years, or were raised in single-parent households; median, 0.23; 90% range, 0.08-0.46), deprivation average (proportion of children with parents unemployed, parents receiving welfare benefits, or parents in lowest 10% of income; median, 0.15; 90% range, 0.05-0.30), and low grade average (proportion of children scoring in lowest 10% of grade score; median, 0.10; 90% range, 0.02-0.18).

Municipality-level data included measures of urbanicity (city [Stockholm, Gothenburg, and Malmo], town [>20 000 inhabitants in 1980], rural [≤20 000 inhabitants]), population density, and markers of deprivation (derived by summing *z* scores for mean income, proportion unemployed, and proportion receiving welfare benefits) and social fragmentation (derived by summing *z* scores for proportion of people migrating in/out of the municipality, voting in municipality elections, individuals married, and single-person households).

STATISTICAL ANALYSIS

Multilevel models were derived using MLwiN software.[33] Null, random-effects models were first derived, and then individual-, school-, and finally municipality-level fixed effects were subsequently added to the models in this order. Birth year was included in all random-effects and fixed-effects models. Because outcomes were binary, we used multilevel logistic regression. In a binary response multilevel model, the measurement level (in our case, person) variance is a function of the mean and is on the probability scale. The variances of higher-level effects are on the logistic scale. We can translate the person-level variance onto the logistic scale if we are prepared to assume a continuous latent variable with a threshold defining a binary outcome. In this case the person-level variance is standardized to the standardized logistic variance of $\pi^2/3 \approx 3.29$. If, in a 3-level model, unexplained variance at level 2 is v_2 and at level 3 is v_3, the proportion of the total unexplained variance at level *j* is estimated as $v_j/(v_2+v_3+3.29)$.

In the logistic models, parameters were estimated by means of Markov chain Monte Carlo methods.[34] Markov chain Monte Carlo computations with 10 000 simulations were used to estimate fixed-model parameters, with 100 000 simulations used to estimate random-model parameters and their 95% confidence interval estimates. Effects for school-level variables are reported per 10% increase in proportion, and those for municipality-level variables are per standard deviation increase. Statistical significance of fixed-effect estimates, including cross-level interactions, were tested by deriving *Z* ratios and comparing against a normal distribution.

To investigate whether individual-level characteristic varied according to context, we created the following variables for testing cross-level interactions: (1) individual-level deprivation (summed score of parental unemployment [yes/no], family receiving welfare benefits [yes/no], and family income in lowest 10th percentile [yes/no]; score range, 0-3); and (2) individual-level social fragmentation (summed score of single-parent family [yes/no], immigrated during childhood [yes/no], and moved into a different municipality between ages 8 and 16 years [yes/no]; score range, 0-3).

Interactions were first examined with the use of all nonaffective psychoses as our outcome. However, to maximize power for the study of interactions, we then combined all nonaffective psychoses with affective psychoses (*ICD-8* and *ICD-9* codes 296.1-296.8, 298.0-298.1; *ICD-10* codes F31, F30.2, F33.3) and other psychoses (*ICD-8* and *ICD-9* codes 296 [unspecified], 296.0, 296.9, 298.0, 298.1) as our outcome. We examined 4 different interactions within multiplicative statistical models: (1) individual foreign-born × school-level foreign-born average; (2) individual social fragmentation × school-level social fragmentation average; (3) individual deprivation × school-level deprivation average; and (4) individual grade × school-level grade average.

RESULTS

Of the 203 829 subjects, 328 (0.16%) were ever admitted with a diagnosis of schizophrenia, 741 (0.36%) with other nonaffective psychoses, 355 (0.17%) with affective psychoses, and 953 (0.47%) with other psychoses. Individuals may have received more than 1 diagnosis during follow-up. The total with any nonaffective psychosis, our primary outcome, was 881 (0.43%; 95% confidence interval, 0.40%-0.46%).

MAIN EFFECT OF URBANICITY

As shown in **Table 1**, all individual-, school-, and municipality-level variables were associated both with urbanicity (dichotomized for the purpose of this table *only*) and with risk of nonaffective psychosis. The potential effect of confounding for most of these variables was that they could explain an association between urbanicity and psychosis. The exceptions to this were family income and school grade, in which the patterns of associations meant that confounding by these variables could obscure an association between urbanicity and psychosis.

The risk of nonaffective psychosis was higher in cities and towns than in rural areas (**Table 2**). The association between living in a city and psychosis was attenuated, but nevertheless persisted, when adjustment was made for individual-level factors (Table 2). This association was eliminated when we adjusted further for school- and municipality-level factors. The factors that attenuated the urban association the most were school-level social fragmentation and municipality-level population density.

All school-level characteristics were associated with nonaffective psychosis in the crude analysis (**Table 3**; model 0), but, with the exception of social fragmentation, these associations were eliminated after adjustment only for individual-level effects (data not shown). Similarly, all municipality-level characteristics were associated with psychosis in the crude analysis (Table 3; model 0); after adjustment for individual-level factors, the association with social fragmentation was eliminated, whereas those with population density and with deprivation persisted (model 1; data not shown).

Table 1. Distribution of Confounders in Relation to Urbanicity and Any Nonaffective Psychosis

Confounder	City	Town/Rural	Psychosis[a]	No Psychosis[b]
% of Sample With Confounder Within City/Rural or Psychosis/Nonpsychosis Groups				
Individual				
Family history	3.9	3.5	13.7	3.5
≥1 Foreign-born parent	27.6	14.2	32.2	18.3
Single-parent family	17.4	11.0	22.2	12.7
Parent unemployed	4.3	3.4	9.0	3.8
Parent receiving welfare benefits	6.7	5.5	12.4	6.0
Parental income in lowest 10%	9.2	10.0	16.4	9.9
Parental higher education	41.0	31.9	36.4	34.2
School grade in lowest 10%	8.7	10.8	22.6	10.2
School[c]				
Foreign-born	27.9	14.4	23.5	18.7
Social fragmentation	32.8	21.9	28.9	25.1
Deprivation	15.8	15.3	18.6	15.8
Low grade average	8.8	10.7	9.1	9.9
Mean Standardized Score (SD) of Confounder Within City/Rural or Psychosis/Nonpsychosis Groups				
Municipality				
Population density	0.92 (1.7)	−0.33 (0.1)	0.20 (1.2)	−0.01 (1.0)
Foreign-born	0.61 (1.7)	−0.21 (0.5)	−0.02 (0.9)	−0.00 (1.0)
Social fragmentation	1.04 (1.1)	−0.36 (0.7)	0.12 (1.0)	−0.01 (1.0)
Deprivation	−0.50 (1.6)	0.16 (0.6)	−0.12 (1.0)	0.00 (1.0)

[a] Any nonaffective psychosis.
[b] No diagnosis of any nonaffective psychosis.
[c] Percentages of individuals within school with 1 or both parents born abroad, 1 or more markers of social fragmentation, 1 or more markers of deprivation, and grade average in lowest 10%; urbanicity was dichotomized for the purpose of this table *only*.

Table 2. Association for Any Nonaffective Psychosis According to Urbanicity Status

	OR (95% CI)			
	Model 0[a]	Model 1[b]	Model 2[c]	Model 3[d]
Rural	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Town	1.12 (0.92-1.35)	1.06 (0.85-1.33)	1.05 (0.83-1.32)	1.01 (0.80-1.29)
City	1.41 (1.09-1.82)	1.32 (1.01-1.72)	1.23 (0.90-1.67)	1.10 (0.77-1.57)
Trend	1.17 (1.03-1.34)	1.14 (0.99-1.31)	1.10 (0.94-1.29)	1.04 (0.88-1.25)
P value for trend	.02	.06	.22	.62

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Includes birth year and variance components at school, municipality, and county levels.
[b] Same as model 0, with adjustment for sex, family history of psychosis, being foreign-born, moving from the area, parental education, parental socioeconomic position/unemployment, receipt of welfare benefits, family income, single-parent family, and school grade.
[c] Same as model 1, with additional adjustment for school-level social fragmentation, deprivation, and percentage of foreign-born parents.
[d] Same as model 2, with additional adjustment for municipality-level social fragmentation, deprivation, and population density.

In the fully adjusted final model (Table 3; model 3) that included all individual-, school-, and municipality-level variables, school-level social fragmentation was the only contextual effect that remained associated with nonaffective psychosis. Individual-level characteristics associated with psychosis in the final model included family history, being foreign-born, being raised in a single-parent household, and obtaining lower scores on the school grade score.

AREA-LEVEL VARIATION

The proportion of variation in cumulative risk of nonaffective psychosis at each level is also shown in Table 3. In the null model only 2.2% of the variance was at higher levels, and this estimate was unchanged when individual fixed effects were included. The confidence intervals indicate that, even at its uppermost limit, less than 7% of the variance in cumulative risk of psychosis can be explained by higher-level variation and that almost all variation is due to individual-level variation.

STUDY OF CROSS-LEVEL INTERACTIONS

There was strong statistical evidence of cross-level interactions between (1) being foreign-born × school foreign-born average, (2) social fragmentation × school social fragmentation average, and (3) deprivation × school deprivation average on risk of nonaffective psychosis in the unadjusted analyses. These associations were all partly attenuated, with confidence intervals now including the null effect after adjustment for individual-, school-, and municipality-level variables. However, the patterns of interaction were similar for schizophrenia,

Table 3. Crude and Fully Adjusted Results for Association Between Any Nonaffective Psychosis and Individual-, School-, and Municipality-Level Variables

	OR (95% CI)		
	Model 0[a]	Model 3[b]	*P* Value
Individual			
Family history	4.31 (3.53-5.26)	3.59 (2.80-4.59)	<.001
Foreign-born, parents			
0	1 [Reference]	1 [Reference]	
1	1.93 (1.59-2.34)	1.71 (1.36-2.15)	<.001
2	2.33 (1.91-2.84)	1.91 (1.42-2.55)	
Single parent	1.92 (1.62-2.28)	1.33 (1.05-1.69)	.04
Parent unemployment[c]	2.54 (1.95-3.29)	1.01 (0.68-1.50)	.58
Parental education[d]	0.95 (0.74-1.23)	0.84 (0.63-1.10)	.74
Parent receiving welfare benefits	1.89 (1.49-2.39)	1.14 (0.82-1.58)	.45
Family income[e]	0.74 (0.66-0.84)	0.93 (0.81-1.07)	.31
School grade[e]	0.69 (0.65-0.74)	0.67 (0.62-0.73)	<.001
Moved municipality	1.50 (1.24-1.82)	0.95 (0.74-1.23)	.87
School			
Social fragmentation[f]	1.16 (1.10-1.22)	1.09 (1.01-1.18)	.04
Foreign-born[f]	1.14 (1.07-1.20)	0.95 (0.86-1.04)	.26
Deprivation[f]	1.16 (1.06-1.28)	1.08 (0.94-1.25)	.27
Municipality			
Population density[e]	1.13 (1.03-1.25)	1.04 (0.94-1.14)	.42
Social fragmentation[e]	1.08 (0.99-1.18)	1.03 (0.91-1.15)	.66
Deprivation[e]	0.90 (0.82-0.99)	0.95 (0.79-1.15)	.12

	% Variance (95% CI)[g]	
	Null Model[h]	Full Model[b]
Variance partition coefficients		
County	1.2 (0.2-3.0)	0.3 (0.0-1.5)
Municipality	0.6 (0.0-2.1)	0.3 (0.0-1.1)
School	0.2 (0.0-0.7)	0.1 (0.0-0.2)
School year	0.2 (0.0-0.6)	0.1 (0.0-0.2)
Total higher levels	2.2 (0.2-6.4)	0.8 (0.0-3.0)
Individual level	97.8 (93.6-99.8)	99.2 (97.0-100.0)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Includes birth year and variance components at school, municipality, and county levels.
[b] Includes all variables in this table, plus birth year and variance components at school, municipality, and county levels.
[c] Unemployment vs white-collar employment (*P* value is overall *P* for 4-category variable).
[d] Less than 9 years vs secondary education (*P* value is overall *P* for 4-category variable).
[e] Per standard deviation.
[f] Per 10% increase.
[g] Percentage of overall variance at that level.
[h] Includes birth year as the only fixed effect in model.

other nonaffective psychoses, affective psychoses, and other psychoses when all these psychosis categories were examined separately (eTable; available at http://www.archgenpsychiatry.com). To maximize power, we therefore combined affective and other psychoses (1944 subjects; 0.95% cumulative incidence) with all nonaffective psychoses as our outcome for the study of interactions (although this was not an a priori decision).

For all psychoses grouped together (**Table 4**), there was stronger evidence that individuals who were foreign-born were at a high risk of developing psychosis if they were part of a school group with very few others who were foreign-born, and this risk decreased if their school group consisted of a large proportion of foreign-born individuals (**Figure 1**). An opposite pattern of risks was observed for individuals whose parents were both born in Sweden (adjusted interaction, $P = .02$). Similar patterns of interaction (**Figure 2** and **Figure 3**) were observed for social fragmentation ($P = .004$) and deprivation ($P = .06$) but not for grades ($P = .55$). All 3 interactions are qualitative; in other words, risk of psychosis associated with the presence of an individual-level characteristic changed in an *opposite* direction compared with individuals without that characteristic as the context changed.

Differences from baseline groups for each of the 3 interactions were significant primarily within the lower halves of the school-level averages (eFigures 1 through 3), with greater uncertainty around estimates at the higher ends of the school-level averages because these were based on relatively small proportions of the sample.

The patterns of interaction remained similar when we used different methods of coding individual- and school-level variables (for example, using deciles or grouping with different cutoffs), suggesting that these interactions are robust to variation in the manner in which data were defined.

Table 4. Main Effects and Cross-Level Interactions Between Individual-Level (L1) and School-Level (L2) Variables for Any Psychosis

		OR (95% CI)							
		Crude[c]				Adjusted[d]			
L1 Variable[a]	L2 Variable[b]	Effect of L1	Effect of L2	Interaction Effect	Interaction *P* Value	Effect of L1	Effect of L2	Interaction Effect	Interaction *P* Value
Foreign-born	Foreign-born	1.51 (1.33-1.71)	1.17 (1.08-1.27)	0.95 (0.91-0.98)	.006	1.32 (1.16-1.50)	1.16 (1.02-1.22)	0.95 (0.91-0.99)	.02
Social fragmentation	Social fragmentation	2.14 (1.81-2.53)	1.15 (1.09-1.22)	0.90 (0.85-0.95)	<.001	1.74 (1.45-2.09)	1.12 (1.04-1.20)	0.92 (0.86-0.97)	.004
Deprivation	Deprivation	1.78 (1.48-2.14)	1.17 (1.09-1.26)	0.89 (0.81-0.96)	.005	1.34 (1.11-1.63)	1.10 (1.00-1.21)	0.92 (0.84-1.00)	.06
Grade	Low grade	0.67 (0.58-0.78)	0.89 (0.64-1.26)	1.02 (0.90-1.16)	.71	0.70 (0.60-0.81)	0.78 (0.56-1.10)	1.04 (0.92-1.17)	.55

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Per score of 1.
[b] Per 10% increase.
[c] Models include L1 and L2 variables and their interaction term, birth year, and variance components at school, municipality, and county levels.
[d] Models adjusted for all L1 and L2 variables in this table, plus birth year and variance components at school, municipality, and county levels.

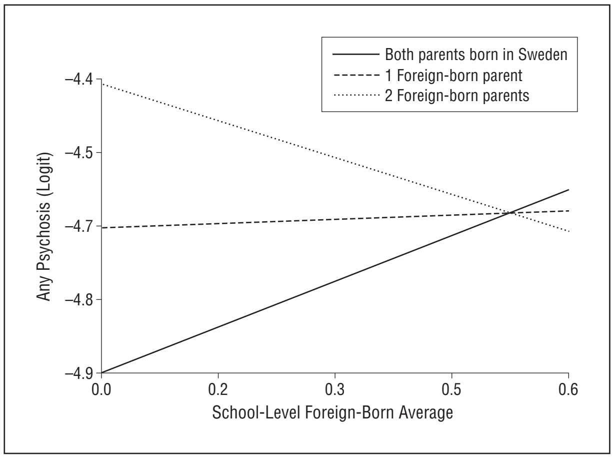

Figure 1. Cross-level interaction between foreign-born status and school-level foreign-born average. For non–foreign-born individuals, risk of any psychosis *increases* as the proportion of foreign-born individuals within the school increases. However, for foreign-born individuals, risk of any psychosis *decreases* as the proportion of foreign-born individuals within the school increases.

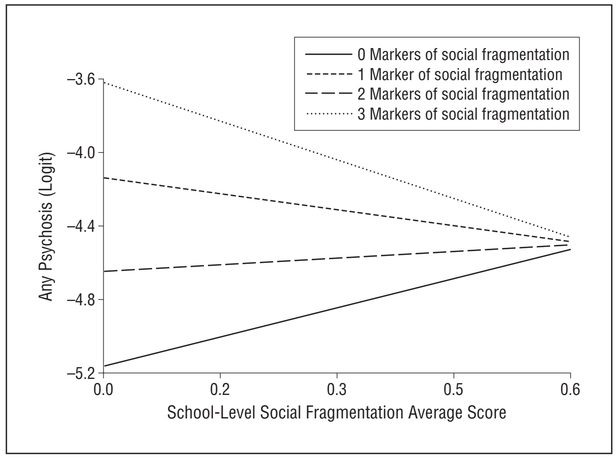

Figure 2. Cross-level interaction between social fragmentation score and school-level social fragmentation average score. For individuals with a low social fragmentation score, risk of any psychosis *increases* as social fragmentation within the school increases. However, for individuals with a high social fragmentation score, risk of any psychosis *decreases* as social fragmentation within the school increases.

COMMENT

Being raised in more urbanized areas was associated with an increased risk of developing any nonaffective psychotic disorder. This association was explained primarily by area characteristics rather than by characteristics of the individuals themselves. Social fragmentation was the most important area characteristic that explained the increased risk of psychosis in individuals brought up in cities.

The school-level aggregate measure of social fragmentation was the only area characteristic for which evidence of association with risk of psychosis persisted after adjustment for all individual-level and higher-level variables available within this data set. Schools in Sweden were based on a catchment-area principle at the time individuals would have started attending their schools, and school-level variables are therefore likely to reflect peer group influences as well as the smaller neighborhoods that individuals are likely to have lived in. The measure of social fragmentation at a municipality level was not associated with risk of psychosis. However, municipality measures reflect an average across larger geographic areas, and a single municipality could encompass within it a number of smaller neighborhoods that have low levels of social fragmentation, as well as neighborhoods with very high levels of fragmentation. This is especially true for municipalities within cities as opposed to those within rural areas (data not shown) and could explain why an association with school-level social fragmentation is not reflected at a municipality level.

The association between increasing levels of school-level social fragmentation and increasing risk of psychosis was attenuated by approximately 50% after adjustment for individual- and area-level characteristics in this data set, and we cannot exclude the possibility that residual confounding might explain this association. A number of ecological studies have observed an association between markers of social fragmentation and risk of

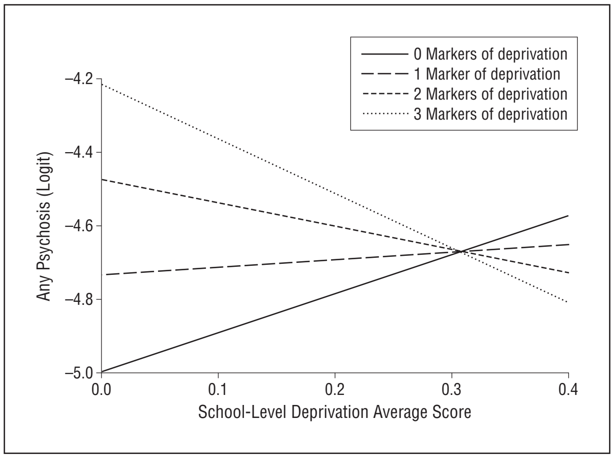

Figure 3. Cross-level interaction between deprivation score and school-level deprivation average score. For individuals with a low deprivation score, risk of any psychosis *increases* as deprivation within the school increases. However, for individuals with a high deprivation score, risk of any psychosis *decreases* as deprivation within the school increases.

schizophrenia.[5,21] Furthermore, when studies have included both individual- and area-level measures within a hierarchical structure as we have done here, associations with area-level measures of social fragmentation have persisted after adjustment for individual characteristics.[13,14,24,25] In comparison, association between aggregate measures of area deprivation and schizophrenia have usually been explained by individual characteristics.[13,22-24] We observed a strong association with population density in this study in the unadjusted analysis, and this was altered hardly at all after adjustment for individual-level variables (data not shown). However, this association was explained, to a large degree, by school-level measures of social fragmentation, indicating that it is this area characteristic—most common in the most dense, usually inner-city, areas—that is more likely to be causally related to psychosis and to explain the association with urbanicity.

The total amount of variation in incidence of any nonaffective psychosis at area (nonindividual) levels was very low, consistent with the revised estimates from the AESOP cohort, and very similar to estimates of area-level variation for other mental health outcomes investigated to date. A substantial amount of variation in incidence of depression has been observed at a household level,[27,35] which could reflect shared psychosocial and environmental as well as, to a lesser extent, genetic influences, but the proportion of variance in incidence of depression at neighborhood levels has consistently been reported as being less than 5%.[26-28,36-38] Note that it is still possible to have a strong effect of an area-level variable, for example, social fragmentation, even if little of the variation in incidence of the disorder is attributable to area-level effects.

We found evidence of a number of cross-level interactions whereby the relative risk between individual characteristics and risk of psychosis differed according to the context where individuals where raised (school-level characteristics). Although it is well established that individuals of minority ethnic status have an increased risk of developing a psychotic disorder, there is also evidence from a number of studies that this risk is much higher if individuals of an ethnic minority live in areas where they are in a relative minority compared with areas where larger proportions of the population are also of an ethnic minority.[13,22,29] We observed such a relationship in our study and also found evidence of interaction between individual- and neighborhood-level markers of both deprivation and, particularly, social fragmentation. The latter is consistent with findings from the Maastricht study, in which risk of schizophrenia associated with being single was higher in areas with fewer single-person households.[14]

All interactions we observed were qualitative. In other words, for ethnicity, deprivation, and social fragmentation, risk of psychosis associated with the presence of any of these individual characteristics (eg, being foreign-born) changed as the neighborhood context changed, but in an *opposite* direction compared with those without those individual characteristics (eg, Swedish-born). The patterns of interaction we observed were similar across all psychosis categories and appeared to be stronger for affective psychoses than schizophrenia, although confidence intervals for these all overlapped.

One of the strengths of this study is that it is based on a large cohort of individuals, with data on a number of important exposures measured during childhood and adolescence and longitudinally with respect to the outcome of psychosis. This is in contrast to almost all other studies of neighborhood-level exposures to date, and it allows us to exclude reverse causation as an explanation for our findings. Furthermore, we were able to examine a much more comprehensive set of both individual and area characteristics than in previous studies, whereas the availability of data at multiple levels allowed us to take a more robust approach to examining possible explanations for the association with urbanicity.

However, we did not have data on all potentially important factors that could confound or explain the associations observed, eg, cannabis use. It is not possible, therefore, to exclude the possibility that the associations observed in our study are due to residual confounding. Furthermore, area-level measures of deprivation, and particularly social fragmentation, are difficult to measure. Routinely collected administrative data frequently used to measure constructs of social cohesion and fragmentation include data on the proportion of people married, voting, renting privately, and living in single-person households, as well as levels of residential stability and population turnover.[39] Such data were available at the municipality level, whereas our school-level measure was based on the proportion of children immigrating, changing area, or being brought up in single-parent households. These measures are likely to capture the construct of social fragmentation to some extent, although ideally we would have liked to survey the schools to obtain a more direct measure of social cohesion within the schools or small neighborhoods in which the children were raised. It is also unclear to what extent our individual-level measure of social fragmentation reflects disrupted family or social relationships. Such direct measures are possible (for example, see Kirkbride et al[40]) but unfortunately are not available in large studies such as ours that rely on administrative data.

Furthermore, there are clearly difficulties in determining the size of "neighborhoods" or how they should be defined. Ideally, neighborhoods would be defined such that contextual characteristics within each neighborhood are homogeneous, but of course in reality research data usually rely on administrative information (eg, schools or municipalities) to define levels. Some caution therefore needs to be applied when interpreting our results for social fragmentation because it is not clear to what extent the measures that we used reflect this construct at a school or small-neighborhood level.

Misclassification of data may be particularly likely for our area-level measures, especially of social fragmentation, but is likely to be nondifferential. If so, effect estimates may have been underestimated. Measurement error may also explain why the estimates of area variation are so low, although our estimates are consistent with those from other studies of psychiatric disorder. Furthermore, the inclusion of a large number of potential confounders in the analyses reduced the sample size and will have reduced our power to observe some associations. Presence of psychosis, as well as presence of most of the exposures examined in this study, was more common in the group of individuals excluded from the analyses because of missing data, and this may have resulted in underestimating some associations. Finally, although this was a large study, the numbers of individuals with psychosis were probably not sufficient to allow us to examine cross-level interactions for each diagnosis separately.

It has been strongly argued that qualitative interactions such as those described herein, rather than quantitative ones, are most likely to be informative about etiologic mechanisms of disease[41,42] and to have implications for intervention or prevention. One interpretation of the interactions we observed is that they lend support to the theory that one of the mechanisms leading to increased risk of psychosis is that of social defeat.[43] Circumstances in which individuals fail to fit in with others in their immediate environment can lead to increased levels of stress, perhaps through discrimination, hostility, or isolation. Such stressors are likely to be highly repetitive, at least in terms of cognitive expectations and perceptions, even if not in terms of actual events. Evidence suggests that repeated stressors, through dopaminergic sensitization within the mesolimbic pathway,[44] can lead to the development of psychotic experiences through an increase in aberrant salience of experiences in the surrounding environment.[45,46] Such a mechanism would of course not be specific to any one characteristic of individuals (eg, ethnicity) but could potentially encompass any characteristic that defines an individual as being different from most other people in that local environment. Cognitive models of psychosis, for example, those that hypothesize that psychotic experience results from accumulation of prediction errors and impaired probabilistic reasoning,[47] provide explanations of how such changes in dopaminergic activity and aberrant salience can lead to subjective experiences of psychosis. Our findings of qualitative patterns of interaction across a number of different domains, if replicated, can inform the development of experimental paradigms within which such models can be tested.

If these qualitative interactions are replicated in other studies, they have potentially important implications for increased understanding about social policy. Integration of individuals within communities is clearly important to minimize risks associated with social isolation[48] and because segregation at local levels may undermine social cohesion in society as a whole.[49] To achieve integration it is necessary to promote development of socially and ethnically mixed communities, and indeed, European policy, for example, has shifted from multiculturalism toward community cohesion, with a focus on residential mixing.[50]

Interactions have not been examined for other psychiatric disorders, and therefore potentially similar effects might also be present for common mental health disorders. Our findings highlight the concern that physical integration alone is not sufficient but that some of the positive characteristics traditionally conferred by segregation, such as a localized sense of safety, cohesion, and community spirit, must also be maintained to enhance the mental health of individuals within the population.

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Correspondence: Stanley Zammit, PhD, Department of Psychological Medicine, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, Wales (zammits@cardiff.ac.uk).
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