Brief Report

Confirmation of Synergy Between Urbanicity and Familial Liability in the Causation of Psychosis

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Objective: This study replicated a previous report that there may be substantial synergism between urbanicity (a proxy environmental risk factor) and familial clustering of psychotic disorder (a proxy genetic risk factor).

Method: The amount of synergism was estimated from the additive statistical interaction between urbanicity of place of birth and family history of schizophrenia or family history of any severe mental disorder in a population-based Danish cohort of 1,020,063 individuals.

Results: There was significant interaction between urbanicity and family history; between 20% and 35% of individuals who had been exposed to both of these risk factors had schizophrenia possibly because of their synergistic effects.

Conclusions: The results suggest that a substantial proportion of the population morbidity force of schizophrenia may be the result of gene-environment interactions associated with urbanicity.

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Urban birth and upbringing are associated with a higher risk of developing schizophrenia (1), a finding that undoubtedly holds part of the key toward unraveling its etiology (2). Previous work has suggested that the effect of this environmental influence is not independent of genetic influences: one may interact synergistically with the other, thus augmenting the other's effects (3). We wished to replicate this finding with a much larger sample in which, similar to the previous study, urbanicity at birth served as the proxy environmental risk factor and a family history of schizophrenia, as the proxy genetic risk factor.

Method

Data from the Danish Civil Registration System were used to obtain a large and representative data set of Danish people. Permission was obtained, as required by law, from the Danish Data Protection Board before initiating this study. We identified all persons whose mothers were born in Denmark on April 1, 1935, or later, who themselves were born in Denmark between Jan. 1, 1950, and Dec. 31, 1976, and who were alive and living in Denmark on their 25th birthday (1,020,063 people). The study population and their mothers, fathers, and siblings were linked with the Danish Psychiatric Central Register, which currently contains data on all admissions to Danish psychiatric inpatient facilities from April 1969 to December 2001. Furthermore, outpatient visits to psychiatric departments were included from 1995.

Cohort members were recorded as having a history of schizophrenia if they had been admitted to a psychiatric hospital or received outpatient care with a diagnosis of schizophrenia or schizophrenia spectrum disorder (ICD-8 code 295 or ICD-10 code F20) before their 25th birthday. Parents and siblings were categorized as having either 1) "schizophrenia" if they had been diagnosed with schizophrenia (ICD-8 code 295 or ICD-10 code F20) or schizophrenia-like psychoses (ICD-8 codes 297, 298.39, 301.83 or ICD-10 codes F21–F29) or 2) "severe mental illness" if they had attracted a diagnosis of schizophrenia as defined or a diagnosis of any mental disorder in combination with inpatient care before the cohort member's 25th birthday. Data were analyzed with a cross-sectional design evaluating outcome and covariates at each cohort member's 25th birthday.

Similar to our previous study (4), an original detailed 12-level classification of urbanization was grouped into five categories: 5=capital, 4=capital suburb, 3=provincial city with more than 100,000 inhabitants, 2=provincial town with more than 10,000 inhabitants, and 1=rural area (Table 1). By place of birth, we are referring to this five-level classification.

Biological synergism (coparticipation) between genetic liability and environmental risk is thought to be common in multifactorial disorders such as schizophrenia (5). The classic problem, however, is how coparticipation between causes in nature (biological synergism) can be inferred from statistical manipulations with research data (statistical interaction), in particular with regard to the choice of additive (change in risk occurs by adding a quantity) or multiplicative (change in risk occurs by multiplying with a quantity) models. It has been shown that the true degree of biological synergism can be better estimated from—but is not the same as—the additive statistical interaction (see reference 6). This new method was recently applied to schizophrenia, showing synergy between traumatic head injury and familial liability (7) and between cannabis and psychosis liability (8). Details on how biological synergism is calculated from the additive statistical interaction has been described in detail elsewhere (6, 8, 9) and will not be shown here.

We calculated the statistical additive interaction and estimated from that the population amount of biological synergism between urbanicity and family history (see reference 6). This was done by using the calculations developed by Darroch (6), requiring a dichotomized measure of urbanicity (1, 2, 3=0 and 4, 5=1). For all other analyses, including the additive interaction, the five-category urbanicity measure was used. In order to calculate the statistical interaction under an additive model, the BINREG procedure in STATA (10), which fits generalized linear models for the binomial family estimating risk differences, was used to model interactions between urbanicity and family history in the risk set. Statistical significance of the interactions was assessed by Wald's χ^2 test. Main effects were also expressed on the additive scale (i.e., as a risk difference rather than a risk ratio). Estimates of risk differences were adjusted for sex and year of birth. Furthermore, estimates were inherently controlled for age as outcome, and covariates were evaluated at each cohort member's 25th birthday.

TABLE 1. Interactions Between Urbanicity and Family History of Schizophrenia or Any Severe Mental Illness in a Population-Based Danish Cohort of 1,020,063 Probands With Schizophrenia

	Probands With a Family History					Probands Without a Family History					Difference in Probands With and Without a Family History of Schizophrenia	
		Probands With Schizophrenia					Probands With Schizophrenia					
				Summary Increase in Risk With One Unit Change in Urbanicity Rating					Summary Increase in Risk With One Unit Change in Urbanicity Rating			
Definition of Family History and Urbanicity Rating[a]	Total N	N	%	%	95% CI	Total N	N	%	%	95% CI	Risk Difference	95% CI
Family history of any psychiatric hospitalization[b]				0.13[c]	0.10–0.16				0.037[c]	0.029–0.045		
Level 1 (lowest)	27,925	159	0.57			179,671	358	0.20			0.37	0.28–0.46
Level 2	62,002	401	0.65			339,993	690	0.20			0.44	0.38–0.51
Level 3	21,216	174	0.82			120,019	326	0.27			0.55	0.42–0.67
Level 4	15,722	157	1.00			72,774	210	0.29			0.71	0.55–0.87
Level 5 (highest)	38,789	406	1.05			141,952	483	0.34			0.71	0.60–0.81
Family history of schizophrenia[d]				0.22[e]	0.09–0.35				0.054[e]	0.046–0.062		
Level 1 (lowest)	3,266	47	1.44			204,330	470	0.23			1.21	0.80–1.62
Level 2	7,475	118	1.58			394,520	973	0.25			1.33	1.05–1.62
Level 3	2,548	55	2.16			138,687	445	0.32			1.84	1.27–2.40
Level 4	2,053	52	2.53			86,443	315	0.36			2.17	1.49–2.85
Level 5 (highest)	5,203	112	2.15			175,538	777	0.44			1.71	1.31–2.11

[a] Urbanization was grouped into five categories: 5=capital, 4=capital suburb, 3=provincial city with more than 100,000 inhabitants, 2=provincial town with more than 10,000 inhabitants, 1=rural area.
[b] Relative had a diagnosis of schizophrenia, as defined in text, or a diagnosis of any mental disorder in combination with inpatient care.
[c] Significant additive interaction (test for significance of difference in increase in risk with one unit change in urbanicity rating between proband groups with and without a family history of severe mental illness) (Wald's χ^2=32.76, df=1, p<0.0001). Approximate proportion of individuals exposed to both urbanicity (urbanicity rating of level 4 or 5) and family history of psychosis who developed psychosis because of the synergistic action of the two causes was 25%–36% (calculated according to the procedure described by Darroch [6]).
[d] Parents and siblings were categorized as "schizophrenia" if they had attracted a diagnosis either of schizophrenia (ICD-8 code 295 or ICD-10 code F20) or schizophrenia-like psychoses (ICD-8 codes 297, 298.39, 301.83 or ICD-10 codes F21–F29).
[e] Significant additive interaction (test for significance of difference in increase in risk with one unit change in urbanicity rating between proband groups with and without a family history of schizophrenia) (Wald's χ^2=6.47, df=1, p<0.02). Approximate proportion of individuals exposed to both urbanicity (urbanicity rating of level 4 or 5) and family history of psychosis who developed psychosis because of the synergistic action of the two causes was 20%–27% (calculated according to the procedure described by Darroch [6]).

Results

The risk of schizophrenia in this sample of 1,020,063 was 0.33% (N=3,364). The risk of a family history of schizophrenia, as defined, was 2.0% (N=20,545), and the risk of a family history of any severe mental illness was 16.2% (N=165,654). There were significant effects of urbanicity (summary risk difference linear trend over five categories: 0.062% (95% CI=0.054–0.071, p<0.001) and both family history of schizophrenia (risk difference=1.57%, 95% CI=1.39–1.76, p<0.001) and family history of any severe mental illness (risk difference=0.54%, 95% CI=0.50–0.59). There was a significant positive interaction between urbanicity and both family history of schizophrenia (χ^2=6.47, df=1, p<0.02) and between urbanicity and any family history of severe mental illness (χ^2=32.76, df=1, p<0.0001). These interactions were not reduced after adjustment for age, sex, and the interaction between age and sex (family history of schizophrenia: χ^2=8.09, df=1, p<0.005; family history of any severe mental illness: χ^2=42.22, df=1, p<0.0001). Stratified analyses revealed that the effect of family history became progressively stronger as the level of urbanicity went up (Table 1) and that between 20% and 35% of the individuals exposed to both urbanicity and familial liability had developed schizophrenia because of the synergistic action of the two proxy causes.

Discussion

The results suggest that in accordance with our previous work, a proxy genetic risk factor for schizophrenia interacts synergistically with a proxy environmental risk factor and that between a fifth to a third of individuals exposed to both the environmental and the genetic risk factors attract the disorder because of their coparticipation. This estimate is an important quantity because it suggests that by eliminating the environmental factor alone, a substantial proportion of the genetic morbidity force in the general population (the proportion that is codependent on the environment to cause disease) will also be neutralized.

Until direct measurements of genes and environment are available, the study of dual-exposure cells with proxy measures can be helpful. Replication of the finding suggestive of biological synergism between the two proxy risk factors for schizophrenia that are represented by familial risk and urbanicity may provide clues to the mechanism underlying a substantial proportion of the prevalence of schizophrenia in the population.

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