

Evidence That the Urban Environment Moderates the Level of Familial Clustering of Positive Psychotic Symptoms

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If the shared familial risk factors that predispose to psychotic disorder interact with early-life exposures in the urban environment, familial correlations of psychosis proneness measures should be higher in the exposed environment. We tested the hypothesis that in sib-pairs with one member affected by psychotic disorder, the familial correlation of psychotic experiences, but not depression, negative symptoms, or intelligence quotient (IQ), would be higher if the nonaffected sibling was raised in an urban environment until age 15 years. The sample analyzed consisted of 959 sib-pairs of whom one was affected with psychotic disorder. Lifetime self-reported psychotic and depressive experiences were measured using the self-reported “Community Assessment of Psychic Experiences” (CAPE). In the unadjusted model of the sibling-patient association in CAPE positive symptoms, there was a significant interaction by urban environment (B interaction = 0.079, 95% CI: 0.021 to 0.137, $P = .007$, $n = 828$). Stratified analyses revealed a strong sib-pair association in the urban environment ($B = 0.077$, 95% CI: 0.037 to 0.117, $P < .001$) and absence of association in the rural environment ($B = -0.002$, 95% CI: -0.044 to 0.039, $P = .920$). Associations were not affected after taking into account confounders and outliers, and there was no evidence that sibling associations in IQ, depression, or negative symptoms were moderated by the urban environment. The results agree with previous work indicating that the effects of the genetic and environmental factors that occasion familial clustering of psychotic disorder depend on whether or not an individual spends his early life in an urban environment.

Key words: schizophrenia/etiology/genes/urbanicity/risk factors

Introduction

It is generally agreed that both genes and environment have an important role in the etiology of psychotic disorder. Growing up in an urban environment until age 15 years is a risk factor for psychotic disorder.^{1,2} While part of the observed risk may be mediated by shared genetic factors,^{3,4} it likely also represents substantial nongenetic risk.⁵ Several studies found evidence for interaction, in that the effect of the urban environment was greater if there was also evidence of familial clustering.^{6–8} These findings suggest that environmental influences associated with growing up in an urban environment may interact with the genetic or environmental factors that occasion familial clustering of psychotic outcomes in families.

One way to take these findings further is to examine the degree of familial clustering of psychosis-related phenotypes in sib-pairs exposed and nonexposed to growing up in an urban environment. If familial risk-environment interactions play a role in the development of psychotic disorder, and shared genes associated with familial risk play a role, the heritability estimate of the disorder will differ between high-risk and low-risk environments.⁹ Given that heritability estimates are based on measures of phenotypic correlation between related individuals, examination of these as a function of environmental exposures represents an elementary first test to what degree the impact of a given environmental exposure may be moderated by familial risk. Thus, in the case of developmental urbanicity, if there is gene-environment interaction, one expects greater sib-pair correlations for psychosis-related measures in sibs who grew up in the exposed environment. Given that the great majority of sib-pairs share the place of growing up before the age of 15 years, the design cannot be biased by

genetic risk factors impacting on sibs differentially choosing to live in an urban or a rural environment.

Familial correlation is the correlation of a trait among family members. Familial correlation is a fundamental analytic tool to investigate the influences of shared genes and shared environments on a continuous trait. For a defined relationship (eg, parent-offspring, siblings, or cousins, etc.), familial correlation greater than zero implies that shared genes or shared environments influence the trait. We wished to study the hypothesis that in families where at least one family member was affected by psychosis, familial correlation of psychotic experiences would be higher in an urban environment. To check if findings were specific to the dimension of psychosis, we examined the same correlations for depressive experiences, as a measure of common psychopathology, for negative symptoms, as a measure of motivational alterations in psychotic disorder, and for intelligence quotient (IQ) as a summary measure of cognitive performance.

Method

Subjects

The data pertain to the baseline sample of the GROUP study.¹⁰ The full GROUP sample at baseline consisted of 1119 patients with nonaffective psychotic disorder, 1059 siblings of these patients, 920 parents of the patients, and 586 unrelated healthy comparison subjects.¹⁰ Inclusion criteria were: (1) age range 16 to 50 years and (2) good command of Dutch language. For patients, an additional inclusion criterion was the presence of a clinical diagnosis of nonaffective psychotic disorder. Healthy comparison subjects status was confirmed by using the Family Interview for Genetic studies¹¹ with the healthy comparison subject as informant, to establish absence of first-degree relatives with a psychotic disorder. Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria,¹² assessed with the Comprehensive Assessment of Symptoms and History (CASH) interview¹³ or Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1).¹⁴ The majority of patients had a DSM-IV diagnosis of schizophrenia (DSM-IV 295.x; $n = 940$, 84%).

The study was approved by the standing ethics committee of Utrecht University Medical Centre, and all the subjects gave written informed consent in accordance with the committee's guidelines.

Urban Exposure

We generated a historical population density record for each municipality from 1930 onwards using the Dutch Central Bureau of Statistics (CBS) and equivalent Belgium database. When data were not available, linear extrapolations were computed. When historical names of municipalities disappeared from historical records (eg, due to city

mergers), we used the available data from the agglomerate city. Subjects were asked to describe where they lived during their life. This resulted in a number of records for each subject, containing locations by age period. For each of these records, we computed the average population density (by square kilometer, excluding water) of the municipality for the matching year periods. Subsequently, it was determined where the subject lived at birth, between ages 0–4 years; 5–9 years; 10–14 years; 15–19 years; 20–39 years; 40–59 years; and 60+ up to the actual age. Average population density over the period was categorized conform the Dutch CBS urbanicity rating (1 = <500/km²; 2 = 500–1000/km²; 3 = 1000–1500/km²; 4 = 1500–2500/km²; 5 = 2500+/km²). The periods 0–4 years, 5–9 years, and 10–14 years were merged to average urbanicity exposure between 0 and 14 years. The median value of urbanicity between 0 and 14 years in the controls was used to define a dichotomous urbanicity exposure.

Psychosis Measures in Sib-Pairs

The Community Assessment of Psychic Experiences (CAPE; www.cape42.homestead.com) was developed in order to rate self-reports of lifetime psychotic experiences.¹⁵ Items are modeled on patient experiences as contained in the Present State Examination, 9th version (PSE-9),¹⁶ schedules assessing negative symptoms such as the Scale for the Assessment of Negative Symptoms (SANS)¹⁷ and the Subjective Experience of Negative Symptoms (SENS),¹⁸ and scales assessing depressive symptoms such as the Calgary Depression Scale.¹⁹ Items are scored on a 4-point scale. In the current analyses, CAPE dimensions of frequency of positive experiences (20 items), negative experiences (14 items), and depressive experiences (8 items) were included, representing the person's perceived psychosis load over the lifetime. A total score representing the mean of all items was calculated for each dimension. For the current analyses, the dimensions of psychotic, depressive, and negative experiences were used.

Intelligence Quotient

IQ was estimated based on the 4-subtest version (Information, Block Design, Digit Symbol Coding and Arithmetic)²⁰ of the Wechsler Adult Intelligence Scale (WAIS-III).²¹

Analysis

Analyses are based on version 5.0 of the GROUP database. Analyses were done using Stata, version 14.²² For the sibling-patient analyses, as per our main hypothesis, we calculated the cross-sib, within-trait association for CAPE psychosis, with sibling CAPE as dependent variable and patient CAPE as the independent variable, as well as possible moderation thereof by the binary urban environment variable. To check for specificity, we made

similar calculations for the association with IQ, CAPE negative symptoms, and CAPE depression.

In the case of significant interaction, stratified results were calculated from the model containing the interaction, using the Stata MARGINS procedure.

Given hierarchical clustering of the data (clustering of siblings in the same family), multilevel random intercept regression models were applied to the data using the XTREG routine in the Stata statistical program.²³

Analyses were corrected a priori for age, sex, ethnic group (white European vs other), and educational level (continuous variable ranging from 0 [no education], 3–5 [school diploma] to 8 [university degree]).

Results

Sample

The total number of sib-pairs, consisting of one patient and one healthy sibling, for analysis at baseline was 1092. Of these, 959 sib-pairs had valid data on urban exposure until age 15 years, of whom 86% were concordant for urban exposure (table 1). There was no evidence of an urbanicity main effect on CAPE positive symptoms, corrected for ethnic group, age, sex, and educational level, in either the patients ($P = .080$) or their siblings ($P = .651$).

Sibling-Patient Association as a Function of Urban Living

In the unadjusted model of the sibling-patient association in CAPE positive symptoms, there was a significant interaction by urban environment (B interaction = 0.079, 95% CI: 0.021 to 0.137, $P = .007$, $n = 828$) (table 2; figure 1).

Stratified analyses revealed a strong sibling association in the urban environment ($B = 0.077$, 95% CI: 0.037 to 0.117, $P < .001$) and absence of association in the rural environment ($B = -0.002$, 95% CI: -0.044 to 0.039 , $P = .920$).

If analyses were limited to the sib-pairs who were concordant for the urban exposure, the interaction was not attenuated (B interaction = 0.087, 95% CI: 0.022 to 0.152, $P = .009$, $n = 661$).

To check whether this association was due to outliers, analyses were repeated with the log-transformed CAPE positive symptom score revealing a difference of the same order of magnitude between the sibling association in urban and rural environments (B interaction = 0.207, 95% CI: -0.26 to 0.439 , $P = .082$, $n = 828$). Stratified analyses revealed a similarly strong sibling association in the urban environment ($B = 0.222$, 95% CI: 0.064 to 0.381, $P = .006$) and absence of association in the rural environment ($B = -0.0157$, 95% CI: -0.156 to 0.188 , $P = .858$).

The association results also remained similar after adjusting for confounders (age, sex, ethnicity, and level of education of both siblings) (table 2).

There was no evidence that sibling associations in IQ, CAPE depression, or CAPE negative symptoms were moderated by the urban environment (IQ: B interaction = -0.080 , 95% CI: -0.21 to 0.050 , $P = .235$; depression: B interaction = -0.036 , 95% CI: -0.134 to 0.062 , $P = .474$; negative symptoms: B interaction = -0.029 , 95% CI: -0.131 to 0.073 , $P = .581$) (figures 2–4).

Discussion

The results show that familial correlation in positive psychotic symptoms was moderated by having lived, during

Table 1. Sample Descriptives by Group (Siblings, Patients) and Urbanicity (Median Split Around Control Value)

			Age	Proportion Female	Proportion Ethnic Minority	Education	CAPE Positive	CAPE Depressive	IQ
Siblings	Rural	Mean or %	28.05	0.52	0.10	2.52	0.20	0.62	102.65
		SD	8.48			1.45	0.19	0.40	16.08
		n	444	444	444	441	405	407	429
	Urban	Mean or %	27.94	0.57	0.21	2.58	0.22	0.67	102.83
		SD	8.22			1.49	0.22	0.42	15.07
		n	576	576	576	575	507	507	552
Total	Mean or %	27.99	0.55	0.16	2.55	0.22	0.65	102.75	
	SD	8.33			1.47	0.21	0.41	15.51	
	n	1020	1020	1020	1016	912	914	981	
Patients	Rural	Mean or %	27.28	0.27	0.10	1.96	0.74	1.05	95.55
		SD	7.91			1.31	0.51	0.60	15.08
		n	453	453	453	451	396	396	420
	Urban	Mean or %	27.12	0.17	0.21	2.01	0.66	1.00	97.84
		SD	6.86			1.35	0.48	0.58	14.75
		n	555	555	555	552	451	456	520
Total	Mean or %	27.19	0.21	0.16	1.98	0.70	1.02	96.81	
	SD	7.35			1.33	0.50	0.59	14.94	
	n	1008	1008	1008	1003	847	852	940	

Note: CAPE, Community Assessment of Psychic Experiences.

Table 2. Results of Multilevel Random (XTREG) Intercept Regression Analyses in Sib-Pairs (Patients and Siblings), as a Function of Urban Upbringing

Measure	Sib-Pair (Sibling-Patient) Association			Log-Transformed Sib-Pair Association			Sib-Pair Association Corrected for Age, Sex, Ethnicity, and Level of Education		
	B (95% CI)	P	n	B (95% CI)	P	n	B (95% CI)	P	n
CAPEPOS (total)	0.079 (0.021 to 0.137)	.007	828	0.207 (-0.26 to 0.439)	.082	828	0.076 (0.019 to 0.133)	.009	815
CAPEPOS (urban)	0.077 (0.037 to 0.117)	<.001	828	0.222 (0.064 to 0.381)	.006	828	0.073 (0.033 to 0.112)	<.001	815
CAPEPOS (rural)	-0.002 (-0.044 to 0.039)	.920	828	-0.0157 (-0.156 to 0.188)	.858	828	-0.004 (-0.045 to 0.038)	.865	815

Note: B, regression coefficient; 95% CI, 95% confidence interval; P, P value; n, number of observations; CAPEPOS, dimension of positive psychotic experiences of CAPE (Community Assessment of Psychic Experiences).

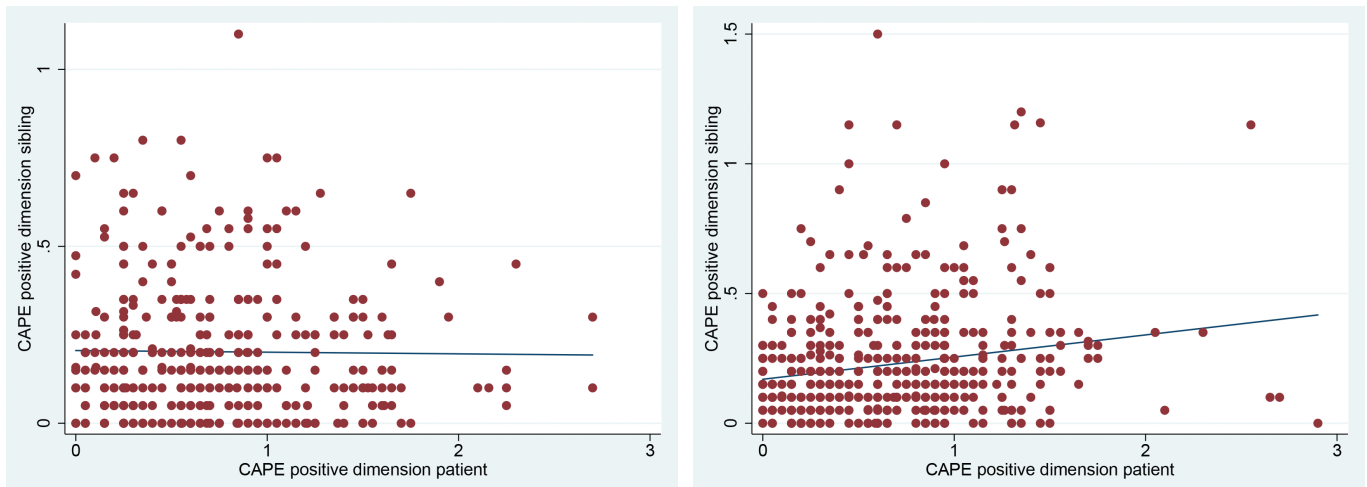


Fig. 1. Correlation between patient positive psychotic symptoms and sibling positive psychotic symptoms (left panel in rural environment and right panel in urban environment). CAPE, Community Assessment of Psychic Experiences.

the first 15 years of life, in an urban environment. The results also show that moderation by the urban environment was not present for IQ and depressive or negative symptoms in the same individuals. Thus, urbanicity may act synergistically as an environmental factor with the genetic and/or environmental factors that occasion familial clustering of psychotic disorder, to produce symptoms of psychosis. This synergistic process is specific for the dimension of psychosis associated with “aberrant salience,” or the liability to perceive signal in random noise,²⁴ that does not apply to the expression of depression, motivation, or intelligence. This type of interaction is not exclusive to urbanicity, as a similar interaction was found in the same cohort between genes and cannabis use in the development of psychosis.^{25,26}

The large sample size of this study is a strength. Also, conducting correlation analyses between patients and siblings has certain advantages over case-control studies. This is because in the sibling design there is automatic

control for shared circumstances that can influence mental health which can potentially act as confounding factors. Also, given that the environmental exposure of urbanicity was shared between sib-pairs, bias due to differential exposure to the urban environment as a function of genetic risk can be discarded.

Similarly, the results cannot be confounded by main effects of the urban environment on psychosis proneness. First, there was no significant main effect of urban environment in either patients or siblings. Second, the urban exposure was included in the interaction model, thus effectively controlling for urban environment. Third, a main effect of urban environment on psychosis proneness was not the hypothesis; the hypothesis was that the sib-pair correlation in psychosis proneness would be higher in an urban environment. The sib-pair correlation cannot be confounded by a main effect of urbanicity on psychosis proneness, as both sibs are either “urban” or “rural” in the sensitivity analyses presented.

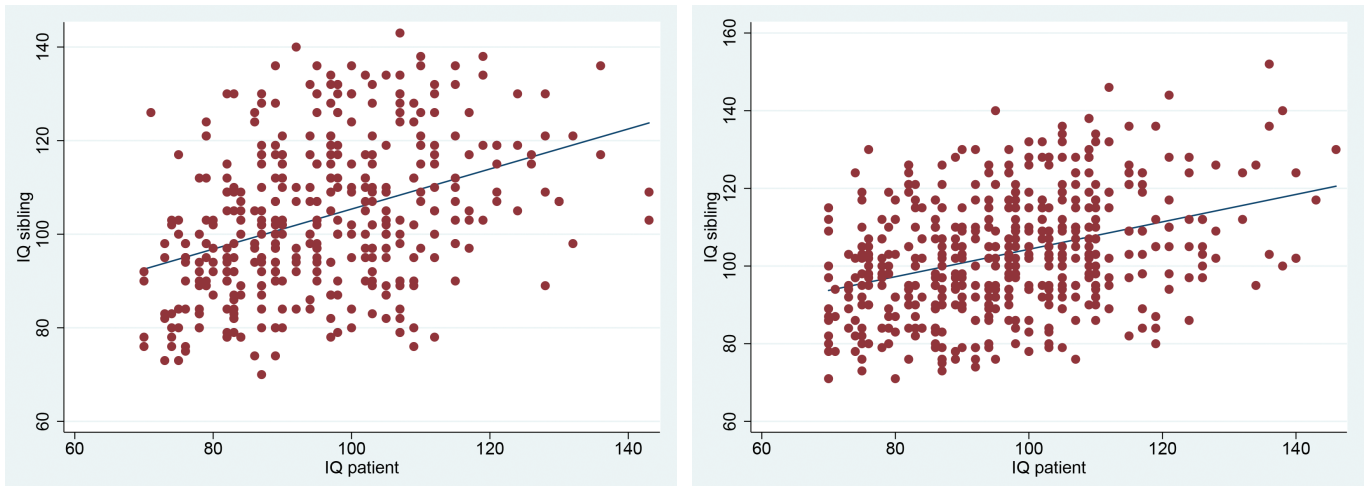


Fig. 2. Correlation between patient and siblings IQ (left panel in rural environment and right panel in urban environment).

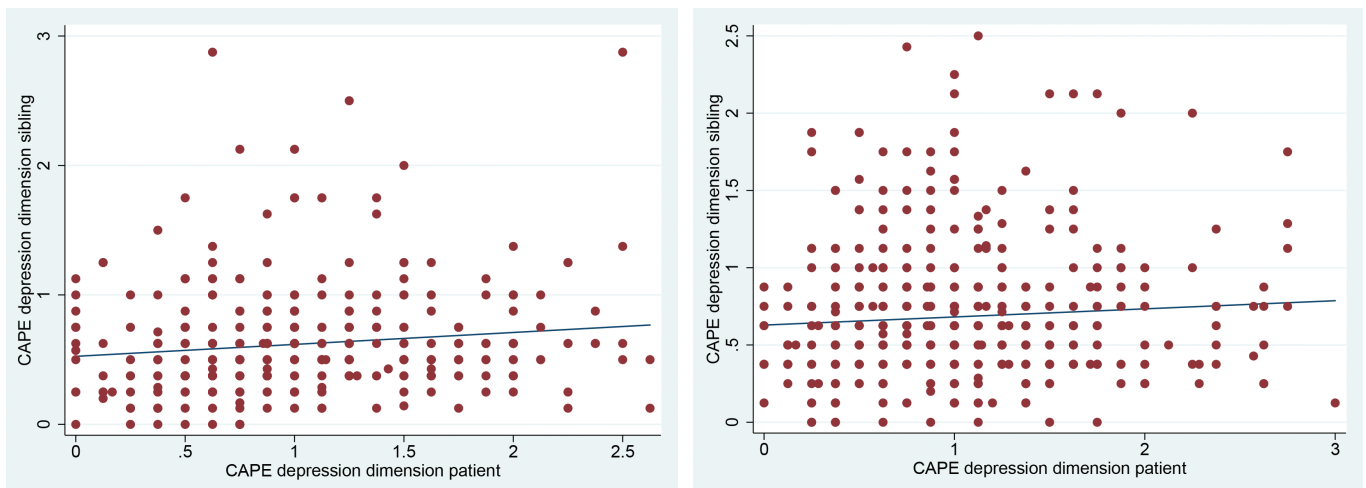


Fig. 3. Correlation between patient and sibling symptoms of depression (left panel in rural environment and right panel in urban environment). CAPE, Community Assessment of Psychic Experiences.

Results can also not be confounded by a main effect of group on CAPE scores. Patients of course had higher scores than siblings. However, what we analyzed was to what degree a (relatively) higher score in a given patient would be accompanied by a (relatively) higher score in the sibling.

The increased risk associated with the urban environment appears to be specific for psychosis outcomes, and not apply, or apply more weakly, to affective dimensions.^{27,28} For example, a weak effect of urban environment on depression was found in one study.²⁹ Therefore, the absence of increased familial correlation of depression as a function of the urban environment is conform expectation. To the degree that the urban environment also increases risk for other mental disorders, a similar mechanism of interaction between familial risk and urban environment may not apply.

Similarly, there was no impact of the urban environment on the size of the sibling correlation in CAPE

negative symptoms. This is in agreement with a similar dissociation in the pattern of association of positive and negative symptoms in a previous publication.³⁰

Cognitive development may be impacted by urban residence, mediated by levels of deprivation,³¹ a finding that is supported by evidence of poverty negatively impacting cognitive function.³² One study reported that cognitive function, as an endophenotype of psychotic disorder, interacts with urban environment in shaping risk for later psychotic disorder.⁶ Another study found that the association between urban environment and psychotic experiences was not mediated by cognitive function.³³ All these findings do not contrast with the current study, which tested a different, specific hypothesis, namely that the urban environment interacts with familial risk to impact cognitive function, which was not the case.

The findings should be interpreted in the light of a number of limitations. First, urbanicity is a proxy for

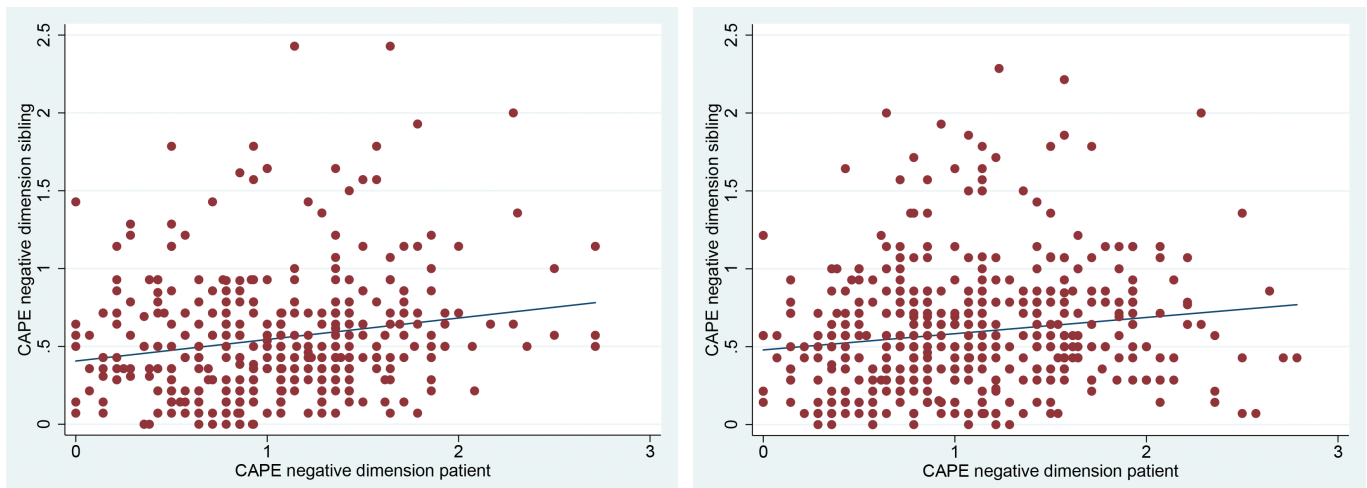


Fig. 4. Correlation between patient and sibling CAPE negative symptoms (left panel in rural environment and right panel in urban environment). CAPE, Community Assessment of Psychic Experiences.

hypothesized factors in the urban environment, the precise nature of which remains elusive. Second, there was no main effect of urban environment, while one was expected. This may be due to chance, given that previous research in the Netherlands has reported such associations.⁸ Third, there was considerable delay between the time of exposure (before age 15 years) and assessment of outcomes in patients and siblings, likely weakening associations. Finally, CAPE measures are self-report, which may again bias findings toward the null.

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