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Variation of subclinical psychosis as a function of population density across different European settings: Findings from the multi-national EU-GEI study

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Abstract

Background: Urbanicity is a well-established risk factor for psychosis. Our recent multi-national study found an association between urbanicity and clinical psychosis in Northern Europe but not in Southern Europe. In this study, we hypothesized that the effect of current urbanicity on variation of schizotypy would be greater in North-western Europe countries than in Southern Europe ones.

Methods: We recruited 1080 individuals representative of the populations aged 18–64 of 14 different sites within 5 countries, classified as either North-western Europe (England, France, and The Netherlands) with Southern Europe (Spain and Italy). Our main outcome was schizotypy, assessed through the Structured Interview for Schizotypy-Revised. Our main exposure was current urbanicity, operationalized as local population density. A priori confounders were age, sex, ethnic minority status, childhood maltreatment, and social capital. Schizotypy variation was assessed using multi-level regression analysis. To test the differential effect of urbanicity between North-western and Southern European, we added an interaction term between population density and region of recruitment.

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Results: Population density was associated with schizotypy ($\beta = 0.248$,95% CI = 0.122–0.375;$p < 0.001$). The addition of the interaction term improved the model fit (likelihood test ratio:$\chi^2 = 6.85$; $p = 0.009$). The effect of urbanicity on schizotypy was substantially stronger in North-western Europe ($\beta = 0.620$,95%CI = 0.362–0.877;$p < 0.001$) compared with Southern Europe ($\beta = 0.190$,95%CI = 0.083–0.297;$p = 0.001$).

Conclusions: The association between urbanicity and both subclinical schizotypy and clinical psychosis, rather than being universal, is context-specific. Considering that urbanization is a rapid and global process, further research is needed to disentangle the specific factors underlying this relationship.

KEYWORDS

population density, psychosis spectrum, schizotypy, urban design, urbanicity

1 | INTRODUCTION

Urbanicity is a well-established risk factor for psychosis, as shown by studies, which examined the urbanicity-psychosis association over different samples and operationalizations of urbanicity.[1] A meta-analysis found a two-fold increase in the odds of schizophrenia in urban versus rural settings.[2] The risk is higher for those born in urban environment or exposed during upbringing.[3–5] Nevertheless, this evidence mostly relies on studies conducted in the Global North, and the World Health Organization (WHO) Mental Health Survey failed to replicate this finding in developing countries.[5] Interestingly, our EUropean network of national schizophrenia networks studying Gene–Environment Interactions (EU-GEI) study on psychosis incidence across different settings in Europe found differential incidence patterns by degree of urbanization comparing Northern European and Southern European countries[6]; this suggests that even within Europe the strength and direction of the association between urbanicity and psychosis varies.

Several mechanisms may underlie this association, including socioeconomic and physical factors. The former comprise, among others, poverty and deprivation, social fragmentation, and lack of social capital.[7,8] Among physical features of cities, the lack of green spaces,[9] greater exposure to noise, and air and light pollution[10,11] have been examined as potential harmful factors for mental health. Given that 68% of the global population is projected to live in cities by 2050,[12] it is vital to understand the link between urban living and psychosis risk.

In the last decades, the traditional concept of psychosis as occurring only in those who are ill has been challenged by multiple lines of evidence,[13,14] leading to the affirmation of the psychosis continuum theory. According to the psychosis continuum model, subthreshold expression of psychotic symptoms in the general population has a shared etiology with full psychotic disorders.[15–18] Several studies looking at intermediate psychosis phenotypes have relied on the analysis of schizotypal traits in individuals with no current or prior history of psychosis or in relatives of affected patients.[19–22] Schizotypal traits encompass a multidimensional range of schizophrenia-like personality traits clustering into positive, negative, and disorganized symptoms domains.[23] Besides continuity at symptoms level, schizotypy and schizophrenia have a shared background of

Significant outcomes

- Urbanicity is a risk factor for subthreshold manifestations of psychosis.
- Operationalized as population density, urbanicity has varying effects across diverse geographic areas.
- Understanding the differential association between urbanicity and psychosis spectrum by place is expected to provide significant insights in the etiology of psychosis.

Limitations

- Analyses were conducted on a limited number of sites across the involved countries.
- Population density does not necessarily capture all aspects of urban living.
- Urbanicity was measured at time of assessment, whereas we acknowledge exposure to urbanicity during childhood or adolescence, may bring higher risk.

genetic and environmental risk factors.[18,23,24] This makes schizotypy an optimal candidate to conduct research into the etiology of schizophrenia. Additional advantages include the potential of overcoming the reverse causation bias, which can arise while testing risk factors for schizophrenia and related clinical disorders. Finally, in accordance with the psychosis spectrum theory, schizotypy can be measured on a dimensional, continuous scale, increasing the statistical power to detect relevant associations, which might be lost when focusing solely on the rare and most severe manifestations of clinical disorders.[23]

Therefore, investigating differential patterns of variation of psychosis spectrum disorders by urbanicity across diverse settings may provide further clues on the factors that contribute to their relationship.

2 | AIMS OF THE STUDY

In a prior EU-GEI study,[24] we found that variation of schizotypal traits among recruited population-based controls varied significantly across sites, with the expression of subclinical psychosis being higher in those sites were incidence of first-episode psychosis (FEP) also peaked. Building on this and on the findings of the EU-GEI FEP incidence study[6] discussed above, we tested the hypothesis that the association between urbanicity and schizotypy would be stronger in North-western Europe (England, France, and The Netherlands) compared with Southern Europe (Italy and Spain). For this purpose, we used data from the EU-GEI study, which recruited individuals across several culturally and ethnically diverse settings putting into efforts to maximize representativeness of the local population in each site.

3 | MATERIAL AND METHODS

3.1 | Study design and participants

The EU-GEI study is a multinational incidence and case-sibling-control study of genetic and environmental determinants of psychotic disorders.[25] The EU-GEI study involved: (1) FEP patients aged 18–64; (2) population-based controls recruited within the same age-span and catchment areas; (3) siblings of participants with FEP. The recruitment took place between 2010 and 2015 from 17 centres in England (South-East London, Cambridgeshire & Peterborough), France (20th arrondissement of Paris, Val-de-Marne, Puy-de-Dôme), the Netherlands (central Amsterdam, Gouda & Voorhout), Italy (part of the Veneto region, Bologna municipality, and Palermo), Spain (Madrid [Vallecas], Barcelona, Valencia, Oviedo, Santiago, and Cuenca), and Brazil (Ribeirão Preto).

In this study, we examined only data from population-based controls. Inclusion criteria for population-based controls were: (1) age between 18 and 64; (2) residence within a clearly defined catchment area; (3) adequate proficiency in the local primary language in order to complete assessment; and (4) no current or past psychotic disorder. Potential participants were systematically screened with an ad-hoc instrument for a history of psychosis and those who reported previous or current treatment for psychosis were excluded. Those responding positively to any question in the screening instrument underwent further interview with standardized tools to ensure that no potential control had past or current psychotic disorder.

For the recruitment we deployed a mixture of random and quota-sampling strategies to maximize representativeness to the population-at-risk by age, sex, and ethnicity in each area. Quotas for sampling were derived from the most accurate local demographic data. A prior EU-GEI publication showed that controls were broadly representative of the local populations, though they were younger in some sites.[26] In some sites, certain groups (e.g., black African and black Caribbean) were purposedly oversampled to allow subsequent sub-group analyses. To account for this, we calculated for each control participant a weight inversely proportional to their probability of selection based on age, sex, and ethnicity using census data. These weights were used in all analyses.

No controls were recruited in the 20th arrondissement of Paris. In Veneto region schizotypy was not assessed due to protocol divergencies. Brazil included only one site, not allowing rural–urban comparison. These sites were therefore excluded.

Ethical approval was granted in each centre.[6] All participants gave written informed consent.

3.2 | Data collection and quality assurance

Participants were interviewed by trained researchers using standardized instruments to collect data on a comprehensive range of relevant factors.[25] Training was provided at the beginning and throughout the study. Inter-rater reliability was assessed annually. Researchers had to achieve and sustain a minimum level of accuracy in their ratings before being permitted to administer the core assessments. To further ensure consistency and reliability of the data gathered across multiple sites, annual meetings were arranged involving principal investigators

and the core researchers to discuss issues related to data collection and provide specific training.

3.3 | Measures

Our primary outcome was a dimensional measure of schizotypy across the general population. Schizotypy was assessed through a semi-structured interview, the Structured Interview for Schizotypy-Revised (SIS-R).[27] It contains 20 schizotypal symptoms and 11 schizotypal signs rated on a 4-point scale (from 0 = absent to 3 = severe). In line with previous work,[19] the 31 item scores were reduced a priori to two-dimensional scores, representing the means of 7 positive schizotypy items (i.e., 2 items on referential thinking, psychotic phenomena, derealization, magical ideation, illusions, and suspiciousness) and 8 negative-disorganized schizotypy items (i.e., social isolation, sensitivity, introversion, and restricted affect, disturbances in associative and goal-directed thinking, poverty of speech, and eccentric behavior). The reliability of the SIS-R has been assessed with a robust test–retest procedure and only sufficiently reliable items were retained in the current version.[27] The SIS-R has been widely used to examine intermediate psychosis phenotypes[19–21] and its measurement invariance has been tested across siblings of individuals with psychosis and population-based controls.[28] We calculated the total schizotypy score as the means of all SIS-R items and negative and positive schizotypy scores as the means of the corresponding SIS-R items (for supplementary analyses). Cohen's kappa was found to be $k = 0.79$, suggesting moderate to strong inter-rater reliability for SIS-R assessment across sites.

3.3.1 | Geographic variables

Countries of recruitment were classified as Southern Europe (Italy, Spain) and North-western Europe (England, France, The Netherlands) based on the geoscheme for Europe provided by the United Nations Statistics Division. Urbanicity was operationalized as site-level population density, calculated as the number of inhabitants per square kilometer and ranging between 11.6/km^2 (Cuenca) and 14,477.9/km^2 (Valencia).

3.3.2 | Social capital

The Social Environment Assessment Tool (SEAT) was used to measure perceived social capital in each individual's immediate neighborhood. This 23-item questionnaire captures four dimensions of social capital: civic disorder (CD), impact of civic disorder (ICD), informal social control (ISC), and social cohesion and trust (SCT).[29–32] Each item is rated on a five-point Likert-scale ranging from 1 = unusual to 5 = very common. The validation of SEAT is currently in preparation for publication by its author (Kirkbride JB, Pignon B. Development of a single tool measuring whole social capital: the SEAT). Nonetheless, a prior EU-GEI study demonstrated its validity in predicting positive, negative, and depressive symptoms in non-clinical populations.[33] Following the aforementioned paper,[33] an overall social capital score was obtained as a weighted sum of the standardized z-scores of each dimension (SEAT social capital score = zCD+(0.51*zICD+1.6*zISC+zSCT)). Weighting was based on the SEAT factorial structure. The social capital score was inverted for analyses so that higher scores represented lower social capital.

3.3.3 | Child maltreatment

Child maltreatment was measured through the Childhood Trauma Questionnaire (CTQ),[34] consisting of 5 items rated on a 5-point Likert-type scale (1 = never true to 5 = very often true) for each trauma subtype (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse). The CTQ has been validated across clinical and non-clinical populations[35,36] and in different languages.[37–39] The reliability of the self-reported childhood maltreatments has been validated against prospective ascertainment of exposure to trauma[40] and psychotherapy outcomes.[41] We used the mean of the 5 CTQ subscale scores (range: 5–25) as an overall child maltreatment score.

3.3.4 | Cannabis use

Patterns of cannabis use were assessed using an updated version of the modified Cannabis Experience Questionnaire.[42] Cannabis users were provided the frequency of use (occasional use, more than once a week or daily use). In this study, we used the prevalence of daily cannabis use in each centre as a site-level variable.[43]

3.3.5 | Sociodemographic and other variables

We also collected information on age, sex, and country for each participant. Self-ascribed ethnicity (Asian, Black, North African, White, Mixed, Other) was dichotomized as white versus other. Parental socio-economic status

(SES) was classified as: professional, intermediate, working class, and long-term unemployed. We further ascertained educational attainment (no qualification; school qualifications; tertiary; vocational; undergraduate; postgraduate) and current employment status (unemployed; economically inactive; student; part-time job; full-time job; self-employed). All sociodemographic variables were collected with an amended version of the Medical Research Council Socioeconomic Schedule.[43,44] Finally, we used the Family Interview for Genetic Studies[45] questionnaire to investigate the history of any mental illness among first-degree relatives.

3.4 | Missing data

The proportion of missing values was low, ranging from none on sex to 5.4% on one SIS-R item. Missing data were handled by multiple imputation (details in online Supplement).

4 | STATISTICAL ANALYSIS

First, we performed preliminary descriptive analyses using χ^2-tests and Student's t-tests to examine the differences in study variables by site and region (Southern vs North-Western Europe).

Secondly, we ran a multi-level linear regression model (accounting for clustering by $N = 14$ sites) with schizotypy as the outcome variable to estimate the main effect of population density on schizotypy, both unadjusted and controlling for age, sex, ethnicity, parental SES, educational attainment, employment, family history of any mental illness, child maltreatment, social capital, and recruitment region. To increase robustness of findings with regards to the assumptions of normality, schizotypy was log-transformed via the Stata command "lnskew0" resulting in a variable with skewness equal to zero.[20] All continuous variables, including schizotypy, were standardized. We added to the model an interaction term between population density and recruitment region to test whether the latter moderated the association between urbanicity and schizotypy. A likelihood-ratio test assessed whether the addition of the interaction term improved the model.[46] To compare the differential effects of urbanicity across different European regions, we finally estimated the slopes of urbanicity for either region using the Stata command "margin." We re-ran the last model substituting region of Europe for country to estimate the differential effect of urbanicity across recruitment countries.

Previous EU-GEI studies found that differences in patterns of cannabis use substantially contributed to psychosis incidence rates variation across study sites[43] and to the severity of self-reported psychotic experiences in population controls.[47] Therefore, we conducted sensitivity analyses adjusting for the standardized prevalence of daily cannabis users in each site. Since Valencia, Oviedo, Santiago, and Cuenca sites had ≥10% missing on cannabis data, sensitivity analyses were restricted to $N = 10$ sites ($N = 933$ individuals).

As supplementary analyses, we re-ran our models to examine variation of negative and positive schizotypy as a function of population density across the diverse settings.

Analyses were performed using RStudio R version 3.6.3[48] and Stata 18.[49]

5 | RESULTS

5.1 | Sample characteristics

$N = 1080$ individuals from the general population were included in these analyses. The sample comprised 571 females (52.9%) and 509 (47.1%) males and most were White ($N = 780$, 72.2%). Mean age was 36.9 ± 13.2 years. Across sites, subjects differed on age ($F = 4.1$; $p < 0.001$), ethnicity ($\chi^2 = 203.1$; $p < 0.001$), child maltreatment ($F = 2.6$; $p = 0.002$), and social capital ($F = 13.5$; $p < 0.001$), but not on sex ($\chi^2 = 4.1$; $p = 0.990$). Total ($F = 25.1$; $p < 0.001$), negative ($F = 13.6$; $p < 0.001$), and positive ($F = 22.9$; $p < 0.001$) schizotypy also differed significantly (Table S2). Distribution of study variables in the sample and of the main variables across sites is shown in Tables 1 and 2.

5.2 | Main effects

In unadjusted regression, each 1-unit increase in standardized population density was associated with 0.223 (95%CI = 0.064–0.382; $p = 0.006$) increase of log-transformed schizotypy score. Adjusting for age, sex, ethnicity, childhood trauma, social capital, and region of recruitment, did not alter the effect of urbanicity on the outcome ($\beta = 0.248$, 95%CI = 0.122–0.375; $p < 0.001$). In adjusted model without interaction term, having been recruited in North-western Europe ($\beta = 0.337$, 95% CI = 0.007–0.667; $p = 0.046$), ethnic minority status ($\beta = 0.155$, 95%CI = 0.023–0.286; $p = 0.021$), educational attainment (vocational v. post-graduate: $\beta = 0.259$, 95% CI = 0.084–0.434; $p = 0.004$; tertiary v. post-graduate: $\beta = 0.269$, 95%CI = 0.084–0.434; $p = 0.002$), child maltreatment ($\beta = 0.159$, 95%CI = 0.106–0.212; $p < 0.001$), and lower social capital ($\beta = 0.102$, 95%CI = 0.047–0.157;

TABLE 1 Distribution of variables in the study sample.

		Unadjusted	
		N	**%**
Age	Mean, SD	36.9	13.2
	Missing	1	0.1%
Sex	Men	509	47.1%
	Women	571	52.9%
	Missing	-	
Ethnicity	White majority	780	72.2%
	Minority	300	27.8%
	Missing	-	
Parental SES	Professional	387	35.8%
	Intermediate	311	28.8%
	Working class	338	31.3%
	Long-term unemployed	3	0.3%
	Missing	41	3.8%
Level of education	Postgraduate	187	17.3%
	Undergraduate	258	23.9%
	Vocational	206	19.1%
	Tertiary	262	24.3%
	School qualifications	134	12.4%
	School, no qualifications	26	2.4%
	Missing	7	0.6%
Employment	Unemployed	155	14.4%
	Economically inactive	108	10.0%
	Student	171	15.8%
	Part-time job	158	14.6%
	Full-time job	415	38.4%
	Self-employed	67	6.2%
	Missing	6	0.6%
Any mental illness in relatives	No	631	58.4%
	Yes	402	37.2%
	Missing	47	4.4%
Child maltreatment	Mean, SD	6.7	2.2
	Missing	10	0.9%
Social capital	Mean, SD	0.0	2.6
	Missing	106	9.8%

Abbreviations: M, mean; SD, standard deviation.

$p < 0.001$) were all associated with increased schizotypy (Table 3).

5.3 | Moderation analyses

The addition of the interaction term "urbanicity*-European region" improved the model (likelihood test ratio: $\chi^2 = 6.85$; $p = 0.009$). The effect of urbanicity was substantially stronger in North-western ($\beta = 0.620$, 95% CI = 0.362–0.877; $p < 0.001$) compared with Southern Europe ($\beta = 0.190$, 95%CI = 0.083–0.297; $p < 0.001$) (Table 3). As shown in Figure 1, visualizing the fitted interaction effects between urbanicity and country on schizotypy, the association between urbanicity and the latter increased as a function of increased population

TABLE 2 Distribution of main study variables across EU-GEI sites.

Region	Country	Site	Age M (SD)	Sex *N* males (%)	Ethnicity *N* majority (%)	Child maltreatment M (SD)	Social capital M (SD)	Schizotypy *M* (SD)	Daily cannabis (%)	Pop. density (N/km^2)
North-western Europe ($N = 693$)	England ($N = 336$)	London ($N = 230$)	34.4 (12.1)	113 (49.1%)	106 (46.1%)	7.2 (2.5)	−0.8 (2.6)	1.6 (0.3)	11.7	6162.3
		Cambridge ($N = 106$)	41.2 (13.2)	50 (47.2%)	85 (80.2%)	7.0 (2.4)	1.6 (2.3)	1.2 (0.2)	4.0	241.5
	The Netherlands ($N = 210$)	Amsterdam ($N = 101$)	36.6 (14.4)	47 (46.5%)	57 (56.4%)	7.1 (2.2)	−0.4 (2.5)	1.6 (0.3)	13.1	4908
		Gouda&Voorhout ($N = 109$)	40.8 (14.3)	52 (47.7%)	103 (94.5%)	7.3 (2.3)	0.5 (1.9)	1.5 (0.3)	6.0	4208
	France ($N = 147$)	Paris (Val-de-Marne) ($N = 100$)	39.4 (15.1)	47 (47.0%)	51 (51.0%)	7.4 (2.5)	−0.4 (2.7)	1.4 (0.2)	11.6	3721.2
		Puy-de-Dôme ($N = 47$)	36.8 (11.3)	21 (44.7%)	43 (91.5%)	6.5 (1.4)	2.4 (2.2)	1.2 (0.2)	6.0	68.5
Southern Europe ($N = 387$)	Spain ($N = 222$)	Barcelona ($N = 37$)	39.9 (12.9)	16 (43.2%)	28 (75.7%)	7.2 (2.8)	−0.4 (2.1)	1.8 (0.5)	8.3	12,326.5
		Cuenca ($N = 38$)	37.6 (12.2)	20 (52.6%)	31 (81.6%)	6.0 (1.7)	0.8 (2.6)	1.2 (0.2)	-	11.6
		Madrid ($N = 38$)	36.4 (14.0)	18 (47.4%)	28 (73.7%)	6.4 (2.2)	0.2 (3.0)	1.3 (0.3)	10.5	4997.2
		Oviedo ($N = 39$)	36.3 (11.7)	19 (48.7%)	33 (84.6%)	6.7 (2.4)	0.4 (2.4)	1.4 (0.3)	-	141.9
		Santiago (N = 38)	37.2 (8.0)	18 (47.4%)	37 (97.4%)	6.4 (1.1)	0.1 (2.1)	1.3 (0.3)	-	102.3
		Valencia ($N = 32$)	37.8 (10.0)	15 (46.9%)	26 (81.3%)	6.0 (1.2)	1.3 (1.2)	1.5 (0.2)	-	14,467.9
	Italy ($N = 165$)	Bologna ($N = 65$)	32.9 (11.9)	24 (36.9%)	60 (92.3%)	6.5 (1.4)	0.0 (2.4)	1.4 (0.2)	4.1	2744
		Palermo ($N = 100$)	32.9 (12.9)	49 (49.0%)	92 (92.0%)	7.1 (1.8)	−1.6 (2.5)	1.3 (0.2)	5.1	4200
Total ($N = 1080$)			36.9 (13.2)	509 (47.1%)	780 (72.2%)	7.0 (2.2)	0.0 (2.6)	1.4 (0.3)		
Missing			1 (0.1%)	-	-	10 (0.9%)	106 (9.8%)	68 (6.3%)		
χ^2/F (*p*-value)			4.1 (<0.001)	4.1 (0.990)	203.1 (<0.001)	2.6 (0.002)	13.5 (<0.001)	25.1 (<0.001)		

Abbreviations: EU-GEI, EUropean network of national schizophrenia networks studying Gene–Environment Interactions; M, mean; SD, standard deviation.

TABLE 3 Crude and adjusted associations of study variables with schizotypy.

		Unadjusted		Adjusted		Adjusted + interaction term	
		β (95%CI)	*p*	*β* (95%CI)	*p*	*β* (95%CI)	*p*
Pop. density		0.223 (0.064–0.382)	0.006	0.248 (0.122–0.375)	<0.001	0.190 (0.083–0.297)	0.001
Region	Southern Europe			Reference		Reference	
	North-western Europe			0.337 (0.007–0.667)	0.046	0.427 (0.168–0.685)	0.001
Interaction	Pop. density × Southern Europe					0.190 (0.083–0.297)	0.001
	Pop. density × North-western Europe					0.620 (0.362–0.877)	<0.001
Age				0.007 (−0.053–0.067)	0.813	0.009 (−0.051–0.069)	0.777
Sex	Female			Reference		Reference	
	Male			0.009 (−0.092–0.110)	0.860	0.008 (−0.093–0.109)	0.873
Ethnicity	White majority			Reference		Reference	
	Minority			0.155 (0.023–0.286)	0.021	0.148 (0.016–0.279)	0.027
Parental SES	Professional			Reference		Reference	
	Intermediate			0.029 (−0.099–0.158)	0.654	0.029 (−0.099–0.157)	0.656
	Long-term unemployed or Working class			0.051 (−0.080–0.181)	0.448	0.055 (−0.076–0.185)	0.410
Level of education	Postgraduate			Reference		Reference	
	Undergraduate			0.152 (−0.010–0.313)	0.066	0.152 (−0.009–0.314)	0.064
	Vocational			0.259 (0.084–0.434)	0.004	0.261 (0.086–0.435)	0.003
	Tertiary			0.269 (0.103–0.435)	0.002	0.265 (0.099–0.431)	0.002
	School qualifications			0.111 (−0.082–0.303)	0.261	0.109 (−0.084–0.302)	0.285
	School, no qualifications			−0.038 (−0.391–0.315)	0.833	−0.042 (−0.396–0.311)	0.814
Employment	Other			Reference		Reference	
	Unemployed			0.120 (−0.025–0.265)	0.105	0.114 (−0.031–0.259)	0.123
Any mental illness in relatives	No			Reference		Reference	
	Yes			0.088 (−0.017–0.193)	0.101	0.092 (−0.014–0.197)	0.087
Child maltreatment				0.159 (0.106–0.212)	<0.001	0.160 (0.107–0.213)	<0.001
Social capital				0.102 (0.047–0.157)	<0.001	0.096 (0.041–0.151)	0.001

Note: 95%CI, 95% confidence interval; *p*, *p*-value. Models were mixed effect models accounting for clustering by site of recruitment ($N = 14$).
Abbreviation: SES, socio-economic status.

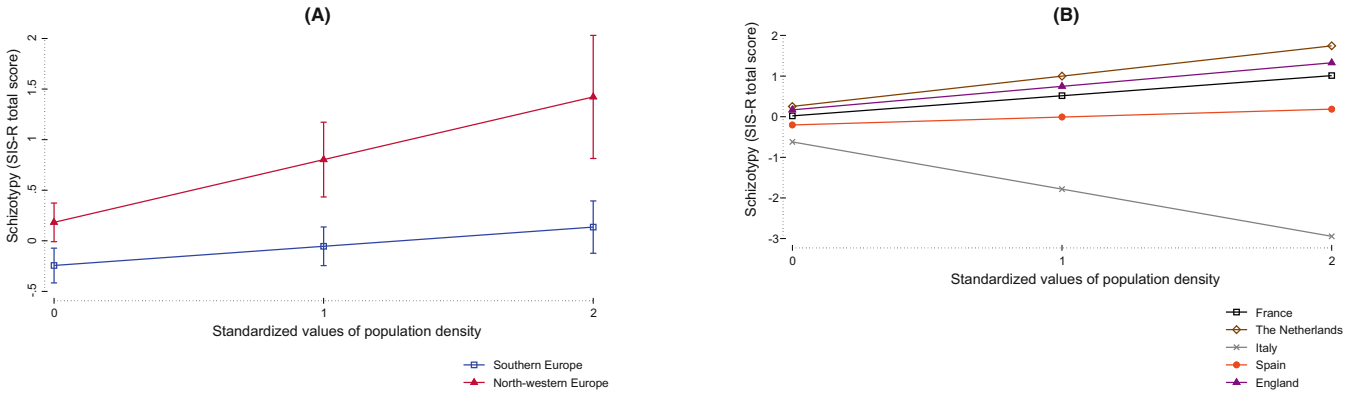

FIGURE 1 Interaction effect of population density and region/country of recruitment on schizotypy. Marginal effect plots based on multilevel linear regression of the interaction between population density (x-axis) and region (A) or country of recruitment (B) on schizotypy (y-axis). For visualization purposes, margins at standardized scores of population density from 0 to 2 were illustrated. SIS-R, Structured Interview for Schizotypy—Revised.

TABLE 4 Results of sensitivity analyses including only those sites with data on cannabis available.

	Unadjusted		Adjusted*		Adjusted* + interaction term	
	β (95%CI)	*p*	*β* (95%CI)	*p*	*β* (95%CI)	*p*
Pop. density	0.404 (0.198–0.611)	<0.001	0.449 (0.310–0.588)	<0.001	0.405 (0.246–0.565)	<0.001
Region						
Southern Europe			Ref.		Ref.	
North-western Europe			0.343 (0.042–0.645)	<0.026	0.387 (0.089–0.685)	0.011
Interaction						
Pop. density × Southern Europe					0.405 (0.246–0.565)	<0.001
Pop. density × North-western Europe					0.551 (0.310–0.791)	<0.001

Note: 95%CI, 95% confidence interval. Models were mixed effect models accounting for clustering by site of recruitment ($N = 10$). The sites of Valencia, Oviedo, Santiago, and Cuenca were excluded due to exceeding missing (>10%) on cannabis data.
*Adjusted for age, sex, ethnicity, parental socio-economic status, educational attainment, employment, any mental illness in first-degree relatives, child maltreatment, social capital, and local proportion of daily cannabis users.

density in England ($\beta = 0.580$, 95%CI = 0.373–0.787; $p < 0.001$) and France ($\beta = 0.496$, 95%CI = 0.107–0.885; $p = 0.013$), while we observed a slighter increase in Spain ($\beta = 0.195$, 95%CI = 0.115–0.274; $p < 0.001$) and an inverse association in Italy ($\beta = -1.162$, 95%CI = -2.091 to −0.233; $p = 0.014$). Findings were less robust with regards to The Netherlands ($\beta = 0.746$, 95% CI = −1.088-2.581; $p = 0.425$) (Figure 1).

5.4 | Sensitivity analyses

Accounting for daily cannabis use did not improve the model fit (likelihood test ratio: $\chi^2 = 2.10$; $p = 0.147$) nor alter our main findings, as we could still detect a 1.4 difference in the effect size of population density on schizotypy comparing North-western Europe sites ($\beta = 0.551$, 95%CI = 0.310–0.791; $p < 0.001$) with Southern Europe ones ($\beta = 0.405$, 95%CI = 0.246–0.565; $p < 0.001$) (Table 4).

5.5 | Analyses of negative and positive schizotypy

Supplementary analyses on negative and positive schizotypy yielded similar results to the analyses on total schizotypy. In unadjusted analyses, population density was associated with increase in log-transformed scores of both negative ($\beta = 0.188$, 95%CI = 0.046–0.329; $p = 0.009$) and positive schizotypy ($\beta = 0.204$, 95%CI = 0.056–0.352; $p = 0.007$), with similar effect sizes. The effect of population density on negative schizotypy was higher in North-western Europe ($\beta = 0.456$, 95%CI = 0.196–0.716; $p < 0.001$) than in Southern Europe ($\beta = 0.153$, 95% CI = 0.044–0.262; $p = 0.006$). The effect of population

density was stronger and with a larger gap with regard to positive schizotypy ($\beta = 0.619$, 95%CI = 0.391–0.848; $p < 0.001$ in North-western Europe $\beta = 0.179$, 95% CI = 0.081–0.276; $p < 0.001$ in Southern Europe). Results are summarized in Tables S3 and S4.

6 | DISCUSSION

To the best of our knowledge, this is the first study that has systematically assessed the variation of schizotypy by population density within different European regions. We found that urbanicity had a substantially greater effect on schizotypy across North-western Europe compared with Southern Europe. This effect was relevant when examining variation of schizotypy by population density in England, France, and, albeit not as robust, in the Netherlands. The association was considerably weaker for Spain and reversed in Italy. Our results were adjusted for a broad range of confounders, including local prevalence of daily cannabis use. Examining the negative and positive dimensions of schizotypy separately, the differential effect was greater for the latter.

Our results partially reflect those from the EU-GEI incidence study,[6] with the association between urbanicity and clinical psychosis being found only in England and The Netherlands, but not in the remaining countries. Recently published incidence studies in Brazil[50] and Chile[51] did not demonstrate effects of urbanicity on psychosis risk. Furthermore, a study conducted across 42 low- and middle-income countries (LMICs) within the World Health Survey[5] also failed to establish an association of urbanicity with subclinical (OR = 0.97, 95% CI = 0.87–1.07) or clinical psychosis (OR = 0.92, 95% CI = 0.73–1.16). More recently, research conducted in Australia even found a protective effect of urbanicity on risk of schizotypy among children,[52] while a study on incidence of psychosis across three diverse settings in the Global South found increased rates of psychosis in more urban areas in Trinidad, but not in India or Nigeria.[53] This evidence is in clear contrast with studies conducted in Western high-income countries (HICs) in Northern Europe[2] and North America,[54] which represent most of the body of research regarding the link between psychosis and urban living. Consistently, our analyses showed that a strong effect of urbanicity could only be detected in North-western regions of Europe.

The global population living in cities is rapidly growing and data from China, which is undergoing a rapid urbanization process, showed that the contribution of expected schizophrenia cases from urban areas doubled in two decades.[55] Thus, a systematic analysis of how rural–urban settings differ between North-western and Southern European countries, or, more broadly, between LMICs and HICs, is needed to understand which aspects of urbanicity increase psychosis risk.

Perhaps one clue comes from the official report on Urban Europe, which reported that the gradient of social exclusion and deprivation comparing urban and rural settings in different European countries is higher in England, France and The Netherlands than in Italy and Spain.[56] Differences in rural–urban patterns of schizotypy comparing North-western with Southern Europe might therefore reflect increased discrepancies between rural and urban settings in exclusion and poverty, which are among the most replicated determinants of poor mental health.[57]

Of note, in Italy, schizotypy was more represented in the least densely populated setting, Bologna, compared with Palermo, both among the most populated cities of Italy and located, respectively, in the North and South of the country. In the latter, research has documented a stronger cultural tendency towards collectivism resulting in firmer familial and community bonds[58] which could buffer the effect of urbanicity and act as a protective factor. This, however, is speculative and requires testing. Furthermore, according to the Italian National Institute of Statistics (ISTAT), the province of Bologna is one of the principal destinations of internal migration for education or economic purposes. Prior research conducted in Bologna[59] documented increased odds of psychosis among internal migrants, possibly underpinned by increased risk of isolation as result of the migratory process.

Our data show a clear discrepancy in the distribution of ethnic minorities across the EU-GEI sites, with the ethnic variation being greater in North-western Europe. Migrant and ethnic minority status are established risk factors for psychosis.[60] In a previous EU-GEI study we found a significant association between first-generation migrant status and schizotypy.[24] Reasons for increased risk of psychosis among migrants and ethnic minorities are yet to be fully understood but a growing body of evidence points at structural inequities in social and environmental conditions.[61–63] Migrants and ethnic minorities tend to reside in highly urbanized cities[64] and, often, in poor living conditions and in areas with high levels of residential instability, all potentially conferring higher psychosis risk via exposure to physical unhealthy environments and social fragmentation.[65,66] It was only from the 1990s that Southern Europe countries became destinations for migrants. In previous decades migration had mostly involved North-western Europe.[67] This difference is reflected in our data with most individuals being White in Spain and Italy (range 73.7–97.4%) and with a larger gradient of ethnic variation across the more and

the less densely populated sites in North-western Europe (e.g., 46.2% were White in South-East London and 80.2% in Cambridge). It is therefore possible that this might at least partly explain our results, since the largest cities of North-western Europe (Amsterdam, London, and Paris) had much higher ethnic diversity compared with the less urbanized counterparts (Gouda&Voorhout, Cambridge, and Puy-de-Dôme, respectively). Even so, the association between urbanicity and schizotypy persisted after adjusting for ethnic minority status and previous research has shown that the effect of urbanicity on psychosis among ethnic minority groups varies along with contextual factors (such as ethnic density) and specific ethnicity.[68]

In our analyses, the effect of urbanicity was not confounded by a lack of social capital and exposure to adverse childhood experiences, which were both associated with schizotypy. Regarding childhood adversities, some research has showed that urban upbringing might affect stress and trauma reactivity, altering the hypothalamus-pituitary–adrenal axis activity, which is implicated in several psychiatric disorders.[69] Nevertheless, it is unlikely that such an effect might be specific to certain countries (i.e., Western HICs) and not generalizable to the others. Even so, urbanization rises concerns also in relation to the increased likelihood of violence and victimization,[70] which might, in turn, increase psychosis risk as per the socio-developmental model of psychosis.[71]

Some family-based studies[72,73] reported that the effect of urbanicity on risk of psychosis may be confounded by genetic influences, leading to the hypothesis that familial factors may condition aggregation of individuals with genetic proneness to psychosis in the most densely populated areas. This hypothesis has been corroborated by recent findings that genetic liability to schizophrenia, possibly expressed as mild psychotic experiences or schizotypy, was associated with moving from rural environments to cities.[74] In our study, we did not adjust for genetic predisposition. Nevertheless, previous evidence[4] has shown that polygenic risk score for schizophrenia only accounts for a minor part of the association between urbanicity and schizophrenia risk. Hence, it is unlikely that differences in genetic predisposition explain the variation of schizotypy by population density in our study.

Finally, in line with prior research,[75] the effect of urbanicity was unspecific and independently associated with both negative and positive schizotypy. Nevertheless, the differential effect was larger for positive schizotypy suggesting that exposure to the most urbanized environment of North-western European cities might particularly favor the emergence of positive symptoms.

This study has several strengths. First, we analyzed data from a large, multi-national study, which collected information on a well-characterized range of socio-environmental exposures using the same validated instruments across settings. We used a multi-level approach to account for the nested structure of the data (by site). Second, the recruitment strategy was specifically conceived to obtain a sample representative of the population-at-risk on key variables, such as age, sex, and ethnicity. To minimize selection bias, our analyses were weighted for the probability of participant being selected based on primary demographic characteristics. Third, schizotypy was assessed using a semi-structured interview[27] conducted by a clinician or a trained researcher to increase reliability.

Several limitations should also be acknowledged. First, our study only involved a relatively small number of sites across the different countries. Thus, our findings might not extend to other areas of Southern or North-western Europe which were not sampled. Furthermore, there are relevant contextual differences between major cities in England and France (i.e., London and Paris) and the rest of the countries, with a bigger gap between the most and the least densely populated sites. Second, this was a cross-sectional study and, while schizotypy was measured through face-to-face interview, many other study variables underwent retrospective assessment raising concerns about recall bias or reverse causality. Third, our exposure was living in urban areas at the time of assessment. Prior research has shown that early exposure to urban environment increases the psychosis risk the most.[3,4] Furthermore, we had no information on how long participants had been residing at the current address, limiting our capability to draw firm conclusions. Future studies should prioritize a comprehensive recollection of the residential history of participants, with particular emphasis on vulnerable periods (i.e., childhood and adolescence), to allow an accurate assessment of environmental and contextual factors on health trajectories. Fourth, urbanicity was operationalized as population density measured at site-level and we need to acknowledge that the latter might not capture all the aspects related to urbanicity.[76] Fifth, our analyses were adjusted for child maltreatment, lack of social capital, and ethnic minority status, but several other important risk factors for psychosis were not taken into account. Finally, subclinical psychotic symptoms and, as such, schizotypal traits, can be associated with a broad range of non-psychotic mental disorders.[77] EU-GEI potential control participants were excluded if they had current or prior episode of psychosis while other conditions were not specifically ruled out. To conclude, the expression of schizotypy as a function of increased population density showed substantial differences across multiple European sites; importantly these reflected our previous findings on

the incidence of clinical psychosis.[6] These findings align with emerging evidence that urbanicity, rather than being a universal risk factor for psychosis spectrum disorders, may be context-specific. Exact mechanisms underlying the increased risk remain unknown. Yet, existing evidence points towards multiple mediators and moderators of the association, including psychosocial and physical exposures. Further research should investigate the association in diverse settings and examine the interplay of individual factors, such as migrant status, isolation, or drug use, and contextual factors, such as social capital or fragmentation, the physical environment of cities.

AFFILIATIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request under the condition of the approval of the EU-GEI steering committee.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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