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Variation of subclinical psychosis across 16 sites in Europe and Brazil: findings from the multi-national EU-GEI study

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Original Article

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Abstract

Background. Incidence of first-episode psychosis (FEP) varies substantially across geographic regions. Phenotypes of subclinical psychosis (SP), such as psychotic-like experiences (PLEs) and schizotypy, present several similarities with psychosis. We aimed to examine whether SP measures varied across different sites and whether this variation was comparable with FEP incidence within the same areas. We further examined contribution of environmental and genetic factors to SP.

Methods. We used data from 1497 controls recruited in 16 different sites across 6 countries. Factor scores for several psychopathological dimensions of schizotypy and PLEs were obtained using multidimensional item response theory models. Variation of these scores was assessed using multi-level regression analysis to estimate individual and between-sites variance adjusting for age, sex, education, migrant, employment and relational status, childhood adversity, and cannabis use. In the final model we added local FEP incidence as a second-level variable. Association with genetic liability was examined separately.

Results. Schizotypy showed a large between-sites variation with up to 15% of variance attributable to site-level characteristics. Adding local FEP incidence to the model considerably reduced the between-sites unexplained schizotypy variance. PLEs did not show as much variation. Overall, SP was associated with younger age, migrant, unmarried, unemployed and less educated individuals, cannabis use, and childhood adversity. Both phenotypes were associated with genetic liability to schizophrenia.

Conclusions. Schizotypy showed substantial between-sites variation, being more represented in areas where FEP incidence is higher. This supports the hypothesis that shared contextual factors shape the between-sites variation of psychosis across the spectrum.

Introduction

The incidence of psychotic disorders varies substantially across geographic regions. A recent meta-analysis (Jongsma, Turner, Kirkbride, & Jones, 2019) estimated an almost 15-times variation across 17 different countries. Individual characteristics have been linked to a higher incidence of psychotic disorders, including younger age, male sex (Aleman, Kahn, & Selten, 2003; Van Der Werf et al., 2014), migration (Selten, Van Der Ven, & Termorshuizen, 2019; Tarricone et al., 2021), education (Dickson et al., 2020), genetic liability(Lewis & Knight, 2012), adverse childhood experiences (Morgan & Gayer-Anderson, 2016; Varese et al., 2012), and cannabis use (Di Forti et al., 2019). Site-level factors such as urbanicity (March et al., 2008; Vassos, Pedersen, Murray, Collier, & Lewis, 2012), neighbourhood ethnic density (Schofield et al., 2023), higher latitude (Saha, Chant, Welham, & McGrath, 2006), socio-economic inequality (Burns & Esterhuizen, 2008; Kirkbride, Jones, Ullrich, & Coid, 2014), social fragmentation (Allardyce et al., 2005; Ku, Compton, Walker, & Druss, 2021), and patterns of cannabis abuse (Di Forti et al., 2019) have also been associated with increased rates.

The traditional concept of psychosis as occurring only in those who are ill has been challenged by increasing evidence of several psychosis phenotypes which are below the threshold for being clinically relevant or impairing one's global functioning (Van Os, Linscott, Myin-Germeys, Delespaul, and Krabbendam, 2009). Manifestations of non-clinical psychosis are commonly referred to as 'subclinical psychosis' (SP) and encompass a broad spectrum of entities along a continuum of frequency and severity.

Psychotic-like Experiences (PLEs) are defined as 'psychotic symptoms in the absence of illness' (Kelleher & Cannon, 2011). The estimated prevalence is 7.2% (Linscott & Van Os, 2013), more than 2-times higher than the comparable life-time rate of psychotic disorders (3.06%) (Perälä et al., 2007). PLEs are mostly transient and only about 7–8% progress to full-blown psychotic disorder (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Linscott & Van Os, 2013).

Schizotypy is a multidimensional range of personality traits on a dimensional continuity with schizophrenia. Schizotypy traits cluster into positive, negative, and disorganized symptoms domains (Kwapil & Barrantes-Vidal, 2015). Contrarily to the initial postulations (Meehl, 1962, 1990; Rado, 1953), it is nowadays assumed that schizotypy traits are normally distributed within the general population along continuous dimensions(Claridge, 1997) and are not necessarily linked to psychopathology (Mohr & Claridge, 2015). Nevertheless, schizotypy can predict the onset of psychosis (Debbané et al., 2015; Flückiger et al., 2016; Salokangas et al., 2013; Shah et al., 2012).

Given the continuity between SP and threshold psychotic disorders, some authors have proposed the use of population-level measures of PLEs or schizotypy as surrogates of clinical disorders for research purposes (Szöke, Kirkbride, & Schürhoff, 2014). While prior research has shown a substantial overlap in terms of risk factors between clinical and subclinical forms of psychosis (Linscott & Van Os, 2013; Pries et al., 2018), less is known about geographic variation of SP.

In this context, we aimed to examine whether measures of SP had a within-site variation across 16 sites and 6 different countries and if this variation was in parallel with the previously estimated incidence rates of first-episode psychosis (FEP) within the same catchment areas and timespan. Furthermore, we sought to examine environmental and genetic contributions to the phenotypic SP expression.

Methods

Eu-GEI study

This study is part of the EUropean network of national schizophrenia networks studying Gene–Environment Interactions (EU-GEI study, http://www.eu-gei.eu), a multi-national incidence and case-sibling-control study of genetic and environmental determinants of psychotic disorders (Gayer-Anderson et al., 2020). Three groups of participants were recruited: (1) first-episode psychosis (FEP) patients aged 18–64; (2) population-based healthy controls within the same age-span and catchment area; (3) siblings of FEP participants. The recruitment took place between 1 May 2010 and 1 April 2015 and involved 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). Ethical approval was granted in each study centre.

In this investigation, we included only population-based controls.

Study population

Population-based controls aged 18–64 years were recruited from the same catchment areas as FEP patients and over the same time span. In each area, the recruitment was conducted using a mixture of random and quota-sampling strategies, to maximize representativeness to the population-at-risk by age, sex and ethnicity. Quotas for sampling were derived from the most accurate local demographic data. Individuals with a history of psychotic disorder or taking anti-psychotic medication were not eligible (Di Forti et al., 2019; Gayer-Anderson et al., 2020).

For the current study, one French site (20th arrondissement of Paris) was excluded as no controls were recruited there.

Measures

Outcome. Our primary outcomes were dimensions of SP in the general population. We measured schizotypy with the Structured Interview for Schizotypy-Revised (SIS-R) (Kendler, Lieberman, & Walsh, 1989; Vollema & Ormel, 2000) and PLEs with the Community Assessment of Psychic Experiences (CAPE) (Konings, Bak, Hanssen, Van Os, & Krabbendam, 2006).

SIS-R

The SIS-R (Kendler et al., 1989; Vollema & Ormel, 2000) is a semi-structured interview containing 20 schizotypal symptoms and 11 schizotypal signs rated on a 4-point scale (from 'absent' to 'severe'). It covers three dimensions of schizotypal personality: cognitive-perceptual alterations, disorganization, and negative dimension. Details of how we operationalised SIS-R scores as our outcome measure for statistical analyses are provided below.

CAPE

The CAPE (Konings et al., 2006) (www.cape42.homestead.com) provides a self-reported measure of lifetime PLEs. It has 42 items rated on a 4-point scale (from 'never' to 'nearly always'). The CAPE covers three domains: depressive, negative, and positive symptomatology. Details of how we operationalised CAPE scores as our outcome measure for statistical analyses are provided below.

FEP incidence

A previous EU-GEI study (Jongsma et al., 2018) estimated the incidence of FEP across 17 sites in the counties involved in the project. All individuals who had contact with mental health services in the catchment areas for a suspected FEP were identified and ascertained. Potential participants were included if: (1) were resident within the catchment area; (2) were aged between 18 and 64 years; and (3) met the diagnostic criteria for FEP according to the International Classification of Diseases, Tenth Revision (ICD-10), codes F20-F33. Individuals who had previous contact with mental health services for psychosis, organic psychosis, or transient psychotic symptoms due to acute intoxication, as defined by ICD-10 codes F1X.5, were excluded. The most accurate local census data stratified by age, sex, and ethnicity were used in each catchment area to estimate the population-at-risk. Person-

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years at risk were estimated multiplying the population-at-risk by the duration of case ascertainment in each study site. Crude incidence rates of FEP (ICD-10 codes F20-F33) per 100 000 person-years at risk were then estimated for each study site. We used standardized incidence rates of FEP to examine the association between variation of SP across study sites by local FEP incidence.

Socio-demographic characteristics

We collected data on age, sex (male/female), migrant status (foreign-born), education (no qualification/school-college-vocational/higher), relational (single/other) and employment status (unemployed/other), using an amended version of the Medical Research Council Socioeconomic Schedule (Mallet, 1997).

Other exposures

Current cannabis (no/yes) use was derived from a modified version of the Cannabis Experience Questionnaire (Di Forti et al., 2019). Childhood trauma was assessed through Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) and Childhood Experience of Care and Abuse (CECA) (Bifulco, Brown, & Harris, 1994). From CTQ, we derived the mean score of the five subscales (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse). From the CECA interview, we only used the item on having been the victim of bullying.

Genetic liability

We used Schizophrenia Polygenic Risk Scores (SCZ-PRS) as a measure of genetic liability to schizophrenia (Lewis & Knight, 2012). Samples for genomic study were processed at the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff (UK). The calculation of SCZ-PRS was based on the latest Psychiatric Genomics Consortium (PGC) data (Trubetskoy et al., 2022). The procedure is detailed elsewhere (Quattrone et al., 2021).

Missing data

The proportion of missing values was low, ranging from 0.1% on ethnicity to 11.6% on one SIS-R item. Missing data were handled by multiple imputation (details in online Supplementary Materials).

Statistical analyses

First, we ran descriptive analyses on the whole sample to obtain frequencies and means of the study variables.

Then, data from SIS-R and CAPE were analysed using Multidimensional Item Response Theory (MIRT) to operationalise our outcome measures. Bifactor models were chosen for both phenotypes based on a previous EU-GEI publication (Quattrone et al., 2021) and on empiric evidence. For SIS-R we thus extracted a general factor (SIS-R_{GEN}) along with three uncorrelated factors, i.e. Cognitive-Perceptual (SIS-$R_{COG-PER}$), Negative (SIS-R_{NEG}), and Paranoid (SIS-R_{PAR}). For CAPE, we estimated the general factor ($CAPE_{GEN}$) and the depressive ($CAPE_{DEP}$), negative ($CAPE_{NEG}$), and positive ($CAPE_{POS}$) domains. For details see online Supplementary Materials.

The CAPE and SIS-R factor scores were extracted and compared across the EU-GEI sites using one-way ANOVA followed by Tukey HSD post-hoc analysis. For each site, the mean score of each factor was compared with FEP incidence using Pearson's product-moment correlations.

Then, we used multilevel regression to investigate schizotypy and PLEs by study site considering both individual and contextual factors (FEP incidence) (Von Korff, Koepsell, Curry, & Diehr, 1992). All models were random intercept models allowing our outcome measures to vary across catchment areas ($N = 15$ sites for SIS-R_{GEN} analyses and $N = 16$ sites for $CAPE_{GEN}$ analyses). First, we looked for evidence of significant between-sites variation of SIS-R_{GEN} and $CAPE_{GEN}$ by comparing null single-level model with the correspondent null two-level model (individuals – level 1 – nested in recruitment sites – level 2) with a likelihood-ratio test, by inspecting the estimated shrunken residuals on a 'caterpillar' plot (Rasbash, Steele, Browne, Goldstein, & Charlton, 2012), and by examining the intra-class correlation coefficients (ICC). In two-level models the ICC represents the proportion of variance that is accounted for by the group level and ranges between 0 and 1, with the value of 0 or close suggesting that a multilevel structure is probably absent (Merlo, Chaix, Yang, Lynch, & Merlo, 2005). Moreover, we compared the variance explained across three different models at both individual and site levels, measuring their proportional change in variance (PCV) (Merlo et al., 2005). Model 1 was adjusted for age and sex. Model 2 was further adjusted for the following individual-level variables: education, relational status, employment status, current cannabis use, migrant status, childhood trauma, and bullying. Finally, in Model 3 we added standardised FEP incidence rate as site-level variable. The choice of covariates was made a priori based on extensive literature review on the subject (Linscott & Van Os, 2013; Pignon et al., 2021; Van Os et al., 2009) and consensus of the research team. Multicollinearity was checked by examining the correlation between the independent variables and estimating the variance inflation factors (VIF) for each covariate (online Supplementary Materials). We further tested the distribution of the standardized residuals by visually inspecting the qq-plots and using the Kolmogorov–Smirnov test (online Supplementary Materials).

Lastly, we tested for the association between SP and SCZ-PRS, to see whether genetic liability to schizophrenia explained schizotypy or PLEs in our sample. We ran two-level linear regression models with either SIS-R or CAPE general factor scores as dependent variables. To control for population stratification, we conducted a principal component analysis to generate 10 principal components which were used as covariates in the regression models. Analyses were further adjusted conducted covarying for age and sex.

Sensitivity analyses were performed for the Models 1–3 on the complete-cases sample. Inverse probability weights were generated for each participant based on key demographics (age, sex, ethnicity) to account for the potential over- or under-sampling and used in sensitivity analyses (online Supplementary Materials).

Analyses were performed using RStudio R version 3.6.3 (RStudio Team, 2020) and Stata 17 (StataCorp., 2021).

Results

We recruited 1497 controls. The sample characteristics are presented in online Supplemental Table S1.

Bifactor model of SIS-R and CAPE SP

The bifactor model was found to be the best fit for the SIS-R items (online Supplemental Table S2). The factor loadings and communalities are shown in online Supplemental Table S3. All items

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showed moderate to strong positive loading on the general dimension. The magnitude of item loadings on the specific factors was also moderate to strong, apart from the items 'hypersensitivity' and 'suspiciousness' which were therefore kept in the general factor only.

The factor loadings of CAPE items are presented in online Supplemental Table S4.

Variation of SIS-R and CAPE and correlation with FEP incidence by study site

One-way ANOVA showed variation in all the domains of the SIS-R by study site (online Supplemental Figure S1). Scores on the SIS-R_{GEN} ($F = 21.419$; $p < 0.001$, partial-$\eta^2 = 0.180$) were higher in Amsterdam, Barcelona, Gouda&Voorhout, and London compared with the other sites. SIS-$R_{COG-PER}$ factor scores were higher in Amsterdam, Barcelona, London, and Sao Paulo and were lower in Oviedo, Santiago, and Palermo ($F = 18.859$; $p < 0.001$, partial-$\eta^2 = 0.162$). SIS-R_{NEG} scores were higher in Amsterdam, Paris, Gouda&Voorhout, and London (14.567; $p < 0.001$, partial-$\eta^2 = 0.130$). Finally, SIS-R_{PAR} had the lowest degree of variation by site ($F = 4.116$; $p < 0.001$, partial-$\eta^2 = 0.040$), with greater scores in the Spanish sites (Oviedo, Santiago, and Valencia).

Compared with SIS-R, CAPE SP domains showed less dispersion by study sites (online Supplemental Figure S2), especially regarding the $CAPE_{NEG}$ ($F = 1.517$; $p = 0.097$, partial-$\eta^2 = 0.014$). The $CAPE_{GEN}$ scores were greater in Bologna, Palermo, and Santiago ($F = 3.366$; $p < 0.001$, partial-$\eta^2 = 0.035$), while the $CAPE_{POS}$ was more represented in Bologna, Cuenca, London, and Palermo ($F = 9.345$; $p < 0.001$, partial-$\eta^2 = 0.094$). The $CAPE_{DEP}$ scores were generally higher among the French sites ($F = 1.854$; $p = 0.024$, partial-$\eta^2 = 0.019$).

Both SIS-R_{GEN} (Pearson's $r = 0.684$; $p = 0.005$) and SIS-R_{NEG} (Pearson's $r = 0.642$; $p = 0.010$) were strongly correlated with the incidence of FEP across the study centres. The correlation coefficients for SIS-$R_{COG-PER}$ and SIS-R_{PAR} factors were of 0.439 ($p = 0.102$) and −0.384 ($p = 0.158$) respectively. On the other hand, CAPE domains were not correlated with FEP incidence. The Pearson's coefficients ranged between −0.146 ($p = 0.590$) for $CAPE_{GEN}$ and 0.157 ($p = 0.564$) for $CAPE_{NEG}$ (Fig. 1).

Multi-level regression analysis

Random and fixed effects from the two-level regression models are presented in Tables 1–2.

Random effects

The site-level variance of the SIS-R_{GEN} null model was 0.10 (95% CI = 0.05–0.21), with an ICC of 0.15 (95%CI = 0.007–0.27), suggesting that about 15% of the individual differences in schizotypy general factor was at the site level. The likelihood-ratio test comparing the null single-level model (log-likelihood = −1693) with the null two-level model (log-likelihood = −1583) was significant ($\chi^2 = 220.09$; $p < 0.001$). The caterpillar plot (Fig. 2A) shows the distribution of the shrunken residuals around the mean, with 9 out of 15 study sites included in SIS-R analysis having a significant shift from the mean. The individual-level variance, however, was much higher (0.56, 95%CI = 0.52–0.61) and accounted for the rest of the total variance. Adding age and sex to the null model did not alter the PCV at both site- and individual levels. The addition of the other individual-level covariates (Model 2) brought a 20% reduction in the unexplained site-level variance and a 12.5% reduction in the unexplained individual-level variable. Finally, adding the incidence of FEP as a level-two variable (Model 3) resulted in a further reduction of the unexplained site-level variance of about 40.0%, while the individual-level variance remained unchanged. The ICC of the final model was 0.08 (95%CI = 0.03–0.17), with a PCV of 60.0% compared with the null model.

Site-level variation estimated from the $CAPE_{GEN}$ null two-level model was extremely low (0.02, 95%CI = 0.01–0.08) with an ICC of 0.03 (0.01–0.08). The likelihood-ratio test, however, showed that a two-level model (log-likelihood = 1954) was still significantly better than the single-level model (log-likelihood = 1962) ($\chi 2 = 14.90$; $p < 0.001$). As shown in the caterpillar plot (Fig. 2B), only for 2 sites (Palermo and Madrid) we observed a significant shift from the mean. In this case, the individual-level variance accounted for almost the total $CAPE_{GEN}$ variance and for this reason we considered only the change in the individual-level PCV to compare the models. Adjusting the null model for age and sex only decreased the individual unexplained variance of 1.3%. When all the individual-level variables were added (Model 2), there was a 12.6% decrease in the PCV. The addition of FEP incidence did not affect the PCV (Model 3).

Fixed effects

Schizotypy, as measured by SIS-R_{GEN} was associated with sociodemographic characteristics such as level of education (school/college/vocational v. higher: $\beta = 0.201$,95%CI = −0.118 to 0.284; $p < 0.001$), unemployment ($\beta = 0.121$,95%CI = 0.013–0.229; $p = 0.027$), and migrant status ($\beta = 0.108$,95%CI = 0.012–0.205; $p = 0.028$). The mean CTQ score ($\beta = 0.070$,95%CI = −0.053 to 0.088; $p < 0.001$) and experiences of bullying ($\beta = 0.260$,95%CI = −0.172 to 0.349; $p < 0.001$) were also associated with schizotypy. Finally, we found a 0.227 increase in the SIS-R_{GEN} factor score per each unit of standardised incidence rate ($\beta = 0.227$,95%CI = 0.101–0.354; $p < 0.001$).

PLEs, as measured by the $CAPE_{GEN}$ factor score, were lower in males ($\beta = -0.118$,95%CI = −0.204 to −0.032; $p = 0.007$), and higher in individuals who declared to be single ($\beta = 0.137$,95%CI = 0.041–0.234; $p = 0.005$) or unemployed ($\beta = 0.168$,95%CI = 0.046–0.291; $p = 0.007$). PLEs were also associated with current cannabis use ($\beta = 0.153$,95%CI = 0.011–0.295; $p = 0.035$), CTQ ($\beta = 0.114$,95%CI = 0.093–0.134; $p < 0.001$) and bullying ($\beta = 0.310$,95% CI = −0.210 to 0.410; $p < 0.001$). In the final model higher standardised incidence was associated with a slight $CAPE_{GEN}$ reduction ($\beta = -0.098$,95%CI = −0.173 to −0.023; $p = 0.010$).

Association of SP with genetic liability

We found evidence of an association between SCZ-PRS and SIS-R_{GEN} in both unadjusted ($\beta = 0.076$,95%CI = −0.021 to 0.131; $p = 0.006$) and adjusted regression analysis ($\beta = 0.078$,95%CI = −0.023 to 0.133; $p = 0.007$). The SCZ-PRS was also associated with an increased score on the $CAPE_{GEN}$ ($\beta = 0.075$,95%CI = 0.011–0.139; $p = 0.021$). The association withheld adjustment for age and sex ($\beta = 0.075$,95%CI = 0.011–0.138; $p = 0.021$) (Table 3).

Sensitivity analyses

Sensitivity analyses on the weighted complete-cases sample yielded very similar results to those from analyses conducted on the imputed dataset (online Supplementary Materials).

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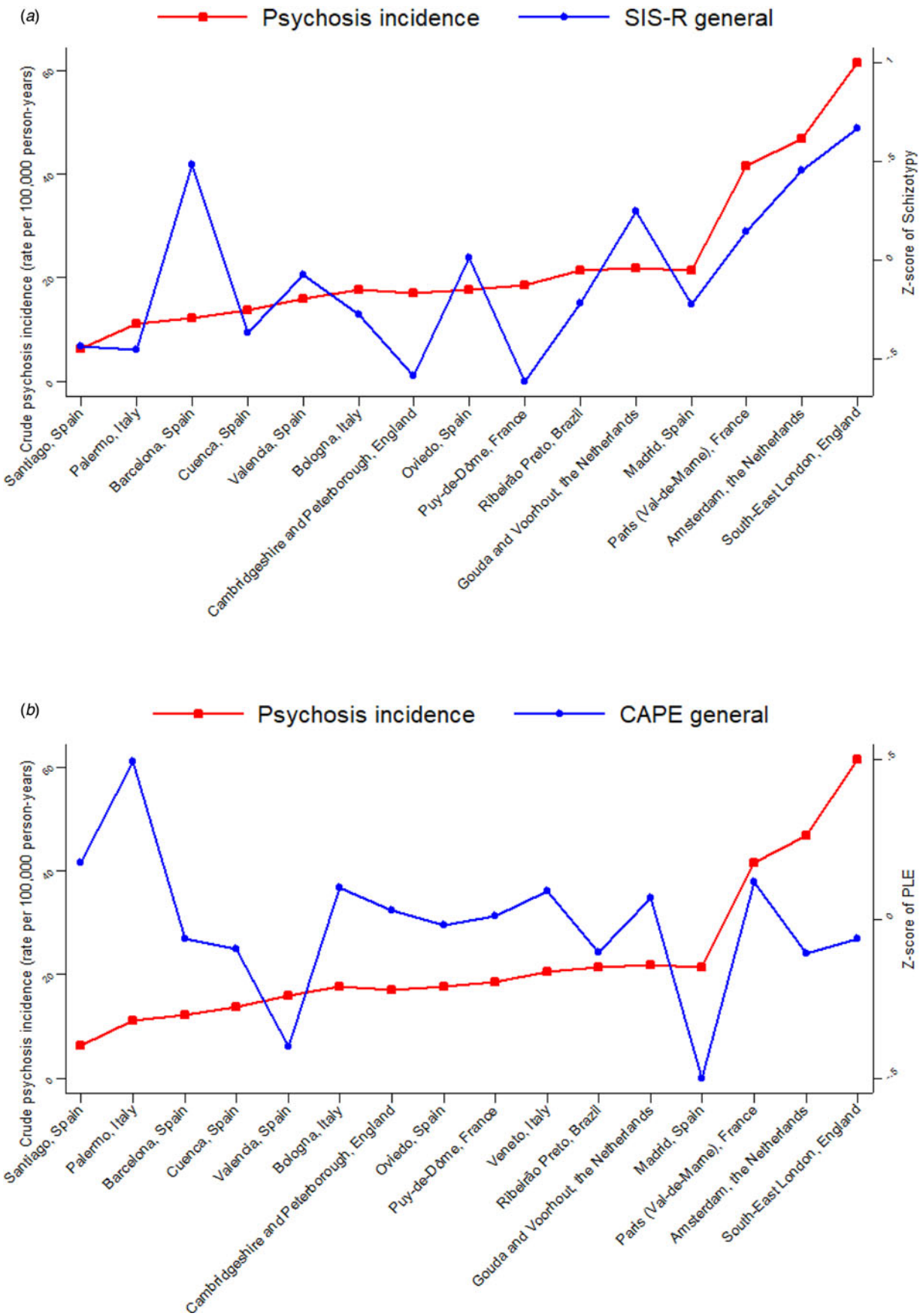

Figure 1. Crude incidence rates for all psychosis across the EU-GEI sites plotted against the mean *z*-scores of dimensions of schizotypy (A) and PLEs (B).

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Table 1. Multilevel regression analysis of SIS-R general factor score from 15 catchment areas in Europe and Brazil

	Null model (*N* = 1382)	Model 1 (*N* = 1382)	Model 2 (*N* = 1382)	Model 3 (*N* = 1382)
Fixed effects				
Individual level				
Age		**−0.004 (−0.007- −0.001)**	−0.003 (−0.006-0.001)	−0.003 (−0.006-0.001)
Sex				
Female		Ref.	Ref.	Ref.
Male		−0.069 (−0.148-0.010)	−0.052 (−0.128-0.025)	−0.053 (−0.129-0.024)
Education				
Higher			Ref.	Ref.
School, college, vocational			**0.196 (0.113-0.279)**	**0.201 (0.118-0.284)**
No qualification			0.178 (−0.009-0.364)	0.178 (−0.009-0.364)
Relational status				
Other			Ref.	Ref.
Single			0.081 (−0.006-0.168)	0.079 (−0.008-0.166)
Employment				
Other			Ref.	Ref.
Unemployed			**0.120 (0.012-0.228)**	**0.121 (0.013-0.229)**
Current cannabis use				
No			Ref.	Ref.
Yes			0.078 (−0.048-0.203)	0.079 (−0.046-0.204)
Migrant status				
Non-migrant			Ref.	Ref.
Migrant			**0.112 (0.015-0.209)**	**0.108 (0.012-0.205)**
CTQ			**0.071 (0.053-0.089)**	**0.070 (0.053-0.088)**
Bullying				
Never			Ref.	Ref.
Ever			**0.267 (0.178-0.355)**	**0.260 (0.172-0.349)**
Site level				
Incidence of FEP				**0.227 (0.101-0.354)**
Random effects				
Individual variance	0.56 (0.52-0.61)	0.56 (0.52-0.60)	0.49 (0.46-0.53)	0.49 (0.46-0.54)
Site variance	0.10 (0.05-0.21)	0.10 (0.05-0.21)	0.08 (0.04-0.18)	0.04 (0.02-0.10)
PCV				
PCV between individuals	Ref..	0.0%	12.5%	12.5%
PCV between sites	Ref..	0.0%	20.0%	60.0%
ICC	0.15 (0.07-0.27)	0.15 (0.08-0.28)	0.14 (0.07-0.27)	0.08 (0.03-0.17)
Log likelihood	−1584	−1579	−1498	−1493
AIC	3174	3168	3022	3016
BIC	3189	3194	3090	3089

CTQ Childhood Trauma Questionnaire; SCZ-PRS, Schizophrenia Polygenic Risk Score; FEP, First-Episode Psychosis; PCV, Proportional change in variance; ICC, Intraclass correlation coefficitent; AIC, Akaike Information Criterion. Coefficients in bold are statistically significant ($p < 0.05$).

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Table 2. Multilevel regression analysis of CAPE General factor score from 16 catchment areas in Europe and Brazil

	Null model (*N* = 1497)	Model 1 (*N* = 1497)	Model 2 (*N* = 1493)	Model 3 (*N* = 1493)
Fixed effects				
Individual level				
Age		−0.002 (−0.006-0.001)	0.000 (−0.003-0.004)	−0.003 (−0.006-0.001)
Sex				
Female		Ref.	Ref.	Ref.
Male		**−0.132 (−0.221- −0.042)**	**−0.119 (−0.205- −0.033)**	**−0.118 (−0.204- −0.032)**
Education				
Higher			Ref.	Ref.
School, college, vocational			0.003 (−0.091-0.096)	−0.002 (−0.095-0.092)
No qualification			−0.166 (−0.382-0.051)	−0.170 (−0.386-0.046)
Relational status				
Other			Ref.	Ref.
Single			**0.135 (0.038-0.232)**	**0.137 (0.041-0.234)**
Employment				
Other			Ref.	Ref.
Unemployed			**0.167 (0.044-0.290)**	**0.168 (0.046-0.291)**
Current cannabis use				
No			Ref.	Ref.
Yes			**0.151 (0.008-0.293)**	**0.153 (0.011-0.295)**
Migrant status				
Non-migrant			Ref.	Ref.
Migrant			−0.032 (−0.142-0.178)	−0.025 (−0.136-0.085)
CTQ			**0.112 (0.092-0.133)**	**0.114 (0.093-0.134)**
Bullying				
Never			Ref.	Ref.
Ever			**0.300 (0.200-0.400)**	**0.310 (0.210-0.410)**
Site level				
Incidence of FEP				**−0.098 (−0.173- −0.023)**
Random effects				
Individual variance	0.79 (0.73-0.85)	0.78 (0.73-0.84)	0.69 (0.64-0.74)	0.69 (0.64-0.74)
Site variance	0.02 (0.01-0.06)	0.02 (0.01-0.06)	0.02 (0.01-0.05)	0.01 (0.00-0.04)
PCV				
PCV between individuals	Ref.	1.3%	12.6%	12.6%
ICC	0.03 (0.01-0.08)	0.03 (0.01-0.08)	0.03 (0.01-0.07)	0.01 (0.00-0.06)
Log likelihood	−1954	−1949	−1853	−1851
AIC	3915	3909	3732	3729
BIC	3931	3936	3801	3804

CTQ, Childhood Trauma Questionnaire; SCZ-PRS, Schizophrenia Polygenic Risk Score; FEP, First-Episode Psychosis; PCV, Proportional change in variance; ICC, Intraclass correlation coefficitent; AIC, Akaike Information Criterion; Bayesian Information Criterion. Coefficients in bold are statistically significant ($p < 0.05$).

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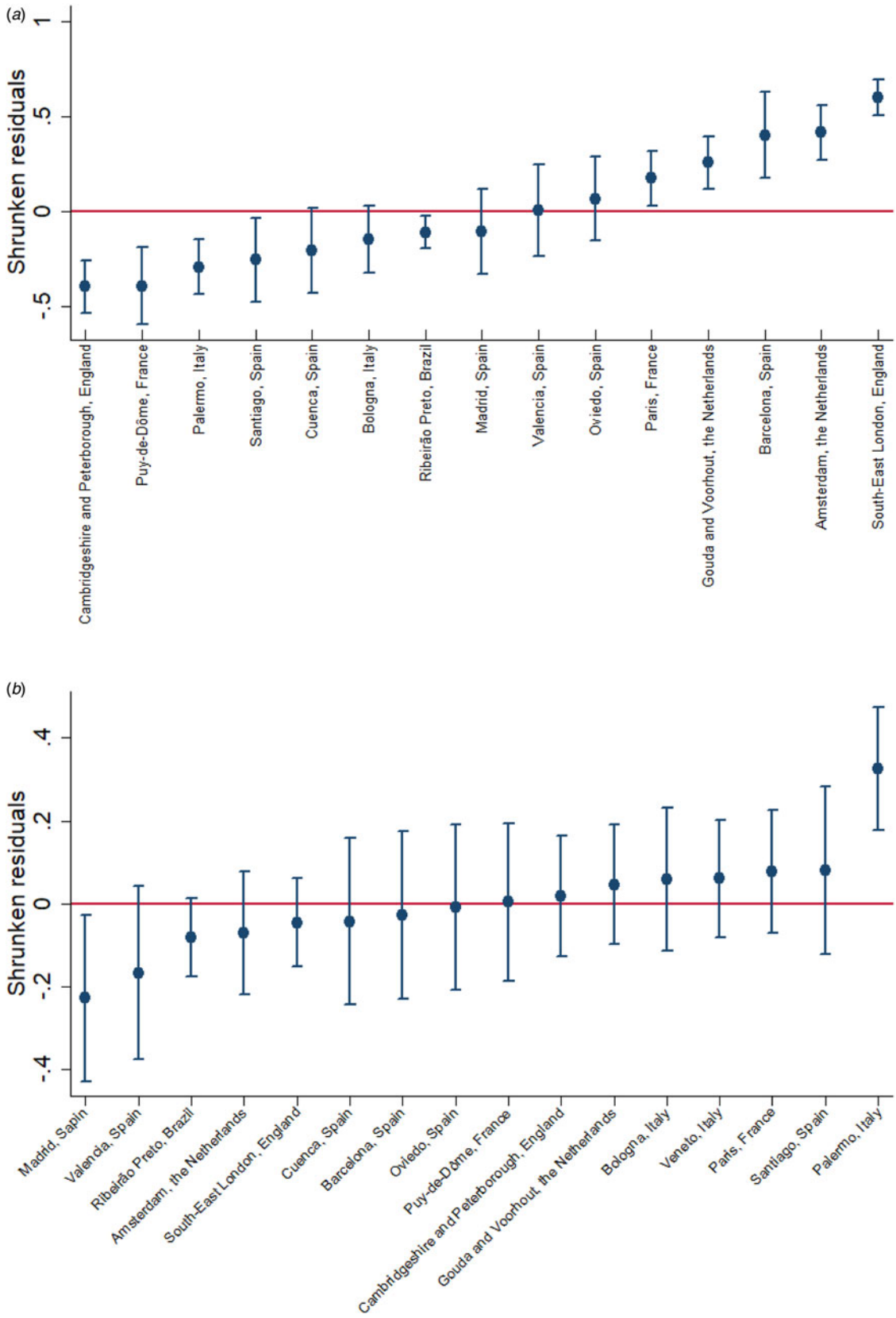

Figure 2. Caterpillar plot of shrunken residuals from the SIS-R_{GEN} (A) and $CAPE_{GEN}$ (B) multilevel regression models.

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Table 3. SP by SCZ-PRS

	$SIS\text{-}R_{GEN}$				$CAPE_{GEN}$			
	unadjusted		adjusted†		unadjusted		adjusted†	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI
SCZ-PRS	**0.076**	**0.021–0.131**	**0.078**	**0.023–0.133**	**0.075**	**0.011–0.139**	**0.075**	**0.011–0.138**

Significant coefficients (<0.05) are in bold. †adjusted for age, sex, and ten principal components.
SCZ-PRS, schizophrenia polygenic risk score; $SIS\text{-}R_{GEN}$, SIS-R general factor; $CAPE_{GEN}$, CAPE general factor.
β: regression coefficient; 95%CI: 95% confidence interval.

Discussion

Main findings

We measured two different SP phenotypes along with their symptom dimensions and examined their variation across several sites from different countries. The factor structures of both phenotypes were better explained by bifactor models, supporting the hypothesis of general psychopathological constructs of SP linking specific symptomatic domains.

PLEs had a more uniform distribution across study sites, with barely 3% of variance attributable to the environment. There was no evidence of a correlation between any of the PLEs dimensions and incidence of psychosis. PLEs expression relied almost uniquely on individual factors, such as female sex, single status, unemployment, current cannabis use, and childhood adverse events.

Schizotypy varied largely between sites and up to 15% of its variance could be attributed to site-level characteristics. Adding local FEP incidence saw a 60% reduction in the unexplained between-sites variance compared with the null model. Furthermore, general and negative dimensions of schizotypy were strongly correlated with incidence of FEP, being more represented in those sites where FEP incidence was higher. At the individual level, schizotypy was associated with lower education, unemployment, migrant status, and childhood adversities.

Finally, we found that SCZ-PRS was associated with both phenotypes.

Comparison with previous literature

To the best of our knowledge, this is the first study which examined variation of SP phenotypes across precisely defined catchment areas. Previous studies have only provided information on the variation of schizotypal traits or PLEs between countries, not allowing speculation on specific site-level potential determinants, making it difficult to directly compare our results with existing literature.

One study (Fonseca-Pedrero et al., 2018) involving 27 001 individuals from 12 countries found a considerable variation in the expression of schizotypal traits by country, but effect sizes were generally smaller than those we found. In line with our findings, both Spain and Italy scored lower than the UK on overall schizotypy. Pre-existing studies had only compared two or four countries (Fonseca-Pedrero et al., 2015; Fonseca-Pedrero, Cohen, Ortuño-Sierra, de Álbeniz, & Muñiz, 2017; Kwapil, Ros-Morente, Silvia, & Barrantes-Vidal, 2012; Ortuño-Sierra et al., 2013; Sierro, Rossier, Mason, & Mohr, 2015). Moreover, none of these used clinician-rated instruments and the study designs were not conceived purposedly to recruit samples representative of the population at risk for FEP in each area.

A multi-national study (Nuevo et al., 2012) found that the prevalence of at least one positive PLEs varied almost 40-fold over 52 countries. This study did not formally test for variation by country, and the broad heterogeneity of culture background and socioeconomic characteristics may have contributed to such divergent cross-national estimates. Two more studies(Jaya et al., 2022; McGrath et al., 2015) compared countries by income, following the World Bank classification(Fantom & Serajuddin, 2016), with contrasting results. Our study included only countries classified as upper-middle (Brazil) or high-income countries (the rest).

In our sample, women presented higher levels of PLEs. Previous findings are mixed (Kelleher et al., 2012; Linscott & Van Os, 2013; Nuevo et al., 2012; Zammit et al., 2013). Current cannabis use was also associated with increased PLEs which is consistent with previous literature (Linscott & Van Os, 2013). A recent EU-GEI study found that cannabis contributes to the emergence of PLEs independently of underlying genetic proneness to schizophrenia (Quattrone et al., 2021). Being single was also significantly associated with PLEs, consistent with previous findings (Linscott & Van Os, 2013; Pignon et al., 2018; Saha, Scott, Varghese, & McGrath, 2013). In our study, unemployment predicted both PLEs and schizotypy. Rates of employment among individuals suffering from schizophrenia are very low (Evensen et al., 2016; Holm, Taipale, Tanskanen, Tiihonen, & Mitterdorfer-Rutz, 2021), while previous studies have failed to demonstrate such an association with SP phenotypes (DeVylder, Lehmann, & Chen, 2015; Linscott & Van Os, 2013; Saha et al., 2013). Childhood adversities were associated with both phenotypes, coherently with prior reports(McGrath et al., 2017; Pignon et al., 2021; Velikonja, Fisher, Mason, & Johnson, 2015) and bullying had the greatest effect size, consistent with previous research (Campbell & Morrison, 2007; Horrevorts, Monshouwer, Wigman, & Vollebergh, 2014; Wolke, Lereya, Fisher, Lewis, & Zammit, 2014; Wong & Raine, 2018). Migrant status and lower level of education were associated with schizotypy but not with PLEs. It is known that migrants have higher rates of psychotic disorders(Selten et al., 2019; Tarricone et al., 2021), but there is still not sufficient evidence to establish whether they are also at higher risk of SP (Leaune et al., 2019; Tortelli et al., 2018). Interestingly, rates of psychosis among migrants also present a considerable between-sites variation, being higher in those sites where the native-born population presents higher rates (Termorshuizen et al., 2020).

We found an association between genetic proneness to schizophrenia and both SP phenotypes. While previous research has consistently replicated the finding regarding PLEs (Legge et al., 2019; Quattrone et al., 2021; Ronald & Pain, 2018), the association between genetic liability and schizotypy is less evident. Previous

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studies reported no association (Nenadić et al., 2022) or even a counterintuitive inverse relationship (Hatzimanolis et al., 2018; Van Os et al., 2020). However, it is likely that, as is the case with schizophrenia, the expression of schizotypal traits is influenced by both genetic proneness and exposure to environmental risk factors (Barrantes-Vidal, Grant, & Kwapil, 2015; Pries et al., 2020a; Pries et al., 2020b).

Schizotypy showed a significant between-sites variation and was strongly intertwined with psychosis incidence within the same catchment area. These findings support the 'psychosis continuum' model (Van Os et al., 2009) and the hypothesis that there are common causes of threshold disorders and subclinical expression of psychosis. Future studies need to clarify the mechanisms underpinning such variation of psychosis spectrum phenotypes by examining variability in the factors that putatively contribute to this discrepancy. The epidemiological continuity we observed adds value to the role of schizotypy in the research of psychosis etiology. Furthermore, by encompassing a wide array of psychopathological manifestations along the psychosis continuum, schizotypy allows to assess a broad range of phenotypes increasing the power to capture relevant factors associated with the etiogenic pathways of psychoses (Barrantes-Vidal et al., 2015). With regards to the latter, this highlights the role of contextual factors implicated in the risk of psychosis. Further research is thus needed to test the differential effect across diverse sites of candidate area-level factors. In this context, the EU-GEI incidence study (Jongsma et al., 2018) has underscored the relevance of social deprivation indicators, such as the proportion of owner-occupied houses, of single households or unemployment across the catchment areas. On the other hand, in our analyses PLEs were ubiquitous and their distribution was not related to the incidence of psychotic disorders. This suggests that factors associated with the development of schizotypy and threshold psychotic disorders might be less relevant for PLEs. Furthermore, previous studies suggest that schizotypy might be a better predictor of psychosis compared with PLEs (Flückiger et al., 2016; Salokangas et al., 2013; Shah et al., 2012). Previous literature on PLEs shows that they are more prevalent in early life-stages, such childhood and adolescence (Healy et al., 2019; Kelleher et al., 2012; Maijer, Begemann, Palmen, Leucht, & Sommer, 2018) to decrease thereafter (Calkins et al., 2014; Peters, Joseph, & Garety, 1999), being mostly transient in nature(Linscott & Van Os, 2013). Nevertheless, recent reports from the Adolescent Brain Cognitive Development (ABCD) (Karcher et al., 2022a., 2022b) study showed that distressing and persisting PLEs were associated with a broad range of negative outcomes in terms of mental health (not limited to psychosis) and general functioning, aligning with previous reports (Van Der Steen et al., 2019; Van Nierop et al., 2012).

Strengths and limitations

To the best of our knowledge, this is the first study that used a multi-level regression analysis approach to examine the variation of SP phenotypes across a mixture of urban and rural sites, considering FEP incidence over the same catchment areas and timespan. The control recruitment strategy was specifically designed to obtain a sample broadly representative of the population at-risk by age, sex, and ethnicity (Gayer-Anderson et al., 2020). In some sites, controls were significantly shifted towards a younger age compared with the local population(Jongsma et al., 2020). Nevertheless, the uniform strategy for recruitment and ascertainment of participants increases the reliability of between-sites comparisons. Differently, from previous research on SP variation (Fonseca-Pedrero et al., 2015; Fonseca-Pedrero et al., 2017, 2018; Jaya et al., 2022; Kwapil et al., 2012; McGrath et al., 2015; Ortuño-Sierra et al., 2013; Sierro et al., 2015), we did not analyse data aggregated by countries, allowing for direct comparisons between different sites within a single country, which may differ for core features such as urbanicity, ethnic composition, or poverty. While previous studies on the cross-national variation of schizotypy relied on self-reported questionnaires (Fonseca-Pedrero et al., 2015; Fonseca-Pedrero et al., 2017, 2018; Ortuño-Sierra et al., 2013), we used a clinician-administered interview (SIS-R). Regarding PLEs, a previous EU-GEI paper demonstrated that CAPE presented equivalent factorial structure, factor loadings, and thresholds across the study countries(Pignon et al., 2019). Interestingly, we did not observe any correlation between SIS-R and CAPE dimensions. Of note, sites with a higher self-reported score on positive PLEs did not show as much comparably high scores on the clinician-rated positive schizotypy. This could be explained by cultural differences that could increase the likelihood of reporting PLEs, such as culturally shaped different levels of PLEs acceptance and experience-related different degrees of distress. However, we have shown that variation in CAPE dimensions across sites was not relevant. Thus, cultural factors are unlikely to have introduced biases in our analyses.

Several limitations need to be acknowledged. First of all, we only included sites located in upper-middle or high-income countries (Fantom & Serajuddin, 2016). This could have limited our ability to a detect more significant variation of PLEs, given previous evidence (though contrasting) (Jaya et al., 2022; McGrath et al., 2015). Nevertheless, heterogeneity of countries by economy could have introduced biases in the assessment of variation due to existing differences in prevalence and incidence of psychotic disorders between higher and lower income countries (McGrath, Saha, Chant, & Welham, 2008), which probably reflect considerable divergences in the societal context. Our sample did not comprise individuals aged under 18 years, thus excluding the age groups with high prevalence of PLEs and schizotypal traits (Fonseca-Pedrero, Lemos-Giráldez, Paino, Sierra-Baigrie, & Muñiz, 2012; Healy et al., 2019; Kelleher et al., 2012; Maijer et al., 2018). However, CAPE investigates lifetime PLEs, while, for schizotypy, the persistence of traits in later life stages could be more insightful. All SIS-R items related to the disorganization domain were excluded due to lack of valid frequency. Recent network analyses (Christensen, Gross, Golino, Silvia, & Kwapil, 2019; Polner et al., 2019) have shown that disorganized schizotypy could be seen as a higher-order factor mediating the presentation of negative and positive symptoms. Furthermore, only about 13% of the individual unexplained variance of SIS-R and CAPE general factors was accounted for by our explanatory variables in the fully adjusted models. We have not included measures of general or social cognition, which are likely to contribute. Finally, analyses of genetic liability were performed only in people of European ancestry, limiting the generalisability of the findings to Caucasian European populations.

Relevance and implications

Both phenotypes of SP are potentially associated with poorer mental health and lower functioning at multiple levels. The differential patterns of variation between the two have several implications. We showed that PLEs present a low degree of variance between sites with their presentation relying almost uniquely on

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individual factors, including genetic liability. Cannabis use can be a target for primary and secondary prevention programmes and effective interventions can be put in place to treat trauma and to support individuals in finding an occupation. Conversely, schizotypy presents a substantial between-sites variation, being more pronounced where FEP incidence peaks. This supports the hypothesis that shared contextual factors influence the local expression of psychosis across the spectrum. High FEP incidence can be considered as a proxy of site-level threats to mental health. Our findings emphasize the need for further research on contextual factors associated with schizotypy in order to increase our understanding of etiology of psychotic disorders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003781.

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