



HAL
open science

Genetic and psychosocial stressors have independent effects on the level of subclinical psychosis: findings from the multinational EU-GEI study

Baptiste Pignon, H. Peyre, A. Ayrolles, J B Kirkbride, Stéphane Jamain, A. Ferchiou, J R Richard, G. Baudin, S. Tosato, H. Jongsma, et al.

► To cite this version:

Baptiste Pignon, H. Peyre, A. Ayrolles, J B Kirkbride, Stéphane Jamain, et al.. Genetic and psychosocial stressors have independent effects on the level of subclinical psychosis: findings from the multinational EU-GEI study. *Epidemiology and Psychiatric Sciences*, 2022, 31, pp.e68. 10.1017/s2045796022000464 . inserm-04197690

HAL Id: inserm-04197690

<https://inserm.hal.science/inserm-04197690>

Submitted on 6 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Original Article

Cite this article: Pignon B *et al* (2022). Genetic and psychosocial stressors have independent effects on the level of subclinical psychosis: findings from the multinational EU-GEI study. *Epidemiology and Psychiatric Sciences* **31**, e68, 1–11. <https://doi.org/10.1017/S2045796022000464>

Received: 13 April 2022

Revised: 6 June 2022

Accepted: 3 August 2022

Key words:







Genes × environment interactions; polygenic risk score for schizophrenia; psychosis; psychosocial stressors

Author for correspondence:

Baptiste Pignon,

E-mail: baptistepignon@yahoo.fr

Genetic and psychosocial stressors have independent effects on the level of subclinical psychosis: findings from the multinational EU-GEI study

B. Pignon¹ , H. Peyre², A. Ayrolles² , J. B. Kirkbride³ , S. Jamain¹, A. Ferchiou¹, J. R. Richard¹, G. Baudin⁴, S. Tosato⁵ , H. Jongsma^{6,7,8}, L. de Haan^{9,10}, I. Tarricone¹¹, M. Bernardo^{12,13,14}, E. Velthorst¹⁵, M. Braca¹⁶, C. Arango^{17,18}, M. Arrojo¹⁹, J. Bobes^{20,21}, C. M. Del-Ben²², M. Di Forti^{23,24}, C. Gayer-Anderson²⁵, P. B. Jones^{26,27}, C. La Cascia²⁸, A. Lasalvia⁵ , P. R. Menezes²⁹, D. Quattrone³⁰, J. Sanjuán^{31,32,33}, J. P. Selten^{34,35}, A. Tortelli³⁶, P. M. Llorca^{37,38}, J. van Os^{39,40,41}, B. P. F. Rutten³⁹, R. M. Murray⁴², C. Morgan²⁵ , M. Leboyer¹, A. Szöke¹ and F. Schürhoff¹

¹Univ Paris Est Créteil, INSERM, IMRB, AP-HP, Hôpitaux Universitaires H. «Mondor», DMU IMPACT, Fondation FondaMental, Créteil F-94010, France; ²AP-HP, Hôpital universitaire Robert Debré, Service de pédopsychiatrie, Paris 75019, France; ³PsyLife Group, Division of Psychiatry, UCL, London W1T 7NF, UK; ⁴Université de Paris, Laboratoire de Psychopathologie et Processus de Santé, Boulogne Billancourt F-92100, France; ⁵Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; ⁶Centre for Transcultural Psychiatry 'Veldzicht', Balkbrug, the Netherlands; ⁷VR Mental Health Group, University Center for Psychiatry, University Medical Centre Groningen, Groningen, the Netherlands; ⁸Centre for Longitudinal Studies, UCL, London, UK; ⁹Amsterdam UMC, Amsterdam, The Netherlands; ¹⁰Arkin, Amsterdam, The Netherlands; ¹¹Department of Medical and Surgical Sciences, Bologna University, Bologna, Italy; ¹²Barcelona Clínic Schizophrenia Unit, Hospital Clínic de Barcelona, Institute of Neuroscience, University of Barcelona, Barcelona, Spain; ¹³Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ¹⁴Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain; ¹⁵Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA; ¹⁶Department of Mental Health and Pathological Addictions, Local Health Authority, Bologna 40100, Italy; ¹⁷Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Gregorio Marañón, (IIGSM), School of Medicine, Universidad Complutense de Madrid, Madrid, Spain; ¹⁸CIBERSAM, Madrid, Spain; ¹⁹Department of Psychiatry, Psychiatric Genetic Group, Instituto de Investigación Sanitaria de Santiago de Compostela, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain; ²⁰Faculty of Medicine and Health Sciences – Psychiatry, Universidad de Oviedo, Oviedo, Spain; ²¹ISPA, INEUROPA CIBERSAM, Oviedo, Spain; ²²Department of Neuroscience and Behaviour, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil; ²³Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK; ²⁴South London and Maudsley NHS Mental Health Foundation Trust, London, UK; ²⁵Department of Health Service and Population Research, Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK; ²⁶Department of Psychiatry, University of Cambridge, Cambridge CB2 0SZ, UK; ²⁷CAMEO, Cambridgeshire & Peterborough NHS Foundation Trust, Cambridge, UK; ²⁸Department Biomedicine, Neuroscience and Advanced Diagnostics, School of Medicine, University of Palermo, Palermo, Italy; ²⁹Department of Preventive Medicine, Faculdade de Medicina, Universidade of São Paulo, São Paulo, Brazil; ³⁰Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; ³¹Biomedical Research Networking Centre in Mental Health (CIBERSAM), Madrid, Spain; ³²Department of Psychiatry, Hospital Clínic Universitario de Valencia, School of Medicine, Universidad de Valencia, Valencia, Spain; ³³Biomedical Research Institute INCLIVA, Valencia, Spain; ³⁴Rivierduinen Institute for mental Health, Leiden, The Netherlands; ³⁵Maastricht University Medical Center, Department of Psychiatry & Neuropsychology, School for Mental Health and Neuroscience, Maastricht, The Netherlands; ³⁶French National Institute of Health and Medical Research (INSERM), U955 – 15, Créteil, France and EPS Maison Blanche, Paris, France; ³⁷CHU Clermont-Ferrand, Psychiatrie B, Clermont-Ferrand F-63003, France; ³⁸Université Clermont Auvergne, EA7280, Clermont-Ferrand F-63000, France; ³⁹Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands; ⁴⁰Department of Psychiatry, UMC Utrecht Brain Centre, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands; ⁴¹Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK and ⁴²The Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

Abstract

Aims. Gene × environment (G×E) interactions, i.e. genetic modulation of the sensitivity to environmental factors and/or environmental control of the gene expression, have not been reliably established regarding aetiology of psychotic disorders. Moreover, recent studies

© The Author(s), 2022. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

have shown associations between the polygenic risk scores for schizophrenia (PRS-SZ) and some risk factors of psychotic disorders, challenging the traditional gene *v.* environment dichotomy. In the present article, we studied the role of GxE interaction between psychosocial stressors (childhood trauma, stressful life-events, self-reported discrimination experiences and low social capital) and the PRS-SZ on subclinical psychosis in a population-based sample.

Methods. Data were drawn from the European network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI) study, in which subjects without psychotic disorders were included in six countries. The sample was restricted to European descendant subjects ($n = 706$). Subclinical dimensions of psychosis (positive, negative, and depressive) were measured by the Community Assessment of Psychic Experiences (CAPE) scale. Associations between the PRS-SZ and the psychosocial stressors were tested. For each dimension, the interactions between genes and environment were assessed using linear models and comparing explained variances of 'Genetic' models (solely fitted with PRS-SZ), 'Environmental' models (solely fitted with each environmental stressor), 'Independent' models (with PRS-SZ and each environmental factor), and 'Interaction' models (Independent models plus an interaction term between the PRS-SZ and each environmental factor). Likelihood ratio tests (LRT) compared the fit of the different models.

Results. There were no genes-environment associations. PRS-SZ was associated with positive dimensions ($\beta = 0.092$, $R^2 = 7.50\%$), and most psychosocial stressors were associated with all three subclinical psychotic dimensions (except social capital and positive dimension). Concerning the positive dimension, Independent models fitted better than Environmental and Genetic models. No significant GxE interaction was observed for any dimension.

Conclusions. This study in subjects without psychotic disorders suggests that (i) the aetiological continuum hypothesis could concern particularly the positive dimension of subclinical psychosis, (ii) genetic and environmental factors have independent effects on the level of this positive dimension, (iii) and that interactions between genetic and individual environmental factors could not be identified in this sample.

Introduction

Both environmental and genetic factors are associated with an increased risk of developing psychotic disorders (van Os *et al.*, 2010). The relationships between these factors have long been discussed, and the hypothesis of genes x environment (GxE) interactions was suggested several decades ago (Strahilevitz, 1974; Murray *et al.*, 1986; Schulsinger *et al.*, 1987). Such interaction can be defined as a genetic modulation of the sensitivity to environmental factors and/or environmental control of the gene expression (Kendler and Eaves, 1986). Numerous studies supported this hypothesis (Collip *et al.*, 2013; Frydecka *et al.*, 2020; Pries *et al.*, 2020a), and particularly one from Caspi *et al.* (2005), in which a significant interaction between cannabis use in adolescence and the genetic variant Val¹⁵⁸Met in the Catechol-O-Methyltransferase (COMT, which metabolises dopamine) gene was found. In this study, in comparison to Val/Val genotype, Met/Met and Met/Val genotypes had a protective effect against the risk of psychotic symptoms and disorders among cannabis users (in the group of subjects without cannabis use, the rates of psychotic symptoms and disorders were similar according to the different genotypes). Of note, although discrepant results have been reported in replication studies (Henquet *et al.*, 2006; Zammit *et al.*, 2007), a meta-analysis confirmed the small protective effect of the Val/Met heterozygous genotype [pooled OR = 0.947 95% CI (0.904–0.993), $p = 0.023$] (Costas *et al.*, 2011). This meta-analysis, that did not take account of the cannabis use, hypothesised that both too high and too low levels of dopamine could be risk factors. Study of GxE interactions is difficult due to the need for large cohorts with well-characterised genetic and environmental data.

To deal with these difficulties, the study of subclinical psychosis in the general population, that can be defined as psychotic

symptoms in subjects who do not meet criteria for psychotic disorders, is convenient (Verdoux and van Os, 2002; McGrath *et al.*, 2015), especially in accordance to the aetiological psychotic continuum hypothesis. According to this hypothesis, subclinical psychosis has a similar origin/aetiology as psychotic disorders (Linscott and van Os, 2013; van Os, 2014; Pignon *et al.*, 2018; Pries *et al.*, 2018). Thus, studying genetic or environmental risk factors associated with subclinical psychosis may provide insights into the aetiology of psychosis and partly reduce the potential interference of reverse causation, i.e. factors are associated with or caused by the clinical disorders themselves [e.g. hospitalisations, stigma, substance use disorders or social drift after onset (Zipursky, 2014; Sariaslan *et al.*, 2016; Pignon *et al.*, 2019a)]. Furthermore, in line with the continuum theory, subclinical psychosis can be characterised by continuous variables, improving statistical power, which is a key issue in GxE interaction studies.

Psychotic disorders are characterised by a polygenic architecture, with thousands of common genetic variants with small effect sizes, and a few rare variants with large effect sizes (Smeland *et al.*, 2020). The genome-wide effects of disease-associated common genetic variants can be summarised in a polygenic risk score (PRS) (Anderson *et al.*, 2019), which offers new opportunities to characterise the complex genetic aetiology of psychotic disorders. In subjects included through the European network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI), the PRS for schizophrenia (PRS-SZ) explained between 7 and 9% of the variance of the case-control status (Di Forti *et al.*, 2019b; Tripoli *et al.*, 2020), consistently with other studies (Vassos *et al.*, 2017). Of note, among patients with psychotic disorders, the PRS-SZ is also associated with antipsychotic treatment response, the level of quality of life, or, in the general population, to the intelligence quotient (IQ), and the risk

of attention-deficit/hyperactivity disorder (ADHD) (Mistry *et al.*, 2018; Legge *et al.*, 2019; Zhang *et al.*, 2019; Pries *et al.*, 2020c).

Studies of associations between subclinical psychosis and the PRS-SZ have produced contradictory results (Zammit *et al.*, 2014; Mistry *et al.*, 2018; Legge *et al.*, 2019; Nenadić *et al.*, 2020), and further studies are needed. Moreover, to date, four studies have investigated the role of GxE interaction on subclinical psychosis using PRS-SZ. Two studies assessed the interaction between PRS-SZ and childhood trauma, but only one reported a significant interaction (Pries *et al.*, 2020b), whereas the other showed an independent (additive) effects of the PRS-SZ and the trauma without significant interaction (Trotta *et al.*, 2016). A recent study assessing the associations between momentary stress and subclinical psychotic symptoms showed that higher levels of PRS-SZ were associated with a higher intensity of symptoms after a momentary stress among controls (Schick *et al.*, 2022). In the fourth study, the authors assessed the interaction between PRS-SZ and smoking status, but did not show significant association (García-González *et al.*, 2020).

In addition to increasing the risk for psychosis by GxE interactions, the PRS-SZ has also been associated with a greater risk of exposure to environmental risk factors for psychosis (Pingault *et al.*, 2018). For instance, several studies have reported associations between the PRS-SZ and cannabis use (Gage *et al.*, 2017; Pasman *et al.*, 2018) or between the PRS-SZ and urbanicity (Colodro-Conde *et al.*, 2018; Paksarian *et al.*, 2018; Maxwell *et al.*, 2021) or the level of neighbourhood deprivation and social fragmentation at birth (Solmi *et al.*, 2020), challenging the traditional gene *v.* environment dichotomy. However, these observations could not explain the strength of the associations between cannabis use or urbanicity and the risk of psychotic disorders (Vassos *et al.*, 2012; Di Forti *et al.*, 2019a). To the best of our knowledge, the genetic-environment (G-E) associations between PRS-SZ and psychosocial stressors have not been studied to date.

In a former study on population-based controls from the EU-GEI work package 2 (WP2) (Pignon *et al.*, 2021), we showed that psychosocial stressors, i.e. childhood trauma, stressful life-events, self-reported discrimination experiences and low social capital, had independent effects on subclinical psychosis dimensions, without significant environment \times environment (ExE) interactions. In the current study, we aimed to study the relationships between these psychosocial stressors, the PRS-SZ, and three dimensions of subclinical psychosis (positive, negative, depressive), looking for GxE interaction. Furthermore, we aimed to study the association between psychosocial stressors and the PRS-SZ, looking for G-E associations.

Methods

EU-GEI WP2 study

Clinical, environmental and genetic data have been collected through the EU-GEI WP2 (named 'Functional Enviromics'), a multicentre case-sibling-control study of genetic and environmental determinants of the occurrence and severity of psychotic disorders. Population-based controls were recruited across 6 countries: Brazil, France, Italy, the Netherlands, Spain, and the United Kingdom. Inclusion criteria were: age 18–64, living in the catchment areas, no evidence of current or past psychotic disorders. These controls were recruited using a mixture of random and quota sampling to ensure that they were broadly representative of the at-risk populations on predefined variables (age, sex, and migration) (Gayer-Anderson *et al.*, 2020).

Ethical approval was obtained from local research ethics committees in each country. The EU-GEI Project was funded by the European Community's Seventh Framework Program under grant agreement no. HEALTH-F2-2010-241909.

Subclinical psychosis and psychosocial stressors assessment

The Community Assessment of Psychic Experiences (CAPE) is a 42-item self-report questionnaire that has been developed to assess lifetime subclinical psychotic dimensions in the general population (Stefanis *et al.*, 2002). For each item, 4 answers were possible according to the frequency of their occurrences (from never to nearly always). To construct the dimension scores [positive, negative and depressive (Mark and Touloupoulou, 2016)], we dichotomised answers of each CAPE item (never *v.* sometimes or more) and summed the positive answers. The cross-national invariance of the CAPE score in the EU-GEI WP2 samples was previously demonstrated (Pignon *et al.*, 2019b).

Childhood trauma was assessed with a short version of the Childhood Trauma Questionnaire (CTQ), with 25 items assessing five different domains (emotional and physical neglect, emotional, physical and sexual abuse) (Bernstein *et al.*, 2003). Only the total score was used. Lifetime self-reported discrimination experiences were assessed with a modified version of the 12-item Williams' major experiences of discrimination scale (unfairly fired or not hired because of your ethnicity/sex/weight/etc., unfairly stopped/questioned/physically threatened or abused by the police, etc.) (Williams *et al.*, 1997; Jongsma *et al.*, 2020). Perceived social capital in each participant's immediate neighbourhood was assessed using the Social Environment Assessment Tool (SEAT), a 23-item questionnaire, that was designed to capture four dimensions of social capital: civic disorder (CD), impact of civic disorder (ICD), informal social control (ISC), and social cohesion and trust (SCT) (Sampson *et al.*, 1997; Lochner *et al.*, 1999; McCulloch, 2003; Drukker *et al.*, 2006). Subjects answer according to a five-point Likert-scale (1: unusual, to 5: very common), and a sum of the weighted scores of the 4 subscales were calculated to obtain the total social capital score (SEAT score = $zCD + 0.51 \times zICD + 1.6 \times zISC + zSCT$). Finally, stressful life events were assessed using the List of Threatening Experiences (LTE) which comprises 20 binary items of events usually associated with major stress over the course of the previous 6 months (e.g. serious injury, death of a parent, separation from a partner, financial difficulties) (Brugha *et al.*, 1985; Motrico *et al.*, 2013).

Calculation of a polygenic risk score for schizophrenia (PRS-SZ)

Blood samples of the control sample were genotyped by the Medical Research Council Centre for Neuropsychiatric Genetics and Genomics (Cardiff, United Kingdom) using a custom 'Illumina HumanCoreExome-24 BeadChip' genotyping array, covering 570 038 genetic variants. As described elsewhere (Di Forti *et al.*, 2019b), the PRS-SZ were generated using PRSice from the summary results of the Psychiatric Genomics Consortium (PGC), wave 2 (Schizophrenia Working Group of the PGC, 2014). Clumping was performed to obtain SNPs in approximate linkage disequilibrium with an $r^2 < 0.25$ within a 250 kb window. PRS-SZ were calculated, at p -value thresholds of 0.05, because this threshold best captures liability to the disorder according to the PGC analysis (Schizophrenia Working Group of the PGC, 2014). The sample was restricted to 706 European descendant

Table 1. Description of the data: socio-demographic, subclinical psychosis, psychosocial stressors and polygenic risk scores variables

	Median (IQR), mean (s.d.) or N (%)
Age	36.00 (22.00), 38.18 (13.35)
Sex	
Women	376 (53.3%)
Men	330 (46.7%)
CAPE dimensions scales	
Positive	4.00 (4.00), 4.51(2.81)
Negative	6.00 (5.00), 6.24 (3.49)
Depressive	4.00 (3.00), 4.39 (1.82)
Psychosocial stressors measures	
Childhood trauma	31.00 (9.75), 33.34 (9.29)
Self-reported discrimination experiences	0.00 (1.00), 0.51 (0.92)
Stressful life events	1.00 (2.00), 1.37 (1.29)
Social capital	0.37 (3.27), 0.37 (2.37)
PRS-SZ	-0.00096 (0.00018), -0.00096 (0.00014)

CAPE, Community Assessment of Psychic Experiences; IQR, interquartile range; PRS-SZ, polygenic risk score for schizophrenia; s.d., standard-deviation.

subjects (due to over-representation of European descendant subjects in the PGC2 training sample used to calculate the PRS-SZ).

Statistical analyses

The G-E association has been assessed by Spearman correlation tests between the 4 psychosocial stressors and the PRS-SZ. Then, linear regression models were used to assess the relationships between the CAPE dimensions scores (positive, negative, depressive), environmental and genetic variables, and to look for GxE interactions. Of note, we consider multiplicative interactions (Rothman *et al.*, 1980; VanderWeele and Knol, 2014).

The different models were adjusted for age, sex, and the 10 first principal components (PCs) of the genetic analyses of the ethnic variance. For each CAPE dimension, thirteen models were tested:

- (1) A 'Genetic model', with the sole PRS-SZ;
- (2) Four 'Environmental models' for each of the 4 psychosocial stressors variables: childhood trauma, stressful life-events, self-reported discrimination experiences and low social capital;
- (3) Four 'Independent models': one for each of the 4 psychosocial stressors variables and the PRS-SZ, without interaction term;
- (4) Four 'Interaction models': each of the 4 psychosocial stressors variables and the PRS-SZ, with a GxE interaction term.

To compare the fit of the different models (and particularly the Independent and the Interaction models), we compared the explained variances (R^2), and use likelihood ratio test (LRT) to assess whether the addition of a factor (E + G *v.* G, E + G *v.* E, E + G + E × G *v.* E + G) improved the fit of the model. To verify that the results were not biased by the imputation of the outcome (CAPE scales), analyses were repeated in a sample without imputation of the CAPE.

Psychosocial variables and PRS-SZ were standardised to Z-scores (i.e. to a mean equal to 0, and a standard-deviation equal to 1). The SEAT (social capital) score was inverted, so that higher scores were associated with *lower* social capital. Missing data of the CAPE (between 3 and 5.9% according to the different dimensions) and the psychosocial stressors variables (between 0.5 and 20.7%) were imputed with multivariate imputation by chained equations (MICE) in 20 resamples (the country was added to CAPE and psychosocial stressors variables for the imputation). R software version 3.6.0 was used for the statistical analyses.

Results

Description of the data

The 706 European descendant subjects without psychotic disorders included in our study showed a sex ratio close to 1 (53% women) and a mean age of 38.2 (s.d. = 13.4) (% of missing data according to the different countries are available in the online Supplementary Table 3). The scores of subclinical psychosis dimensions and psychosocial stressors scales, and the values of PRS-SZ scores are available in the Table 1 (for non-imputed data, see online Supplementary Table 2).

Correlation between genetic vulnerability and environmental factors

Spearman correlation tests did not suggest any evidence of associations between psychosocial stressors levels and the PRS-SZ (Table 2).

Influence of genetic vulnerability and environmental factors on subclinical psychosis dimensions

For the three subclinical psychosis dimensions that we studied, we first assessed the variance that might be explained by the PRS-SZ (Genetic models, Fig. 1 and Table 3). Only the positive dimension was associated with the PRS-SZ ($\beta = 0.086$, p -value = 0.02, with a $R^2 = 7.77\%$).

We then assessed the variance explained by each of the 4 psychosocial stressors, i.e. discrimination, childhood trauma, stressful events and low social capital (Environmental models). Each psychosocial stressor was associated with the three subclinical psychosis dimensions, except the low level of social capital that was not associated with the positive dimension (Fig. 1 and Table 3). Of note, when associated with subclinical dimensions, the variance explained by Environmental models was always higher than the one explained by Genetic models (except, concerning the positive dimension, for the low level of social capital).

Combination of genetic and environmental factors

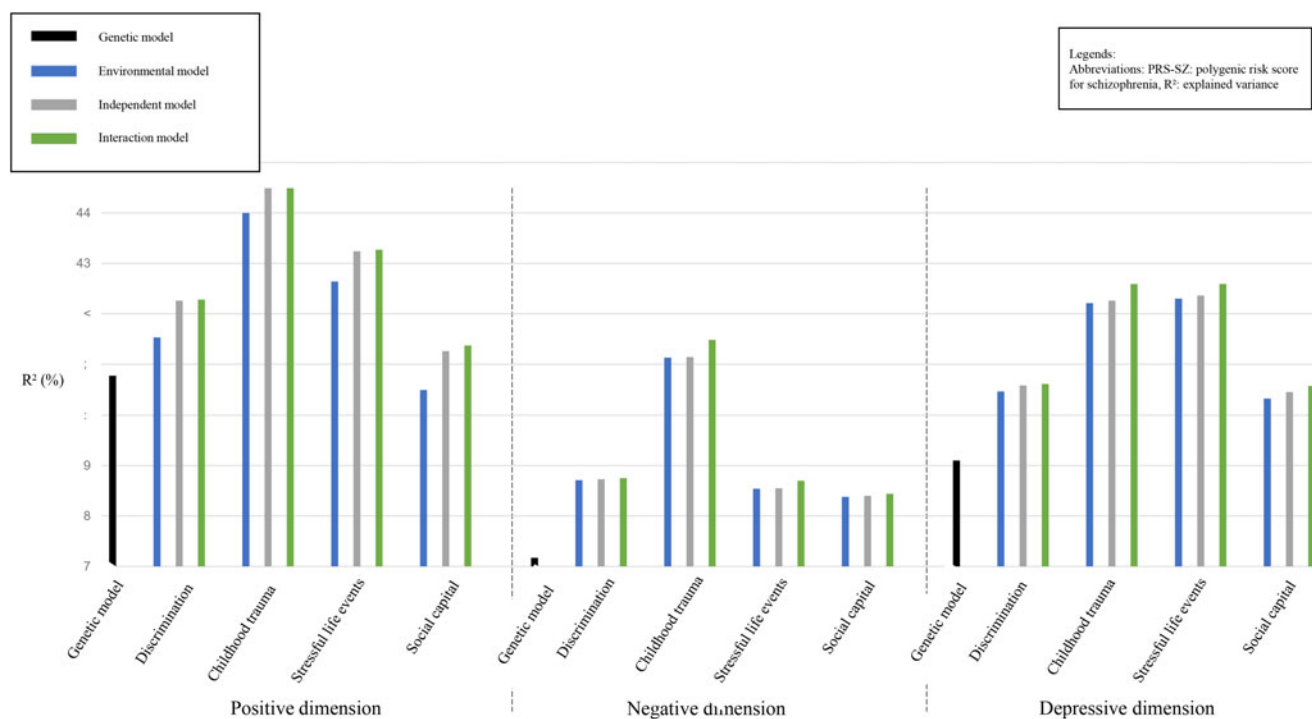
In the Independent models, for the 3 dimensions, the explained variances were better than in the Genetic models, which was confirmed by the LRT (p -values < 0001 for almost all models, Fig. 1 and Table 3, except for the low level of social capital in the positive dimension).

However, concerning the negative and depressive dimensions, in comparison to Environmental models, the Independent models did not fit better. In other words, adding the PRS-SZ to the Environmental factors did not improve the explained variances

Table 2. Spearman tests between Z-scores of genetic and environmental factors among subjects with complete data ($N = 456$)

	Childhood trauma	Self-reported discrimination experiences	Stressful life events	Social capital
Polygenic risk score for schizophrenia	$\rho = 0.063$ (p -value = 0.18)	$\rho = -0.047$ (p -value = 0.32)	$\rho = 0.083$ (p -value = 0.08)	$\rho = 0.032$ (p -value = 0.48)

Legend: ρ : Spearman correlation coefficient.

**Fig. 1.** Explained variances of the different models.

of these models. Concerning the positive dimension, the Independent models fitted better than both Genetic and Environment models (LRT: p -values between 0.013 and 0.041, Table 3).

In the Interaction models, no significant GxE interaction was observed: adding a GxE interaction term in the Independent models was associated with modest increases of the explained variance, and no interaction term was significantly associated with one of the 3 subclinical psychosis dimension scores. The LRT confirmed that the Interaction models did not fit better than Independent models (Table 3). The analyses presented in Table 3 were repeated in a sample without imputation of the CAPE, without significant change (see online Supplementary Table 3).

Discussion

In this population-based subjects without psychotic disorders transnational study on the relationships between subclinical psychosis and genetic and environmental (psychosocial stressors) risk factors, the PRS-SZ was associated with the positive dimension but not with the negative and the depressive dimensions. By contrast, the psychosocial stressors were positively associated with the 3 dimensions, except for the low level of social capital, which was not associated with the positive dimension.

Moreover, considering the positive dimension, PRS-SZ and psychosocial stressors were independently associated, without GxE interaction, consistently with independent effects of genetic and environmental risk factors.

A genetic psychotic continuum?

The association between the PRS-SZ and the positive dimension is consistent with the hypothesis of an aetiological psychotic continuum, with subclinical psychosis and psychotic disorders sharing aetiological – genetic and environmental – factors (Linscott and van Os, 2013). This hypothesis could not be verified concerning the other dimensions. A precedent EU-GEI study analysing in controls the relationships between subclinical psychosis and another factor associated with the risk of psychotic disorders, i.e. advanced paternal age, found consistent results: significant association with the positive dimension, but not to negative and depressive dimensions (Schürhoff *et al.*, 2020). The aetiological psychotic continuum could concern particularly the positive dimension. Indeed, in comparison to the negative and depressive dimensions, the positive symptoms are the most specific of psychotic disorders (Hanssen *et al.*, 2003). Furthermore, in a study analysing the associations between the PRS-SZ and clinical dimensions among antipsychotic-naïve patients with first episode of psychotic disorders (FEP), Santoro *et al.* (2018) found an

Table 3. Model comparison of the explained variances of the subclinical psychosis dimensions

		Explained variance by the models (R^2) (%)	PRS-SZ			LRT: comparison of 'G' and 'E + G' models (p -values)	Environmental factor			LRT: comparison of 'E' and 'E + G' models (p -values)	Interaction term between the PRS-SZ and the environmental factor			LRT: comparison of 'E + G' and 'E + G + E × G' models (p -values)	
			β	s.d.	p -value		β	s.d.	p -value		β	s.d.	p -value		
Positive dimension	G	7.77	0.086	0.037	0.024	-	-	-	-	-	-	-	-	-	
	Self-reported discrimination experiences	E	8.53	-	-	-	-	0.122	0.037	0.001	-	-	-	-	-
		E + G	9.26	0.085	0.037	0.026	0.006	0.122	0.037	0.001	0.013	-	-	-	-
		E + G + E × G	9.28	0.085	0.037	0.026	-	0.127	0.038	0.001	-	0.006	0.037	0.776	0.884
	Childhood trauma	E	11.00	-	-	-	-	0.199	0.036	<0.001	-	-	-	-	-
		E + G	11.49	0.069	0.036	0.065	<0.001	0.193	0.036	<0.001	0.041	-	-	-	-
		E + G + E × G	11.49	0.069	0.036	0.065	-	0.192	0.037	<0.001	-	0.004	0.036	0.887	0.937
	Stressful life events	E	9.64	-	-	-	-	0.162	0.036	<0.001	-	-	-	-	-
		E + G	10.24	0.076	0.036	0.044	<0.001	0.157	0.036	<0.001	0.037	-	-	-	-
		E + G + E × G	10.27	0.076	0.037	0.045	-	0.157	0.037	<0.001	-	-0.007	0.037	0.714	0.652
	Low level of social capital	E	7.50	-	-	-	-	0.069	0.037	0.087	-	-	-	-	-
		E + G	8.26	0.086	0.037	0.024	0.066	0.068	0.037	0.088	0.013	-	-	-	-
E + G + E × G		8.37	0.085	0.037	0.026	-	0.066	0.037	0.101	-	-0.029	0.036	0.470	0.650	
Negative dimension	G	4.17	0.014	0.038	0.718	-	-	-	-	-	-	-	-	-	
	Self-reported discrimination experiences	E	5.71	-	-	-	-	0.125	0.037	0.001	-	-	-	-	-
		E + G	5.73	0.012	0.037	0.748	<0.001	0.125	0.037	0.001	0.910	-	-	-	-
		E + G + E × G	5.75	0.012	0.037	0.747	-	0.125	0.037	0.001	-	-0.012	0.038	0.740	0.777
	Childhood trauma	E	8.13	-	-	-	-	0.200	0.037	<0.001	-	-	-	-	-
		E + G	8.14	-0.004	0.037	0.854	<0.001	0.200	0.037	<0.001	0.723	-	-	-	-
		E + G + E × G	8.48	-0.006	0.037	0.838	-	0.213	0.038	<0.001	-	-0.057	0.036	0.125	0.188
	Stressful life events	E	5.54	-	-	-	-	0.117	0.037	0.007	-	-	-	-	-
		E + G	5.55	0.006	0.038	0.830	<0.001	0.117	0.037	0.007	0.883	-	-	-	-
		E + G + E × G	5.70	0.005	0.038	0.835	-	0.118	0.037	0.006	-	-0.035	0.038	0.386	0.304
	Low level of social capital	E	5.38	-	-	-	-	0.110	0.037	0.008	-	-	-	-	-
		E + G	5.40	0.014	0.037	0.723	<0.001	0.109	0.037	0.009	0.897	-	-	-	-
E + G + E × G		5.44	0.014	0.037	0.712	-	0.111	0.037	0.008	-	0.016	0.037	0.660	0.870	

for such interactions, that found a significant GxE interaction between the PRS-SZ and childhood trauma (Pries *et al.*, 2020b; Schick *et al.*, 2022). Another study using the PRS-SZ and conducted in adults looked for interaction with other environmental factors, i.e. smoking status, without finding any GxE interaction (García-González *et al.*, 2020).

One hypothesis to explain the negative results of this GxE interaction study is that the PRS-SZ is not the appropriate tool for the study of GxE interaction in psychosis (Assary *et al.*, 2018). Indeed, this statistical tool summarises essentially monogenic factors with small effects sizes; and GxE interaction could only involve monogenic factors (Caspi *et al.*, 2005; Stefanis *et al.*, 2007; Alemany *et al.*, 2011). However, other studies used PRS and found GxE interaction, for instance between childhood trauma and the PRS for depression in the risk of major depressive disorder (Peyrot *et al.*, 2014), or between this PRS and stressful life events in the level of depressive symptoms (Domingue *et al.*, 2017), as well as studies on non-psychiatric diseases, e.g. for breast cancer (Meisner *et al.*, 2019; Shi *et al.*, 2020). The problem could concern specifically PRS-SZ, with (i) an insufficient sample of subjects included in the genome-wide association studies (GWAS) used to calculate it, which is a major issue concerning PRSs (Plomin and von Stumm, 2018), and (ii) the fact that the PRS-SZ performed better among European descendants (which has prevented the inclusion of subjects from ethnic minorities) (Vassos *et al.*, 2017). Moreover, the PRS does not take copy number variant (CNVs) or epigenetic factors in account, and they are associated with the risk of schizophrenia (and with childhood trauma concerning epigenetic factors) (St Clair, 2009; Shorter and Miller, 2015; Parade *et al.*, 2021). Another hypothesis states that the genes that increase the sensibility to environmental stressors could be different from the genes that increase the risk of schizophrenia (displayed in the GWAS). Furthermore, GxE interactions could also concern other environmental factors (urbanicity, advanced paternal age, migration, etc.). Finally, the study GxE interactions using exposome scores (Pries *et al.*, 2020a), that takes account of several environmental exposures (including psychosocial stressors), could be instructive.

Limitations

Some limitations should be acknowledged. First, due to the cross-sectional nature of EU-GEI study, the assessment of both subclinical psychosis and psychosocial stressors was retrospective, thus susceptible to be biased (e.g. recall bias) and influenced by clinical variables as depressive or positive symptoms (MacDonald *et al.*, 2015). These potential biases, especially concerning psychosocial stressors assessment (particularly the low level of discrimination experience), have been discussed previously (Pignon *et al.*, 2021). Moreover, regarding the sample size, that could be considered as insufficient to enhance an GxE interaction, Pries *et al.* (2020a) found an interaction between childhood adversity and PRS-SZ concerning subclinical psychosis (with an ecological momentary assessment) with a lower sample ($n = 593$). The absence of subjects from ethnic minorities, is a major limitation (Tortelli *et al.*, 2018). Indeed, these minorities are exposed to higher levels of psychosocial stress (Hatch *et al.*, 2016). Contrary to the CAPE (Pignon *et al.*, 2019b), concerning the assessment of these psychosocial stressors, the cross-national invariance of the different tools that were used (CTQ, Williams' major experiences of discrimination scale, LTE, SEAT) has not been studies. Moreover, as the sampling was not fully at random,

we cannot assume that our sample was representative of the general population.

Conclusion

This general population-based study revealed an association between PRS-SZ and the subclinical positive dimension of psychosis, as well as independent effects of the PRS-SZ and of the psychosocial stressors (childhood trauma, stressful life events, self-reported discrimination experiences) on the positive dimension, contrary to the negative and depressive dimensions. Moreover, concerning the 3 dimensions, this study did not evidence any GxE interaction, or any G-E association.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S2045796022000464>.

Data. Data is confidential and not available.

Acknowledgements. None.

Conflict of interest and Financial support. Dr Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda. Dr Arango has received support by the Spanish Ministry of Science and Innovation. Instituto de Salud Carlos III (SAM16PE07CP1, PI16/02012, PI19/024), co-financed by ERDF Funds from the European Commission, 'A way of making Europe', CIBERSAM. Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds. European Union Seventh Framework Program under grant agreements FP7-4-HEALTH-2009-2.2.1-2-241909 (Project EU-GEI) and FP7-HEALTH-2013-2.2.1-2-603196 (Project PSYSCAN); and European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking (grant agreement No 115916, Project PRISM, and grant agreement No 777394, Project AIMS-2-TRIALS), Fundación Familia Alonso and Fundación Alicia Koplowitz. Dr James B. Kirkbride has received consultancy fees from Roche and the Health Services Executive, Ireland. He is supported by the National Institute of Health Research University College London Hospital Biomedical Research Centre.

Ethical standards. Ethical approval was obtained from local research ethics committees in each country. The EU-GEI Project was funded by the European Community's Seventh Framework Program under grant agreement no. HEALTH-F2-2010-241909.

References

- Alemany S, Arias B, Aguilera M, Villa H, Moya J, Ibáñez MI, Vossen H, Gastó C, Ortet G and Fañanás L (2011) Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences. *The British Journal of Psychiatry* **199**, 38–42.
- Alloza C, Blesa-Cábez M, Bastin ME, Madole JW, Buchanan CR, Janssen J, Gibson J, Deary IJ, Tucker-Drob EM, Whalley HC, Arango C, McIntosh AM, Cox SR and Lawrie SM (2020) Psychotic-like experiences, polygenic risk scores for schizophrenia, and structural properties of the salience, default mode, and central-executive networks in healthy participants from UK Biobank. *Translational Psychiatry* **1**, 1–13.
- Anderson JS, Shade J, DiBlasi E, Shabalin AA and Docherty AR (2019) Polygenic risk scoring and prediction of mental health outcomes. *Current Opinion in Psychology* **27**, 77–81.
- Assary E, Vincent JP, Keers R and Pluess M (2018) Gene-environment interaction and psychiatric disorders: review and future directions. *Seminars in Cell & Developmental Biology* **77**, 133–143.
- Baudin G, Szöke A, Richard J-R, Pelissolo A, Leboyer M and Schürhoff F (2017) Childhood trauma and psychosis: beyond the association. *Child Abuse & Neglect* **72**, 227–235.

- Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D and Zule W (2003) Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect* 27, 169–190.
- Brugha T, Bebbington P, Tennant C and Hurry J (1985) The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychological Medicine* 15, 189–194.
- Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R and Craig IW (2005) Moderation of the effect of adolescent-onset Cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological Psychiatry* 57, 1117–1127.
- Collip D, Myin-Germeys I, Wichers M, Jacobs N, Derom C, Thiery E, Lataster T, Simons C, Delespaul P, Marcelis M, van Os J and van Winkel R (2013) FKBP5 as a possible moderator of the psychosis-inducing effects of childhood trauma. *The British Journal of Psychiatry: The Journal of Mental Science* 202, 261–268.
- Colodro-Conde L, Couvy-Duchesne B, Whitfield JB, Streit F, Gordon S, Kemper KE, Yengo L, Zheng Z, Trzaskowski M, de Zeeuw EL, Nivard MG, Das M, Neale RE, MacGregor S, Olsen CM, Whiteman DC, Boomsma DI, Yang J, Rietschel M, McGrath JJ, Medland SE and Martin NG (2018) Association between population density and genetic risk for schizophrenia. *JAMA Psychiatry* 75, 901–910.
- Costas J, Sanjuán J, Ramos-Rios R, Paz E, Agra S, Ivorra JL, Páramo M, Brenlla J and Arrojo M (2011) Heterozygosity at catechol-O-methyltransferase Val158Met and schizophrenia: new data and meta-analysis. *Journal of Psychiatric Research* 45, 7–14.
- Derks EM, Vorstman JAS, Ripke S, Kahn RS, Consortium TSPG and Ophoff RA (2012) Investigation of the genetic association between quantitative measures of psychosis and schizophrenia: a polygenic risk score analysis. *PLoS One* 7, e37852.
- Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, Jongsma HE, Ferraro L, La Cascia C, La Barbera D, Tarricone I, Berardi D, Szöke A, Arango C, Tortelli A, Velthorst E, Bernardo M, Del-Ben CM, Menezes PR, Selten J-P, Jones PB, Kirkbride JB, Rutten BP, de Haan L, Sham PC, van Os J, Lewis CM, Lynskey M, Morgan C, Murray RM, Amoretti S, Arrojo M, Baudin G, Beards S, Bernardo M, Bobes J, Bonetto C, Cabrera B, Carracedo A, Charpeaud T, Costas J, Cristofalo D, Cuadrado P, Díaz-Caneja CM, Ferchiou A, Franke N, Frijda F, García Bernardo E, García-Portilla P, González E, Hubbard K, Jamain S, Jiménez-López E, Leboyer M, López Montoya G, Lorente-Rovira E, Marcelino Loureiro C, Murrizzo G, Martínez C, Matteis M, Messchaert E, Moltó MD, Nacher J, Olmeda MS, Parellada M, González Peñas J, Pignon B, Rapado M, Richard J-R, Rodríguez Solano JJ, Roldán Díaz L, Ruggeri M, Sáiz PA, Sánchez E, Sanjuán J, Sartorio C, Schürhoff F, Seminerio F, Shuhama R, Sideli L, Stilo SA, Termorshuizen F, Tosato S, Tronche A-M, van Dam D and van der Ven E (2019a) The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *The Lancet Psychiatry* 6, 427–436.
- Di Forti M, Wu-Choi B, Quattrone D, Richards AL, Freeman TP, Tripoli G, Gayer-Anderson C, Rodriguez V, Jongsma H, Ferraro L, Cascia CL, Tosato S, Tarricone I, Berardi D, Szöke A, Arango C, Bobes J, Sanjuán J, Santos JL, Arrojo M, Velthorst E, Bernardo M, Ben CMD, Selten J-P, Jones PB, Kirkbride JB, Rutten BN, de Haan L, van Os J, Lynskey M, Morgan C, Vassos E, O'Donovan M, Lewis C, Sham PC, Murray RM and Group E-GW (2019b) The independent and combined influence of schizophrenia polygenic risk score and heavy cannabis use on risk for psychotic disorder: a case-control analysis from the EUGEI study. *Preprint (bioRxiv)* 844803.
- Domingue BW, Liu H, Okbay A and Belsky DW (2017) Genetic heterogeneity in depressive symptoms following the death of a spouse: polygenic score analysis of the U.S. Health and Retirement Study. *The American Journal of Psychiatry* 174, 963–970.
- Drukker M, Krabbendam L, Driessen G and van Os J (2006) Social disadvantage and schizophrenia. A combined neighbourhood and individual-level analysis. *Social Psychiatry and Psychiatric Epidemiology* 41, 595–604.
- Etain B, Henry C, Bellivier F, Mathieu F and Leboyer M (2008) Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disorders* 10, 867–876.
- Frydecka D, Kotowicz K, Gawęda Ł, Prochwicz K, Kłosowska J, Rymaszewska J, Samochowiec A, Samochowiec J, Podwalski P, Pawlak-Adamska E, Szmida E, Cechnicki A and Misiak B (2020) Effects of interactions between variation in dopaminergic genes, traumatic life events, and anomalous self-experiences on psychosis proneness: results from a cross-sectional study in a nonclinical sample. *European Psychiatry: The Journal of the Association of European Psychiatrists* 63, e104.
- Gage SH, Jones HJ, Burgess S, Bowden J, Smith GD, Zammit S and Munafò MR (2017) Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. *Psychological Medicine* 47, 971–980.
- García-González J, Ramírez J, Howard DM, Brennan CH, Munroe PB and Keers R (2020) The effects of polygenic risk for psychiatric disorders and smoking behaviour on psychotic experiences in UK Biobank. *Translational Psychiatry* 1, 1–10.
- Gayer-Anderson C, Jongsma HE, Di Forti M, Quattrone D, Velthorst E, de Haan L, Selten J-P, Szöke A, Llorca P-M, Tortelli A, Arango C, Bobes J, Bernardo M, Sanjuán J, Santos JL, Arrojo M, Parellada M, Tarricone I, Berardi D, Ruggeri M, Lasalvia A, Ferraro L, La Cascia C, La Barbera D, Menezes PR, Del-Ben CM, Hubbard K, Beards S, Reininghaus U, Tripoli G, Stilo SA, Parellada M, Roldán L, López G, Matteis M, Rapado M, González E, Martínez C, Cuadrado P, Solano JJR, Carracedo A, Costas J, Bernardo EG, Sánchez E, Olmeda MS, Cabrera B, Lorente-Rovira E, García-Portilla P, Jiménez-López E, Franke N, van Dam D, Termorshuizen F, van der Ven E, Messchaert E, Leboyer M, Schürhoff F, Baudin G, Ferchiou A, Pignon B, Jamain S, Richard J-R, Charpeaud T, Tronche A-M, Frijda F, Sideli L, Seminerio F, Sartorio C, Murrizzo G, Loureiro CM, Shuhama R, Ruggeri M, Tosato S, Bonetto C, Cristofalo D, Rutten BP, van Os J, Jones PB, Murray RM, Kirkbride JB, Morgan C and EU-GEI WP2 Group (2020) The European network of national schizophrenia networks studying gene–environment interactions (EU-GEI): incidence and first-episode case–control programme. *Social Psychiatry and Psychiatric Epidemiology* 55, 645–657.
- Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H and van Os J (2003) How psychotic are individuals with non-psychotic disorders? *Social Psychiatry and Psychiatric Epidemiology* 38, 149–154.
- Hatch SL, Gizard B, Williams DR, Frissa S, Goodwin L and Hotopf M (2016) Discrimination and common mental disorder among migrant and ethnic groups: findings from a South East London Community sample. *Social Psychiatry and Psychiatric Epidemiology* 51, 689–701.
- Henquet C, Rosa A, Krabbendam L, Papiol S, Fañanas L, Drukker M, Ramaekers JG and van Os J (2006) An experimental study of catechol-O-methyltransferase Val158Met moderation of Δ -9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* 12, 2748–2757.
- Jongsma HE, Gayer-Anderson C, Tarricone I, Velthorst E, van der Ven E, Quattrone D, di Forti M, Group E-GW, Menezes PR, Del-Ben CM, Arango C, Lasalvia A, Berardi D, Cascia CL, Bobes J, Bernardo M, Sanjuán J, Santos JL, Arrojo M, de Haan L, Tortelli A, Szöke A, Murray RM, Rutten BP, van Os J, Morgan C, Jones PB and Kirkbride JB (2020) Social disadvantage, linguistic distance, ethnic minority status and first-episode psychosis: results from the EU-GEI case-control study. *Psychological Medicine* 51, 1536–1548.
- Kendler KS and Eaves LJ (1986) Models for the joint effect of genotype and environment on liability to psychiatric illness. *The American Journal of Psychiatry* 143, 279–289.
- Legge SE, Jones HJ, Kendall KM, Pardiñas AF, Menzies G, Bracher-Smith M, Escott-Price V, Rees E, Davis KAS, Hotopf M, Savage JE, Posthuma D, Holmans P, Kirov G, Owen MJ, O'Donovan MC, Zammit S and Walters JTR (2019) Association of genetic liability to psychotic experiences with neuropsychotic disorders and traits. *JAMA Psychiatry* 76, 1256–1265.
- Linscott RJ and van Os J (2013) An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence

- to dimensional expression across mental disorders. *Psychological Medicine* 43, 1133–1149.
- Lochner K, Kawachi I and Kennedy BP** (1999) Social capital: a guide to its measurement. *Health & Place* 5, 259–270.
- MacDonald K, Thomas ML, MacDonald TM and Sciolla AF** (2015) A perfect childhood? Clinical correlates of minimization and denial on the childhood trauma questionnaire. *Journal of Interpersonal Violence* 30, 988–1009.
- Mark W and Touloupoulou T** (2016) Psychometric properties of ‘community assessment of psychic experiences’: review and meta-analyses. *Schizophrenia Bulletin* 42, 34–44.
- Markota M, Coombes BJ, Larrabee BR, McElroy SL, Bond DJ, Veldic M, Colby CL, Chauhan M, Cuellar-Barboza AB, Fuentes M, Kung S, Prieto ML, Rummans TA, Bobo WV, Frye MA and Biernacka JM** (2018) Association of schizophrenia polygenic risk score with manic and depressive psychosis in bipolar disorder. *Translational Psychiatry* 1, 1–7.
- Maxwell JM, Coleman JRI, Breen G and Vassos E** (2021) Association between genetic risk for psychiatric disorders and the probability of living in urban settings. *JAMA Psychiatry* 78, 1355–1364.
- McCulloch A** (2003) An examination of social capital and social disorganisation in neighbourhoods in the British household panel study. *Social Science & Medicine* (1982) 56, 1425–1438.
- McGrath JJ, Saha S, Al-Hamzawi A, Alonso J, Bromet EJ, Bruffaerts R, Caldas-de-Almeida JM, Chiu WT, de Jonge P, Fayyad J, Florescu S, Gureje O, Haro JM, Hu C, Kovess-Masfety V, Lepine JP, Lim CCW, Mora MEM, Navarro-Mateu F, Ochoa S, Sampson N, Scott K, Viana MC and Kessler RC** (2015) Psychotic experiences in the general population: a cross-national analysis based on 31,261 respondents from 18 countries. *JAMA Psychiatry* 72, 697–705.
- Meisner A, Kundu P and Chatterjee N** (2019) Case-only analysis of gene-environment interactions using polygenic risk scores. *American Journal of Epidemiology* 188, 2013–2020.
- Mistry S, Harrison JR, Smith DJ, Escott-Price V and Zammit S** (2018) The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: systematic review. *Schizophrenia Research* 197, 2–8.
- Motrico E, Moreno-Küstner B, de Dios Luna J, Torres-González F, King M, Nazareth I, Montón-Franco C, Josefa Gilde Gómez-Barragán M, Sánchez-Celaya M, Ángel Díaz-Barreiros M, Vicens C, Moreno-Peral P and Ángel Bellón J** (2013) Psychometric properties of the List of Threatening Experiences – LTE and its association with psychosocial factors and mental disorders according to different scoring methods. *Journal of Affective Disorders* 150, 931–940.
- Murray RM, Reveley AM and McGuffin P** (1986) Genetic vulnerability to schizophrenia. *Psychiatric Clinics of North America* 9, 3–16.
- Nenadić I, Meller T, Schmitt S, Stein F, Brosch K, Mosebach J, Ettinger U, Grant P, Meinert S, Opel N, Lemke H, Fingas S, Förster K, Hahn T, Jansen A, Andlauer TFM, Forstner AJ, Heilmann-Heimbach S, Hall ASM, Awasthi S, Ripke S, Witt SH, Rietschel M, Müller-Myhsok B, Nöthen MM, Dannlowski U, Krug A, Streit F and Kircher T** (2020) Polygenic risk for schizophrenia and schizotypal traits in non-clinical subjects. *Psychological Medicine*, 1–11 (in press).
- Paksarian D, Trabjerg BB, Merikangas KR, Mors O, Borglum AD, Hougaard DM, McGrath JJ, Pedersen CB, Mortensen PB and Agerbo E** (2018) The role of genetic liability in the association of urbanicity at birth and during upbringing with schizophrenia in Denmark. *Psychological Medicine* 48, 305–314.
- Parade SH, Huffhines L, Daniels TE, Stroud LR, Nugent NR and Tyrka AR** (2021) A systematic review of childhood maltreatment and DNA methylation: candidate gene and epigenome-wide approaches. *Translational Psychiatry* 1, 1–33.
- Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, Abdellaoui A, Nivard MG, Baselmans BML, Ong J-S, Ip HF, van der Zee MD, Bartels M, Day FR, Fontanillas P, Elson SL, 23andMe Research Team, de Wit H, Davis LK, MacKillop J, Substance Use Disorders Working Group of the Psychiatric Genomics Consortium, International Cannabis Consortium, Derringer JL, Branje SJT, Hartman CA, Heath AC, van Lier PAC, Madden PAF, Mägi R, Meeus W, Montgomery GW, Oldehinkel AJ, Pausova Z, Ramos-Quiroga JA, Paus T, Ribases M, Kaprio J, Boks MPM, Bell JT, Spector TD, Gelernter J, Boomsma DI, Martin NG, MacGregor S, Perry JRB, Palmer AA, Posthuma D, Munafò MR, Gillespie NA, Derks EM and Vink JM** (2018) GWAS Of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nature Neuroscience* 21, 1161–1170.
- Peyrot WJ, Milaneschi Y, Abdellaoui A, Sullivan PF, Hottenga JJ, Boomsma DI and Penninx BWJH** (2014) Effect of polygenic risk scores on depression in childhood trauma. *The British Journal of Psychiatry* 205, 113–119.
- Pignon B, Schürhoff F, Szöke A, Geoffroy PA, Jardri R, Roelandt J-L, Rolland B, Thomas P, Vaiva G and Amad A** (2018) Sociodemographic and clinical correlates of psychotic symptoms in the general population: findings from the MHGP survey. *Schizophrenia Research* 193, 336–342.
- Pignon B, Eaton S, Schürhoff F, Szöke A, McGorry P and O’Donoghue B** (2019a) Residential social drift in the two years following a first episode of psychosis. *Schizophrenia Research* 210, 323–325.
- Pignon B, Peyre H, Ferchiou A, van Os J, Rutten BPF, Murray RM, Morgan C, Leboyer M, Schürhoff F, Szöke A and EU-GEI WP2 Group Author** (2019b) Assessing cross-national invariance of the Community Assessment of Psychic Experiences (CAPE). *Psychological Medicine* 49, 2600–2607.
- Pignon B, Lajnef M, Kirkbride JB, Peyre H, Ferchiou A, Richard J-R, Baudin G, Tosato S, Jongsma HE, de Haan L, Tarricone I, Bernardo M, Velthorst E, Braca M, Arango C, Arrojo M, Bobes J, Del-Ben CM, Di Forti M, Gayer-Anderson C, Jones PB, La Cascia C, Lasalvia A, Menezes PR, Quattrone D, Sanjuán J, Seltén J-P, Tortelli A, Llorca PM, van Os J, Rutten BPF, Murray RM, Morgan C, Leboyer M, Szöke A and Schürhoff F** (2021) The independent effects of psychosocial stressors on subclinical psychosis: findings from the multinational EU-GEI study. *Schizophrenia Bulletin* 47, 1674–1684.
- Pingault J-B, O’Reilly PF, Schoeler T, Ploubidis GB, Rijsdijk F and Dudbridge F** (2018) Using genetic data to strengthen causal inference in observational research. *Nature Reviews Genetics* 9, 566–580.
- Plomin R and von Stumm S** (2018) The new genetics of intelligence. *Nature Reviews Genetics* 19, 148–159.
- Pries L-K, Gülöksüz S, Ten Have M, de Graaf R, van Dorsselaer S, Gunther N, Rauschenberg C, Reininghaus U, Radhakrishnan R, Bak M, Rutten BPF and van Os J** (2018) Evidence that environmental and familial risks for psychosis additively impact a multidimensional subthreshold psychosis syndrome. *Schizophrenia Bulletin* 44, 710–719.
- Pries L-K, Ferro GAD, van Os J, Delespaul P, Kenis G, Lin BD, Luyck JJ, Richards AL, Akdede B, Binbay T, Altınyazar V, Yalınçetin B, Gümüş-Akay G, Cihan B, Soyğür H, Ulaş H, Cankurtaran EŞ, Kaymak SU, Mihajlevic MM, Petrovic SA, Mirjanic T, Bernardo M, Mezquida S, Amoretti S, Bobes J, Saiz PA, Garcia-Portilla MP, Sanjuan J, Aguilar EJ, Santos JL, Jiménez-López E, Arrojo M, Carracedo A, López G, González-Peñas J, Parellada M, Maric NP, Atbaşoğlu C, Uçok A, Alptekin K, Saka MC, Investigators GR and O of P (GROUP), Arango C, O’Donovan M, Tosato S, Rutten BPF and Gülöksüz S** (2020a) Examining the independent and joint effects of genomic and exomic liabilities for schizophrenia across the psychosis spectrum. *Epidemiology and Psychiatric Sciences* 29, 1–10.
- Pries L-K, Klingenberg B, Menne-Lothmann C, Decoster J, van Winkel R, Collip D, Delespaul P, Hert MD, Derom C, Thiery E, Jacobs N, Wichers M, Cinar O, Lin BD, Luyck JJ, Rutten BPF, van Os J and Gülöksüz S** (2020b) Polygenic liability for schizophrenia and childhood adversity influences daily-life emotion dysregulation and psychosis proneness. *Acta Psychiatrica Scandinavica* 141, 465–475.
- Pries L-K, van Os J, Ten Have M, de Graaf R, van Dorsselaer S, Bak M, Lin BD, van Eijk KR, Kenis G, Richards A, O’Donovan MC, Luyck JJ, Rutten BPF and Gülöksüz S** (2020c) Association of recent stressful life events with mental and physical health in the context of genomic and exomic liability for schizophrenia. *JAMA Psychiatry* 77, 1296–1304.
- Rothman KJ, Greenland S and Walker AM** (1980) Concepts of interaction. *American Journal of Epidemiology* 112, 467–470.
- Sampson RJ, Raudenbush SW and Earls F** (1997) Neighborhoods and violent crime: a multilevel study of collective efficacy. *Science (New York, N.Y.)* 277, 918–924.
- Santoro ML, Ota V, de Jong S, Noto C, Spindola LM, Talarico F, Gouvea E, Lee SH, Moretti P, Curtis C, Patel H, Newhouse S, Carvalho CM,**

- Gadelha A, Cordeiro Q, Bressan RA, Belangero SI and Breen G (2018) Polygenic risk score analyses of symptoms and treatment response in an antipsychotic-naïve first episode of psychosis cohort. *Translational Psychiatry* 8, 1–8.
- Sariaslan A, Fazel S, D’Onofrio BM, Långström N, Larsson H, Bergen SE, Kuja-Halkola R and Lichtenstein P (2016) Schizophrenia and subsequent neighborhood deprivation: revisiting the social drift hypothesis using population, twin and molecular genetic data. *Translational Psychiatry* 6, e796.
- Schick A, van Winkel R, Lin BD, Luykx JJ, de Zwart SMC, van Eijk KR, GROUP Investigators, Myin-Germeys I and Reininghaus U (2022) Polygenic risk, familial liability and stress reactivity in psychosis: an experience sampling study. *Psychological Medicine*, 1–10 (in press).
- Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427.
- Schulsinger F, Parnas J, Mednick S, Teasdale TW and Schulsinger H (1987) Heredity-environment interaction and schizophrenia. *Journal of Psychiatric Research* 21, 431–436.
- Schürhoff F, Pignon B, Lajnef M, Denis R, Rutten B, Morgan C, Murray RM, Leboyer M, van Os J and Szöke A (2020) Psychotic experiences are associated with paternal age but not with delayed fatherhood in a large, multinational, community sample. *Schizophrenia Bulletin* 46, 1327–1334.
- Seiler N, Nguyen T, Yung A and O’Donoghue B (2020) Terminology and assessment tools of psychosis: a systematic narrative review. *Psychiatry and Clinical Neurosciences* 74, 226–246.
- Shi M, O’Brien KM and Weinberg CR (2020) Interactions between a polygenic risk score and non-genetic risk factors in young-onset breast cancer. *Scientific Reports* 10, 3242.
- Shorter KR and Miller BH (2015) Epigenetic mechanisms in schizophrenia. *Progress in Biophysics and Molecular Biology* 118, 1–7.
- Smeland OB, Frei O, Dale AM and Andreassen OA (2020) The polygenic architecture of schizophrenia – rethinking pathogenesis and nosology. *Nature Reviews Neurology* 16, 366–379.
- Solmi F, Lewis G, Zammit S and Kirkbride JB (2020) Neighborhood characteristics at birth and positive and negative psychotic symptoms in adolescence: findings from the ALSPAC birth cohort. *Schizophrenia Bulletin* 46, 581–591.
- St Clair D (2009) Copy number variation and schizophrenia. *Schizophrenia Bulletin* 35, 9–12.
- Stefanis NC, Hanssen M, Smirnis NK, Avramopoulos DA, Evdokimidis IK, Stefanis CN, Verdoux H and van Os J (2002) Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological Medicine* 32, 347–358.
- Stefanis NC, Henquet C, Avramopoulos D, Smyrnis N, Evdokimidis I, Myin-Germeys I, Stefanis CN and van Os J (2007) COMT Val158Met moderation of stress-induced psychosis. *Psychological Medicine* 37, 1651–1656.
- Strahilevitz M (1974) Possible interaction of environmental and biological factors in the etiology of schizophrenia: review and integration. *Canadian Psychiatric Association Journal* 19, 207–217.
- Tortelli A, Nakamura A, Suprani F, Schürhoff F, Van der Waerden J, Szöke A, Tarricone I and Pignon B (2018) Subclinical psychosis in adult migrants and ethnic minorities: systematic review and meta-analysis. *BJPsych Open* 4, 510–518.
- Tripoli G, Quattrone D, Ferraro L, Gayer-Anderson C, Rodriguez V, La Cascia C, La Barbera D, Sartorio C, Seminerio F, Tarricone I, Berardi D, Szöke A, Arango C, Tortelli A, Llorca P-M, de Haan L, Velthorst E, Bobes J, Bernardo M, Sanjuán J, Santos JL, Arrojo M, Del-Ben CM, Menezes PR, Selten J-P, EU-GEI WP2 Group, Jones PB, Jongsma HE, Kirkbride JB, Lasalvia A, Tosato S, Richards A, O’Donovan M, Rutten BPF, van Os J, Morgan C, Sham PC, Murray RM, Murray GK and Di Forti M (2020) Jumping to conclusions, general intelligence, and psychosis liability: findings from the multi-centre EU-GEI case-control study. *Psychological Medicine* 51, 623–633.
- Trotta A, Iyegbe C, Forti MD, Sham PC, Campbell DD, Cherny SS, Mondelli V, Aitchison KJ, Murray RM, Vassos E and Fisher HL (2016) Interplay between schizophrenia polygenic risk score and childhood adversity in first-presentation psychotic disorder: a pilot study. *PLoS One* 11, e0163319.
- VanderWeele TJ and Knol MJ (2014) A tutorial on interaction. *Epidemiologic Methods* 3, 33–72.
- van Os J (2014) The many continua of psychosis. *JAMA Psychiatry* 71, 985–986.
- van Os J, Kenis G and Rutten BPF (2010) The environment and schizophrenia. *Nature* 468, 203–212.
- van Os J, Pries L-K, Delespaul P, Kenis G, Luykx JJ, Lin BD, Richards AL, Akdede B, Binbay T, Altinyazar V, Yalınçetin B, Gümüş-Akay G, Cihan B, Soygür H, Ulaş H, Cankurtaran EŞ, Kaymak SU, Mihaljevic MM, Petrovic SA, Mirjanic T, Bernardo M, Cabrera B, Bobes J, Saiz PA, García-Portilla MP, Sanjuan J, Aguilar EJ, Santos JL, Jiménez-López E, Arrojo M, Carracedo A, López G, González-Peñas J, Parellada M, Maric NP, Atbaşoğlu C, Uçok A, Alptekin K, Saka MC, Genetic Risk and Outcome Investigators (GROUP), Arango C, O’Donovan M, Rutten BPF and Gülöksüz S (2020) Replicated evidence that endophenotypic expression of schizophrenia polygenic risk is greater in healthy siblings of patients compared to controls, suggesting gene-environment interaction. The EUGEI study. *Psychological Medicine* 50, 1884–1897.
- Varese F, Smeets F, Drukker M, Lieveerse R, Lataster T, Viechtbauer W, Read J, van Os J and Bental RP (2012) Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophrenia Bulletin* 38, 661–671.
- Vassos E, Pedersen CB, Murray RM, Collier DA and Lewis CM (2012) Meta-analysis of the association of urbanicity with schizophrenia. *Schizophrenia Bulletin* 38, 1118–1123.
- Vassos E, Di Forti M, Coleman J, Iyegbe C, Prata D, Euesden J, O’Reilly P, Curtis C, Koliakou A, Patel H, Newhouse S, Traylor M, Ajnakina O, Mondelli V, Marques TR, Gardner-Sood P, Aitchison KJ, Powell J, Atakan Z, Greenwood KE, Smith S, Ismail K, Pariante C, Gaughran F, Dazzan P, Markus HS, David AS, Lewis CM, Murray RM and Breen G (2017) An examination of polygenic score risk prediction in individuals with first-episode psychosis. *Biological Psychiatry* 81, 470–477.
- Verdoux H and van Os J (2002) Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophrenia Research* 54, 59–65.
- Williams DR, Yu Y, Jackson JS and Anderson NB (1997) Racial differences in physical and mental health socio-economic status, stress and discrimination. *Journal of Health Psychology* 2, 335–351.
- Zammit S, Spurlock G, Williams H, Norton N, Williams N, O’Donovan MC and Owen MJ (2007) Genotype effects of CHRNA7, CNR1 and COMT in schizophrenia: interactions with tobacco and cannabis use. *The British Journal of Psychiatry* 191, 402–407.
- Zammit S, Hamshere M, Dwyer S, Georgiva L, Timpson N, Moskvina V, Richards A, Evans DM, Lewis G, Jones P, Owen MJ and O’Donovan MC (2014) A population-based study of genetic variation and psychotic experiences in adolescents. *Schizophrenia Bulletin* 40, 1254–1262.
- Zhang J-P, Robinson D, Yu J, Gallego J, Fleischhacker WW, Kahn RS, Crespo-Facorro B, Vazquez-Bourgon J, Kane JM, Malhotra AK and Lencz T (2019) Schizophrenia polygenic risk score as a predictor of anti-psychotic efficacy in first-episode psychosis. *American Journal of Psychiatry* 176, 21–28.
- Zipursky RB (2014) Why are the outcomes in patients with schizophrenia so poor? *The Journal of Clinical Psychiatry* 75(suppl. 2), 20–24.