Synopsis no.: *S2.60*

Preliminary title: Exposome score for schizophrenia and subclinical psychosis in controls from EU-GEI (WP2) study

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Work Packages involved:
WP2

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All partners/sites involved in WP2

Scientific background

Epidemiological research has identified several environmental risk factors for schizophrenia. These risk factors include childhood trauma, immigration, cannabis use, minority status, seasonality of birth, etc. It is accepted that none of these factors are necessary for developing psychosis (Uher et al. 2017). However, most of the research has focused on a single environmental exposure. This approach, as it is also the case for genetic risk factors, fails to acknowledge the complexity of the multiplicity of environmental exposures. To better understand, the conjoint effects of several environmental factors on the risk for schizophrenia, the concept of "exposome score for schizophrenia (ES-SCZ)" has been proposed (Pries et al. 2019). This score aims at capturing the combined effect of different environmental exposures by using an aggregate environmental vulnerability score for schizophrenia.

This approach parallels the genetic approach. For example, the Psychiatric Genomics Consortium has identified 145 significant loci associated with schizophrenia (Pardinas *et al*., 2018). It is now possible to calculate an individual score summarising the level of genetic risk for schizophrenia, known as polygenic risk score for schizophrenia (PRS-SCZ) (Pardinas *et al*., 2018).

The continuum theory of psychosis suggests that subclinical psychotic symptoms or traits (e.g. psychotic symptoms, psychotic-like experiences, schizotypal traits) exist at various degrees in different individuals from the general population (Linscott and van Os, 2013). This continuum theory also posits that these attenuated traits/symptoms have an origin/ etiology similar to the full-blown pathology (Verdoux and van Os, 2002; Binbay et al., 2012). The demonstration of an association between the ES-SCZ and the level of subclinical psychosis would provide arguments for similar aetiology across the phenotypic continuum. A previous study using data from the WP6 EU-GEI study showed that ES-SCZ was associated with all dimensions of schizotypy as measured by the SIS-R interview. Furthermore, in this study, the authors found an interaction between PRS-SCZ and ES-SCZ. According to the authors, these data need to be further replicated. In addition, as part of the WP2 of the EU-GEI study, our team has recently showed that PRS-SZ was associated with positive dimension (β = 0.092, R^2 = 7.50%) of psychosis measured with the CAPE (Pignon et al. 2022).

Synopsis for EU-GEI Publication

Objective

1. We aim to investigate whether the ES-SCZ is associated with the level of subclinical psychosis measured with the CAPE (3 dimensions: positive, negative, depressive) and the SIS-R (cognitive-perceptual, disorganized and negative dimension) among controls.
2. We aim to investigate which are the variables (demographic, genetic, i.e PRS-SCZ) that might influence this association

Methods

The sample is composed of the control subjects of the WP2 of the study

The CAPE

As with several other studies using the CAPE (Wigman et al. 2017; Yung et al. 2009), given that scores of 3 or 4 are very rare, we decided to dichotomize each item of the CAPE to reflect the presence of absence of the condition as follows: "never" was rated as "0" and "sometimes, often and nearly always" as "1". We used the sum of endorsed items to quantify the psychotic dimensions, which is usually done in studies using other similar questionnaires, (Raine, 1992, Mason & Claridge, 2006), and has also been advocated by other researchers using the CAPE (van Os et al. 2017; Verdoux & van Os, 2002; Mark & Toulopoulou, 2016; Schlier et al. 2015). A total score representing the sum of all items was calculated for each dimension.

The SIS-R

The SIS-R is a semi-structured interview containing 20 schizotypal symptoms and 11 schizotypal signs rated on a 4-point scale (from "absent" to "severe"). In its shortened version, it covers the three dimensions of schizotypal personality: cognitive-perceptual alterations, disorganization, and negative dimension (Kendler et al. 1989; Vollema & Ormel, 2000).

Exposome score for Schizophrenia

To estimate the cumulative environmental load using the ES-SCZ

We use the exposome score for schizophrenia (ES-SCZ) proposed by Pries et al. 2019, which has been already used in previous EU-GEI study. It takes into account the interdependency of environmental exposures (Guloksuz et al. 2018) and it has a good discriminative function for stratifying psychosis risk in the general population (Pries et al. 2020; Guloksuz et al. 2020)

In line with previous studies (Pries et al. 2019, 2020, Ezrin et al. 2021), we will constitute the ES-SCZ score by summing log-odds weighted environmental exposures (each exposure defined as absent = 0 and present = 1) including cannabis use, hearing impairment, winter-spring birth and childhood adversity domains.

ES-SCZ will be calculated after imputing missing values of the environmental exposures.

The following tools will be used:

1. Childhood trauma: CTQ
2. Cannabis: CEQ
3. Bullying: RBQ
4. Hearing impairment in the last 12 months (absent / present) is assessed using a self-report evaluation
5. Month of birth
6. PRS-SCZ
7. Subclinical psychosis: CAPE
8. Subclinical psychosis: SIS-R

We also use the Maudsley environmental risk score to compare both exposome scores in the same study.

PRS-SZ: The PRS-SCZ is already available for these subjects and has been calculated using summary statistics from the Psychiatric Genomics Consortium (PGC2) genome-wide association study.

Sociodemographic variables (age, sex, education, ethnicity) will also be requested.

Among EUGEI WP2 controls, the effects of continuous measures of PRS-SCZ, ES-SCZ, and of their interaction on continuous measures of CAPE (total, positive, negative and depressive dimensions) and SIS-R (total, cognitive-perceptual, disorganization and negative dimensions) as dependent variables will be tested with multilevel linear regression models, where the coefficient of the product term (PRS-SCZ×ES-SCZ) reflects departure from additivity (Knol *et al*. 2007).

Hypotheses and expected results

1. ES-SCZ is associated with the dimensions of subclinical psychosis in a sample of healthy subjects.
2. We expect to find an interaction between PRS-SCZ and ES-SCZ on the CAPE and SIS-R scores

Data needed for the study:
- WP2 data for controls and siblings
- CEQ (cannabis);
- CAPE
- SIS-R
- CTQ
- RBQ (Retrospective Bullying Questionnnaire)
- Hearing impairment during the last 12 months (Yes/No answer) assessed using a self-report evaluation
- Month of birth
- PRS-SCZ
- Potential confounding factors: age, sex, education, ethnicity.

Other analyses/methods:

None

Involvement of external Parties (non EU-GEI):
None

IPR check:

REFERENCES

Binbay T, Alptekin K, Elbi H, Zağlı N, Drukker M, Aksu Tanık F, Ozkınay F, Onay H, Van Os J. Lifetime prevalence and correlates of schizophrenia and disorders with psychotic symptoms in the general population of Izmir, Turkey. Turk Psikiyatri Derg. 2012 Fall;23(3):149-60.

Erzin G, Pries LK, van Os J, Fusar-Poli L, Delespaul P, Kenis G, Luykx JJ, Lin BD, Richards AL, Akdede B, Binbay T, Altınyazar V, Yalınçetin B, Gümüş-Akay G, Cihan B, Soygür H, Ulaş H, Cankurtaran EŞ, Kaymak SU, Mihaljevic MM, Andric-Petrovic S, Mirjanic T, Bernardo M, Mezquida G, Amoretti S, 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, Ucok A, Alptekin K, Saka MC; Genetic Risk and Outcome of Psychosis (GROUP) investigators, Arango C, O'Donovan MC, Rutten BPF, Guloksuz S. Examining the association between exposome score for schizophrenia and functioning in schizophrenia, siblings, and healthy controls: Results from the EUGEI study. Eur Psychiatry. 2021 Mar 19;64(1):e25.

Guloksuz S, Pries LK, Delespaul P, Kenis G, Luykx JJ, Lin BD, Richards AL, Akdede B, Binbay T,

Altinyazar V, Yalincetin B, Gumus-Akay G, Cihan B, Soygur H, Ulas H, Cankurtaran E, Kaymak SU, Mihaljevic MM, Petrovic SA, Mirjanic T, Bernardo M, Cabrera B, Bobes J, Saiz PA, Garcia-Portilla MP, Sanjuan J, Aguilar EJ, Santos JL, Jimenez-Lopez E, Arrojo M, Carracedo A, Lopez G, Gonzalez-Penas J, Parellada M, Maric NP, Atbasog Lu C, Ucok A, Alptekin K, Saka MC, Genetic Risk Outcome of Psychosis investigators, Arango C, O'Donovan M, Rutten BPF and van Os J (2019) Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. World Psychiatry 18, 173–182.

Kendler KS, Lieberman JA, Walsh D. The Structured Interview for Schizotypy (SIS): a preliminary report. *Schizophr Bull*. 1989;15(4):559-571. doi:10.1093/SCHBUL/15.4.559.

Knol MJ, van der Tweel I, Grobbee DE, Numans ME and Geerlings MI (2007) Estimating interaction on an additive scale between continuous determinants in a logistic regression model. International Journal of Epidemiology 36, 1111–1118.

Linscott RJ, van Os J. 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. *Psychol Med* 2013; 43: 1133-1149.

Mark W, Toulopoulou T. Psychometric Properties of “Community Assessment of Psychic Experiences”: Review and Meta-analyses. Schizophr Bull 2016; 42: 34–44.

Mason O, Claridge G. The Oxford-Liverpool Inventory of feelings and experiences (O-LIFE): further description and extended norms. Schizophr Res 2006; 82: 203-211.

Pardinas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, Legge SE, Bishop S, Cameron D, Hamshere ML, Han J, Hubbard L, Lynham A, Mantripragada K, Rees E, MacCabe JH, McCarroll SA, Baune BT, Breen G, Byrne EM, Dannlowski U, Eley TC, Hayward C, Martin NG, McIntosh AM, Plomin R, Porteous DJ, Wray NR, Caballero A, Geschwind DH, Huckins LM, Ruderfer DM, Santiago E, Sklar P, Stahl EA, Won H, Agerbo E, Als TD, Andreassen OA, Baekvad-Hansen M, Mortensen PB, Pedersen CB, Borglum AD, Bybjerg-Grauholm J, Djurovic S, Durmishi N, Pedersen MG, Golimbet V, Grove J, Hougaard DM, Mattheisen M, Molden E, Mors O, Nordentoft M, Pejovic Milovancevic M, Sigurdsson E, Silagadze T, Hansen CS, Stefansson K, Stefansson H, Steinberg S, Tosato S, Werge T, Gerad Consortium, Crestar Consortium, Collier DA, Rujescu D, Kirov G, Owen MJ, O'Donovan MC and Walters JTR (2018) Common schizophrenia alleles are enriched in mutation intolerant genes and in regions under strong background selection. Nature Genetics 50, 381–389.

Pignon B, Peyre H, Ayrolles A, Kirkbride JB, Jamain S, Ferchiou A, Richard JR, Baudin G, Tosato S, Jongsma H, 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, Selten JP, Tortelli A, Llorca PM, van Os J, Rutten BPF, Murray RM, Morgan C, Leboyer M, Szöke A, Schürhoff F**.** Genetic and psychosocial stressors have independent effects on the level of subclinical psychosis: findings from the multinational EU-GEI study. Epidemiol Psychiatr Sci. 2022 Sep 27;31:e68.

Pries LK, Lage-Castellanos A, Delespaul P, Kenis G, Luykx JJ, Lin BD, Richards AL, Akdede B, Binbay T, Altinyazar V, Yalinçetin 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, Ucok A, Alptekin K, Saka MC; Genetic Risk and Outcome of Psychosis (GROUP) investigators, Arango C, O'Donovan M, Rutten BPF, van Os J, Guloksuz S. Estimating Exposome Score for Schizophrenia Using Predictive Modeling Approach in Two Independent Samples: The Results From the EUGEI Study. Schizophr Bull. 2019 Sep 11;45(5):960-965.

Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-II-R criteria.

Schizophr Bull 1991; 17: 555-564.

Schlier B, Jaya ES, Moritz S, Lincoln TM. The community assessment of psychic experiences measures nine clusters of psychosis-like experiences : a validation of the German version of the CAPE. Schizophr Res 2015; 169: 274-279.

Uher R, Zwicker A.Etiology in psychiatry: embracing the reality of poly-gene–environmental causation of mental illness. World Psychiatry. 2017; 16(2):121-129

van Os J, van der Steen Y, Islam MA, et al. Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopmental, emotion regulation and attribution of salience. Psychol Med 2017; 2421-2437.

Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. Schizophr Res 2002; 54: 59–65.

Vollema MG, Ormel J. The reliability of the structured interview for schizotypy-revised. *Schizophr Bull*. 2000;26(3):619-629. doi:10.1093/OXFORDJOURNALS.SCHBUL.A033482

Wigman JTW, Wardenaar KJ, Wanders RBK, et al. Dimensional and discrete variations on the psychosis continuum in a Dutch crowd-sourcing population sample. Eur Psychiatry 2017; 42: 55–62.

Yung AR, Nelson B, Baker K, Buckby JA, Baksheev G, Cosgrave EM. Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia. Aust NZ J Psychiatry 2009; 43: 118–128.