Synopsis no.: WP6-S6.6

Preliminary title: The cumulative and synergistic effect of environmental risk factors combined with polygenic risk for psychotic disorder on psychosis expression.

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***Senior authors, # first authors**

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Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: GROUP investigators; WP3, WP8

Objectives (scientific background, hypothesis, methods, and expected results):

Background:

According to the liability threshold model, if variation of liability is continuous in the population, phenotypic outcome can be determined quantitatively by the cumulative effect of the genetic load, and the cumulative amount of exposure to environmental factors (environmental load). The liability-threshold model provides a valid theoretical groundwork to study gene-environment interplay underlying psychosis. This model provides a basis to predict phenotypic outcome quantitatively by the cumulative risk load of genetic and environmental factors.

Evidence confirms that up to 30% of the genetic susceptibility for schizophrenia may be explained by the cumulative effect of common alleles with small effect. Based on the findings from the recent large collaborative genome-wide association (GWA) studies, it is now possible to estimate the theoretical polygenic risk score (derived from common alleles) of an individual for schizophrenia by summing the log odds ratios of individual single nucleotide polymorphism (multiplied by the number of risk alleles present at the corresponding loci) for each individual.

Several studies have reported that psychosis outcomes are associated with environmental risk factors such as childhood trauma, urban environment and cannabis use in both clinical and population samples, accompanied with substantial evidence suggesting causality. Furthermore, in keeping with the liability threshold model, several studies showed exposure to more than one environmental risk factor increases odds of psychosis outcome in a dose-response manner.

Although the liability-threshold model was first coined in the late 1960s to date there have been few empirical investigations testing this model in the field of schizophrenia, in particular the issue of gene-environment interplay. In order to distinguish possible GxE (moderation) from rGE (mediation), we will also examine for rGE in EUGEI controls. Case-sibling analyses of gene-environment interplay have the substantial advantage of controlling for a range of intra-familial unmeasured confounders.

Aim:

To examine the interplay between environmental load (urbanicity, ethnic group, bullying, discrimination, cannabis and other drug use, childhood trauma, life events) and polygenic risk score for schizophrenia on (i) psychosis expression and (ii) endophenotype expression.

Hypotheses:

1 - Each environmental risk factor (eg cannabis use, urbanicity, childhood trauma), on the additive scale, will combine with polygenic risk score for schizophrenia in a synergistic fashion to increase odds of schizophrenia (case-sibling analyses) or expression of psychosis endophenotypes in the sibling analyses (schizotypy, neurocognition, probabilistic reasoning bias, aberrant salience in white noise task).

2 - All environmental risk factors (cannabis use, urbanicity, childhood trauma), combined together as a loading variable will show a dose-response relationship in the GxE model of (endophenotypic) psychosis expression.

3 - In the EUGEI control sample, polygenic risk score does not predict exposure to environmental risk factors separately or combined as a loading variable.

Methods

WP6 sample will be used to test these hypotheses.

Expected results

See hypotheses

Data needed for the study:

MRC Sociodemographic Schedule Parts 1 and 2
Bullying
Discrimination
Childhood Experiences of Care and Abuse
Childhood Trauma Questionnaire
Cannabis Experiences Questionnaire
List/Impact of Threatening Events
Structured Interview for Schizotypy- Revised (SIS-R)
The Community Assessment of Psychic Experiences (CAPE)
IQ/composite neurocognitive score (endophenotype)
Beads Task ("jumper" status - endophenotype).
White Noise Task (presence of speech illusion; endophenotypes)
Benton Facial Recognition Test (endophenotype)

Plan for statistical analysis (overall strategy):

For the case-sibling analyses, multilevel logistic regression models will be applied to analyze whether the association between caseness and polygenic risk for schizophrenia is greater if there is also evidence of exposure to environmental risk factors (childhood trauma, urbanicity, cannabis use). We will test for departure from additivity using the interaction contrast ratio (ICR) method. A convincing case exists for additive models to provide the best representation of synergy and that they are the most useful from a public health perspective. This approach allows use of odds ratios (ORs) derived from logistic models to estimate the relative excess risk as a result of synergy for combinations of dichotomous, ordinal and continuous exposures (i.e. ICR = $OR_{\text{exposure A \& exposure B}}$ - $OR_{\text{exposure A only}}$ - $OR_{\text{exposure B only}}$ + 1). ICR greater than zero is defined as positive deviation from additivity.

To test our hypotheses on synergism in the case-sibling analyses, we will enter the four exposure states occasioned by the combination of each environmental factor (eg trauma, urbanicity, cannabis use) and polygenic risk for schizophrenia as independent variables and caseness as the dependent variable in logistic models. Using the odds ratios derived from these models, ICRs (e.g. ICR = $OR_{\text{childhood trauma \& polygenic risk}}$ - $OR_{\text{childhood trauma}}$ - $OR_{\text{polygenic risk}}$ + 1) for each model will be calculated using the Stata NLCOM command. The same strategy will be applied to analyze the cumulative effect of quantitative environmental risk factor load in combination with polygenic risk for schizophrenia on caseness.

For the sibling analyses, interactions between polygenic risk scores and environmental exposures will be examined in (tobit and multiple) regression models of continuous endophenotypic outcomes (schizotypy, white noise speech illusions, neurocognition, JTC probabilistic reasoning bias).

In the rGE analyses, associations between polygenic risk score and environmental exposures will be examined in regression models in the control sample.

All analyses will be adjusted for age, sex, and educational level.

As observations are clustered within countries, hence not a simple random sample, country will be treated as a random effect with observation nested within the country in all regression models. Family will be introduced as an additional level as some families contributed more than one case or sibling.

Other analyses/methods:

Involvement of external Parties (non EU-GEI):

IPR check:

Timeframe: Data to be provided to the analysis team. Analyses to begin, circulation of manuscript to authors, publication by.

Additional comments: