**Synopsis no.:** *S2.59*

**Preliminary title:** Low IQ and subclinical psychosis

**Contact info for the person(s) proposing the synopsis**

**Name: Baptiste Pignon**
**Partner no: 13**
**e-mail address: baptistepignon@yahoo.fr**

**Working and writing group:**
B. Pignon, JP Selten, A. Szöke, F. Schürhoff, M. Lajnef, H. Peyre, A. Ayrolles

**Work Packages involved:**
WP2

**Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated:**
All partners/sites involved in WP2

*Scientific background*

The continuum theory suggests that subclinical isolated 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). The 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). Moreover, studying subclinical psychosis in the general population has several advantages, the most notable being that it reduces the risk for misclassification (inherent to the dichotomous approach), as well as avoiding the bias linked to factors associated with the disease itself, such as hospitalizations, stigma, substance use disorders or social drift after onset (Zipursky, 2014; Sariaslan *et al.*, 2016; Pignon *et al.*, 2019a). Finally, subclinical psychosis can be characterized by quantitative (continuous) variables thus improving statistical power and the capacity to control for more potential confounders.

In previous studies in EUGEI WP2, we have found that the CAPE (the scale that was used to measure the level of subclinical psychosis) could be used reliably in the 6 different countries/languages of the WP2, as this scale showed cross-national invariance (Pignon *et al.*, 2019b). Then, we showed that subclinical psychosis – at least the positive dimension – were associated with several risk factors of psychotic disorders, consistently with the etiological continuum hypothesis: paternal age, childhood trauma, discrimination, stressful life events, low level of capital social, or with the polygenic risk score for schizophrenia (PRS-SZ) (Schürhoff *et al.*, 2020; Pignon *et al.*, 2021, 2022).

Low pre-morbid intellectual quotient (IQ) has been shown to be strongly associated with the risk of schizophrenia (Zammit *et al.*, 2004; Khandaker *et al.*, 2011; Trotta *et al.*, 2015), as well as with psychotic symptoms (Johns *et al.*, 2004; Horwood *et al.*, 2008). However, the reason for the link between low IQ and the risk of schizophrenia remains unknown.

In the first place, low IQ could represent a psychosocial stress in itself, because the person in question is often exposed to ridicule and humiliation. Moreover, low IQ may also contribute to a misinterpretation of complex social events and thus lead to delusion-like symptoms. Moreover, low IQ could be a risk factor of childhood trauma, which is another established risk factor of psychotic disorder. Furthermore, as low IQ is associated with older paternal age (Malaspina *et al.*, 2005), low IQ could be a mediator of the association between paternal age and the risk of psychotic disorder. Finally, as low IQ is associated with the PRS-SZ (Mistry *et al.*, 2018), psychotic disorders and low IQ could share common genetic risk factors, and the association between low IQ and the risk of schizophrenia could be due to a genetic confounding phenomenon (Pingault *et al.*, 2018). The EU-GEI dataset is an opportunity to study these different hypotheses.

According to the social defeat hypothesis of psychosis the combination of low status and repeated humiliation is a common denominator of several schizophrenia risk factors: ethnic disadvantage, childhood trauma, bullying victimization, hearing impairment, homosexual orientation, gender identity disorder and low IQ (Selten & Ormel, submitted). A recent study supports this idea by showing that low self-esteem, anxiety, and sadness mediate the pathways from stress to psychotic-like experiences and paranoia in daily life (Monsonet *et al.*, 2022). A purpose of the present study is to confirm and extend these findings by examining whether the relationship between IQ and subclinical psychosis is mediated by low self-esteem, using measures from the Brief Core Schema Scale (BCSS).

*Objectives*

The first objective will be to study the relationships between the level of IQ and the level of subclinical psychosis (3 dimensions: positive, negative, depressive) among controls.
If the association is significant, we will aim to understand this association, and the role of putative cofounding variables, among these variables: psychosocial stressors (childhood trauma, discrimination, stressful life events, low level of capital social), low self-esteem, parental age, cannabis use, jumping to conclusion (JTC) and the PRS-SZ.

*Methods*

The following tools will be used:

1. IQ: WAIS III
2. Childhood trauma: CTQ
3. Discrimination: Williams' scale
4. Stressful life events: LTE
5. Capital social: SEAT
6. Cannabis: CEQ
7. Subclinical psychosis: CAPE
8. Low self-esteem: BCSS
9. Jumping-to-conclusion (JTC) bias phenomenon.

Genetic (PRS-SZ), sociodemographic (age, sex, migrant status, ethnicity), and parental age data will also be requested.

Concerning the BCSS, in order to create a measure for low self-esteem, we will combine low scores for positive self and high scores for negative self of the BCSS (Fowler *et al.*, 2006).

*Statistical analyses*

We will study the relationships between low IQ and subclinical psychosis (3 dimensions of subclinical psychosis: positive, negative, depressive) using univariate and multivariable (adjustment factors: age, sex, ethnicity) linear models among EUGEI WP2 controls.

Then, if this relationship (concerning the 3 dimensions or some of them) is significant, a multivariable model will be built with some of the significant correlates of subclinical psychosis among EUGEI WP2 controls: psychosocial factors (childhood trauma, discrimination, stressful life events, low level of capital social), low self-esteem, JTC, cannabis, parental age, and PRS-SZ. These models will be adjusted on sociodemographic variables: age, sex, ethnicity.

*Hypotheses and expected results*

1. Low IQ is associated with the 3 dimensions of subclinical psychosis;
2. The association between low IQ and subclinical psychosis is mediated by low self-esteem (i.e., the BCSS measure positive (6 items) and negative self (6 items)) and psychosocial stressors;
3. Low IQ is a mediator between PRS-SZ and the positive dimension of subclinical psychosis.

**Data needed for the study:**

WP2 & WP6 GWAS data *<u>for the controls</u>*:

- basic CEQ information (cannabis and other drugs);
- CAPE
- Psycho-social stress measures: CTQ, LTE, Discriminations (Williams scale), SEAT
- BCSS
- PRS-SZ
- Parental age

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| - Jumping-to-conclusion (JTC) bias phenomenon<br>- Potential confounding factors: age, sex, country, ethnicity, income and parental income. |
| **Other analyses/methods:**<br><br>None |
| **Involvement of external Parties (non EU-GEI):**<br>None |
| **IPR check:** |

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