Utilizing exposome score for schizophrenia to predict mental health outcomes

CHAPTER 8

SUMMARY

Embracing the exposome paradigm, **chapters 2** and **3** provide an overview of the research on the environmental pathoetiology of psychosis spectrum disorders. The exposome entails the network of interconnected non-genetic exposures and embraces the complexity of the environment underlying psychiatric disorders. **Chapter 2** discusses recent findings from emerging exposome research as well as the future of exposome research in psychiatry. **Chapter 3** provides a comprehensive overview and evaluation of aggregate environmental scores that aim to capture exposomic vulnerability for schizophrenia such as the exposome score for schizophrenia (ES-SCZ). Furthermore, **Chapter 3** discusses the pluripotency of exposomic vulnerability for schizophrenia and summarizes findings from gene-environment interaction studies using ES-SCZ.

The study in **chapter 4** analyzed the discriminative function of ES-SCZ to identify schizophrenia and investigates psychosis risk stratification properties of ES-SCZ in the general population. The discriminative function of ES-SCZ was compared to that of an environmental sum score (Esum-SCZ) and an aggregate environmental score weighted by meta-analytical estimates (Emet-SCZ). Eventually, the associations between ES-SCZ and psychiatric diagnoses as well as other medical outcomes were analyzed. ES-SCZ had a better discriminative function compared to Esum-SCZ and Emet-SCZ; and at the optimal cut point, ES-SCZ was associated with increased psychosis risk. Among all clinical outcomes, ES-SCZ was associated with schizophrenia diagnosis with the highest odds ratio and the greatest explained variance. This was followed by the association between ES-SCZ and bipolar disorder, suicide plan, suicidal thoughts, and suicide attempt. The results indicate the potential research utility of ES-SCZ for risk prediction and stratification. Furthermore, the results may help to improve insight into the multicausal effect of the environment on pluripotent psychopathology.

In **chapter 5,** the association between ES-SCZ and global functioning in patients with schizophrenia spectrum disorder, unaffected siblings, and healthy controls was tested. The study was conducted in two independent datasets: the European Network of National Networks Studying Gene–Environment Interactions in Schizophrenia (EUGEI) and the Genetic Risk and Outcome of Psychosis (GROUP).

In the EUGEI dataset, ES-SCZ was associated with the Global Assessment of Functioning (GAF) total, symptom, and disability dimensions in patients, siblings, and healthy controls. The results remained the same after adjusting for genetic vulnerability for schizophrenia assessed through the polygenic risk score for schizophrenia (PRS-SCZ). The associations of ES-SCZ with both the symptom and the disability dimensions were stronger in unaffected siblings than in patients and controls. The result of the association between ES-SCZ and functioning was replicated in patients with schizophrenia from the independent GROUP dataset. The findings suggest that exposomic vulnerability for schizophrenia is not specifically associated with schizophrenia but affects functioning across patients, their siblings and controls.

The study in **chapter 6** investigated the temporal and cross-sectional associations of ES-SCZ with symptom severity and functioning in first-episode psychosis (FEP). Functioning was measured with the GAF and the Personal and Social Performance Scale (PSP). The severity of symptoms of schizophrenia was assessed through the Positive and Negative Syndrome Scale (PANSS). The cross-sectional analyses at baseline and at one-month follow-up showed that ES-SCZ was associated with global functioning (i.e., GAF and PSP total scores) as well as specific functioning domains (socially useful activities and personal and social relationships), also when the analyses were adjusted for different explanatory variables such as age, sex, education, migration, obstetric complications, first language, family history, PANSS total score, antipsychotic medication and duration of untreated psychosis. The longitudinal analyses showed that the GAF and PSP total scores increased from baseline to the 1-month follow-up assessment. However, the changes were not dependent on ES-SCZ as no significant ES-SCZ-by-time interaction on functioning was found. The analyses of clinical features over time showed an ES-SCZ-by-time interaction, indicating that the decrease of clinical features over time might be affected by environmental vulnerability for schizophrenia. The results from **chapter 6** are in line with the results from **chapter 5** showing that ES-SCZ is associated with poor functioning. Additionally, **chapter 6** shows that high ES-SCZ could be an indicator for poor short-term illness trajectory in FEP patients.