Maastricht University

The interplay between the genome and the exposome in psychosis spectrum

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12.3 Impact paragraph

Schizophrenia contributes to €93.9 billion, one of the largest portion of European healthcare costs due to mental disorders[1]. In the Netherlands specifically, it accounts for 0.11% of the GDP with an annual direct cost of $774 million[2]. Furthermore, schizophrenia is associated with decreased functioning, low quality of life, and is among the top five leading causes of disability adjusted life years (DALYs) in the age-group ranging from 15 to 44 years[3]. Therefore, there is an urgent need for a breakthrough in prevention, diagnosis, and management of schizophrenia, which can be achieved through better understanding of pathoetiology.

The studies presented in this thesis, closely tied to the goals of the national research agenda "Nationale Wetenschapsagenda" in the areas of "Gezondheidszorgonderzoek, preventie en behandeling" and "Personalised medicine: uitgaan van het individu", contributes greatly to research on the pathoetiology of psychosis spectrum. The knowledge utilized in this thesis can increase the efficient use of public health care tools and eventually help us to decrease disorder-related burden and costs.

The thesis highlights the importance of the investigation of the whole network of environmental and genomic exposures. The studies underline the opportunity centering on modifiable environmental factors to improve population-based mental health outcomes. Furthermore, presenting the first studies indicating gene-environment interaction (GxE) for psychosis spectrum using exposomic and molecular genomic measures, the studies in this thesis initiates great opportunity for subsequent research on GxE and highlight the importance for the shift from diagnostic category based research towards the investigation of psychosis spectrum.

Refining the toolbox for multimodal research in psychiatry, this thesis generates a knowledgebase for national and international scientific programs of the multilevel etiology of psychiatry. The exposome score applied in this project can be used to reduce the bias due to environmental confounding and increase causal inference in other observational, clinical, or experimental studies of psychotic disorders across Europe, particularly the Netherlands. In future studies, testing the exposome paradigm in the context of biological mechanisms and epigenomic markers will contribute to the global efforts toward a better understanding of psychotic disorders and provide candidate biological targets and processes for translational research. Further, as exposomic and genomic liability does not only play a critical role in psychotic disorders but a range of mental disorders[4-7], this approach may be applied to other

large population cohorts to investigate GxE such as the NIH's "All of US" and emerging exposomic research endeavors[8].

The integration of psychiatric epidemiology and molecular genetic markers offers potential benefits for risk stratification and screening toward personalized medicine. Findings may aid the global efforts toward a diagnostic classification that should ideally be driven by neurobiological substrates and etiologic mechanisms, which in turn would accelerate the delivery of improved health outcomes through more accurate diagnosis, preventive measures, and treatment.

This research line can greatly contribute to the reputation and the impact of the regional academic activities in mental health. Results from the studies presented in this thesis were already picked up by the general public and will be discussed with patient organizations. It will inform patients, general public, policy makers and disseminate the concept that the expression of genetic vulnerability depends on exposure to environmental factors. Eventually, this will greatly help patients in their understanding of their personal background of experiencing psychosis spectrum disorder.

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