Polygenic burden analysis of longitudinal clusters of quality of life and functioning in patients with severe mental illness

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Background
Psychiatric illnesses such as bipolar disorder, schizophrenia and schizoaffective disorder are severe, disabling disorders associated with decreased quality of life (QOL) and functioning (1-3). Stigmatization, co-morbidities, adverse effects of medications and chronic symptoms due to treatment resistance are factors responsible for this association (4,5). In this study, we aim to characterize patients with good and poor outcomes according to QOL and functioning scores. Using cluster analysis, we sought to identify longitudinal trajectories and investigate whether levels of QOL and functioning are associated with schizophrenia polygenic risk scores (SZ-PRS). Determining clusters of patients at higher risk of poorer outcomes is critical to provide early and effective interventions.

Methods
Sample
Longitudinal data was used from the Clinical Research Group 241 and PsyCourse studies in Germany and Austria. Participants were phenotyped using a comprehensive battery including data on socio-demographics, history of illness, symptomatology, QOL and functioning. Data was collected at four equidistant time points over an 18-month period. The selected sample comprised a total of 254 participants (age 45.5 +/- 12.4 years; 45% females) with a DSM-IV diagnosis of SZ, SZA or BD.

Statistical analyses
1) The QOL/functioning domain was defined by 28 longitudinally measured items (WHOQOL-BREF; GAF; work status).
2) To identify latent QOL/functioning dimensions factor analysis for mixed data (FAMD) (6) was applied. This allowed for the computation of abstract data dimensions which were used for calculation of longitudinal trajectories. These trajectories are a representation of the overall status of patients.
3) Both the overall level and the longitudinal change of patient status were used as inputs for k-means clustering for longitudinal data (7) on individual trajectories on 9 significant dimensions. This, in turn, resulted in the identification of three distinct subpopulations of patients.

Association of clusters with schizophrenia-polygenic risk scores (SZ-PRS)
DNA samples were genotyped using the Illumina PsychChip. Imputation was performed using the 1000 Genomes Phase 3 reference panel. SZ-PRS were calculated for all individuals using PLINK 1.07. Allelic effect sizes and P-values were obtained using the PGC2 SZ summary results as a discovery sample. A multinominal regression of cluster membership on SZ-PRS (11 p-value thresholds) was performed.

Results
Individual trajectories across time on nine dimensions were used for cluster analysis. Together, these dimensions explained 27.13% of variance in the data. These dimensions were mainly driven by QOL items. Based on these dimensions a 3 cluster solution was determined to be the best model. A nominally significant effect of SZ-PRS on cluster membership was observed at the threshold 0.2, however this did not survive FDR correction. In terms of cluster membership, the highest polygenic risk loading was observed for cluster B and the lowest for cluster C.

Table 1 Significant differences between cluster

<table>
<thead>
<tr>
<th>Significant differences between clusters</th>
<th>No significant differences between clusters</th>
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<tbody>
<tr>
<td>Proportion of participants hospitalized at baseline in cluster B higher than cluster A</td>
<td>Center Diagnosis Sex Work status Duration of illness</td>
</tr>
<tr>
<td>Baseline GAF scores higher in cluster A than cluster B</td>
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Significance levels for SZ-PRS

Figure 1
Cluster A, B, C: values on dimension 1 at four time points

Figure 2
SZ-PRS: Explained variance for polygenic risk scores at various thresholds; corrected for ancestry principle components (PCs), sex, age, diagnosis, age*sex

Limitations
• Study covers relatively short period of time (1.5 years)
• Severely impaired patients more likely to drop out therefore most likely underrepresented in longitudinal cluster analysis
• Clusters not externally validated

Conclusion
Phenotypic data provides insight to target sufferers of severe mental illness with worse outcomes. Further work is needed to improve methods to deal with missing data and increase sample size and to address possible medication effects. Associations with other biological data will be explored (e.g. microRNA; methylation data; proteomics; imaging data).

References

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