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 (BD), schizophrenia (SZ) and schizoaffective disorder (SZA) are severe, disabling disorders associated with decreased quality of life (QOL) and functioning (1–3). Stigmatization, co-morbidities, adverse effects of medications, care models with deficits in personal and social recovery needs and chronic symptoms due to treatment resistance are factors that can lead to severe reductions in quality of life and functioning (4,5). In this study we aim to characterize patients with good and poor outcomes according to QOL and functioning scores across diagnoses. Using cluster analysis, we sought to identify longitudinal trajectories and investigate whether levels of QOL and functioning are associated with the individual burden of 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

Participants Longitudinal data was used from the Clinical Research Group 241 and PsyCourse studies in Germany and Austria (www.kfo241.de; www.PsyCourse.de). Participants were phenotyped using a comprehensive battery which included 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 198 participants (age 46.9 +- 12.4 years; 46% females) with a DSM-IV diagnosis of SZ, SZA or BD and completed study period.

Genotyping and polygenic scoring The Infinium Psycharray from Illumina was used to genotype patients. For imputation the 1000 Genomes Phase 3 reference panel was used. SZ-PRS were calculated for all individuals using PLINK 1.07. Allelic effect sizes and P-values were determined utilizing the PGC2 SZ results as a discovery sample.

Figure 1
Recruiting centers in Germany and Austria

Statistical analyses

1) A set of 111 longitudinally measured variables on QOL (WHOQOL-BREF), functioning scores (GAF) and the current work status were selected for cluster analyses.
2) Factor analysis for mixed data (FAMD) (6) was applied to reduce the dimensionality and identify key structures of the data. This allowed for the computation of abstract data dimensions which were used for calculation of longitudinal trajectories.
3) These trajectories can be seen as a representation of the overall status of patients and both the overall level as well as the longitudinal change of this status were used as inputs for a k-mean clustering for longitudinal data (7). This, in turn, resulted in the identification of three distinct subpopulations of patients.
4) In a linear regression model we used clusters as predictive variables for polygenic risk scores at 11 thresholds.

References

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Results

The dimension which explained the most variance was used for cluster analysis. Computed by FAMD, the strongest loadings on the first dimension were observed for self-satisfaction, life enjoyment, and ability to cope with daily tasks, energy, and quality of life. Three clusters of longitudinal trajectories were observed on the first dimension: cluster A (39.4%) consisted of participants with the highest average scores for functioning and QOL, cluster B (33.8%) including participants with the lowest average scores for functioning and QOL, and cluster C (26.8%) consisting of participants who had great improvement in functioning and QOL scores over the course of the longitudinal study (see Figure 2).

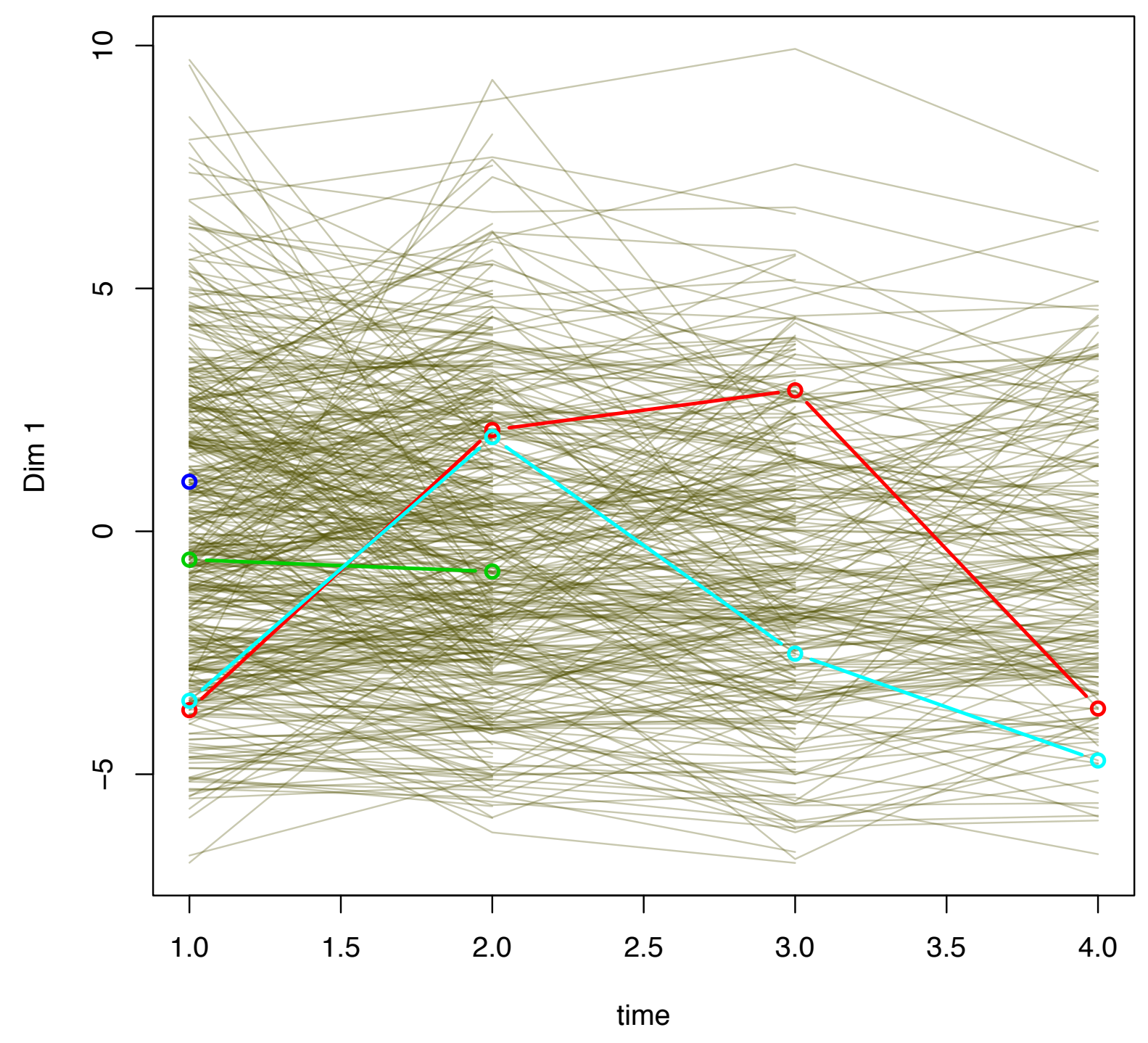

Figure 2
Individual trajectories: values on dimension 1 at four time points.

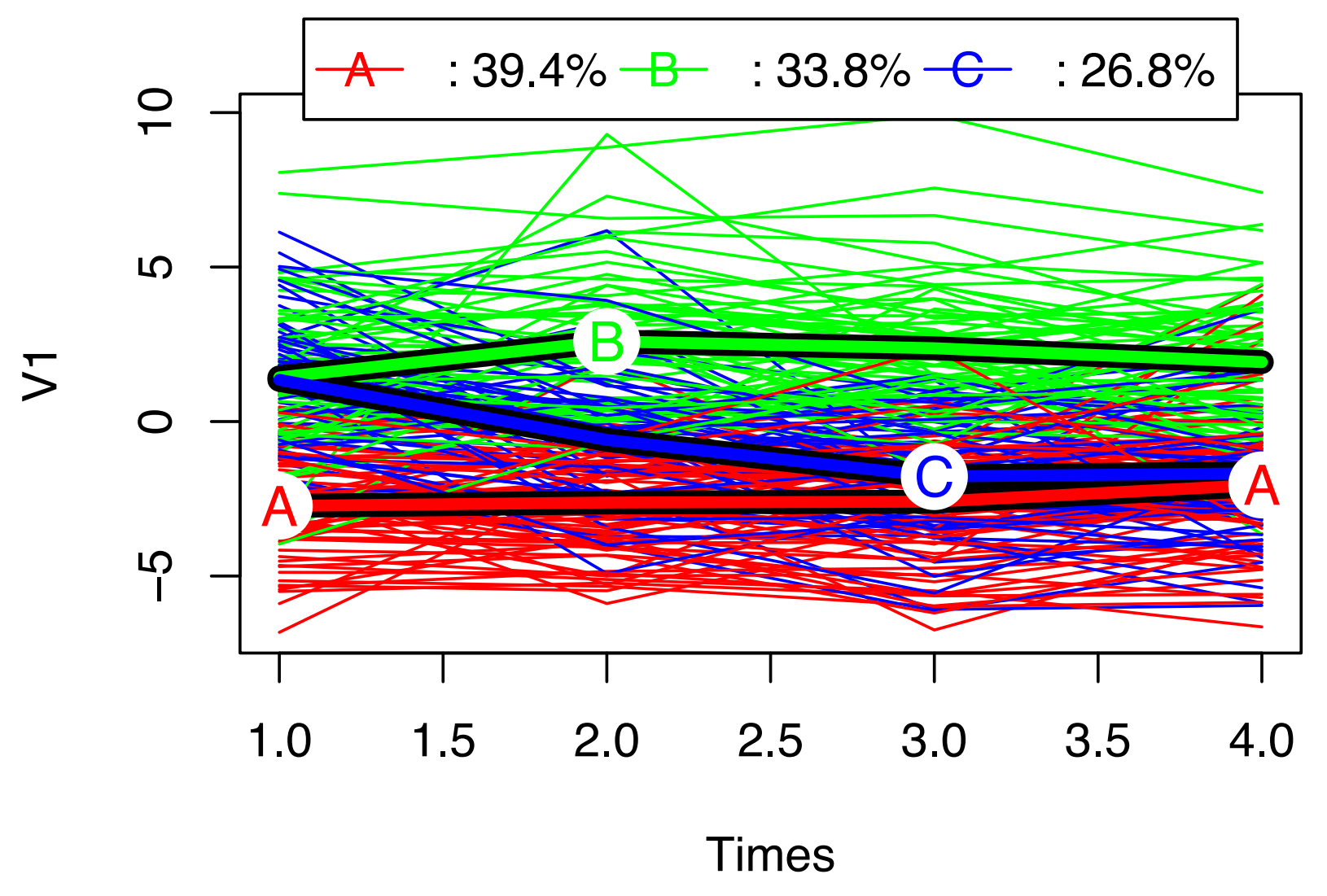

Figure 3
Cluster A, B, C: values on dimension 1 at four time points

Table 1 *Descriptive data of clusters A, B, C*

	Cluster A	Cluster B	Cluster C
	%	%	%
SZ n= 98	47.5	55.2	45.3
BD I/II n= 76	39.7	31.3	45.3
SZA n= 24	12.8	13.4	9.4
Sex females	41.0	35.7	43.3
Unemployed	41.0	62.7	47.2
Part-time	24.4	26.9	22.6
Full-time	34.6	10.4	30.2
Inpatient	85.1	74.6	71.7
Day unit	1.4	6.0	3.8
Outpatient	13.5	19.4	24.5
	mean, SD	mean, SD	mean, SD
Age at interview	47.8, 13.4	46.4, 10.8	46.9, 12.9
Age at onset	31.0, 12.3	28.6, 10.5	29.1, 9.8
Duration of illness	16.4, 12.2	17.8, 10.9	17.8, 11.8
GAF average	66.3, 10.4	53.3, 9.3	64.4, 9.5
GAF gain	3.4, 12.1	2.0, 12.3	9.9, 10.1

There was no significant association between cluster membership and SZ-PRS in the single models. Non-significant trends: Cluster B members show higher polygenic burden versus Cluster A. Cluster C members have less polygenic burden than Cluster A. Overall, SZ-PRS at certain thresholds can be predicted by the clusters (see Figure 4).

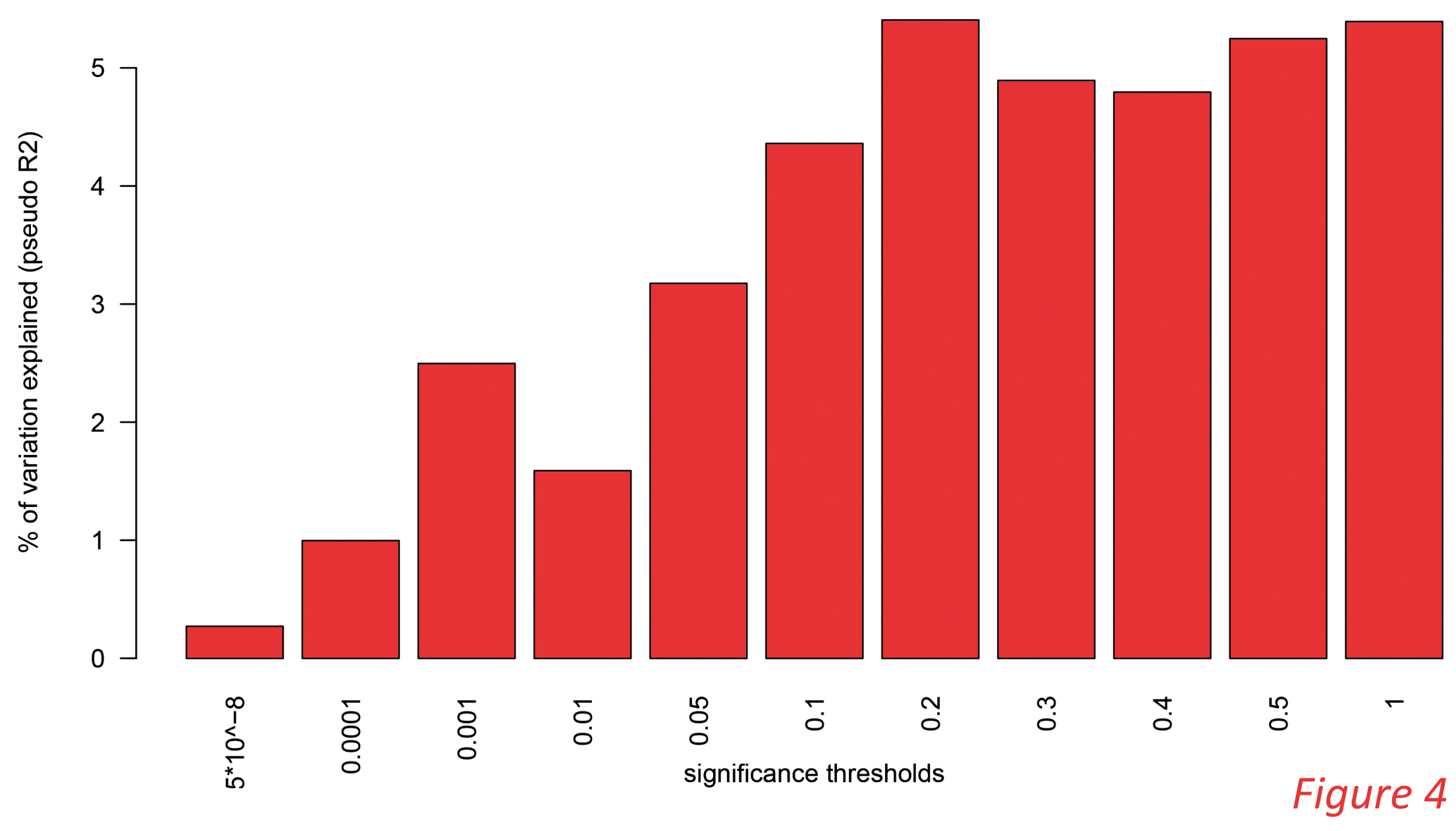

Figure 4
SZ-PRS Explained variance for polygenic risk scores at various thresholds

Conclusion

The results are preliminary and have to be interpreted with caution. Nevertheless, the approach of longitudinal clustering to identify cross-diagnostic subgroups based on a common phenotype seems to be promising. Phenotypic data provide insight to target sufferers of severe mental illness with worse outcomes. Levels of functioning and QOL seem to be associated with SZ-PRS. These analyses will be replicated using the next wave dataset. We expect our findings to remain constant with increased power to reach significance. We hope to explore these clusters further through investigation of proteomics and epigenetics in the near future.

Disclosure

The authors declare no conflict of interest.

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