university of groningen

University Medical Center Groningen

University of Groningen

Data-driven subphenotypic dissection of the clinical heterogeneity of schizophrenia spectrum disorders

Habtewold, Tesfa

DOI:
10.33612/diss.156108872

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Habtewold, T. (2021). *Data-driven subphenotypic dissection of the clinical heterogeneity of schizophrenia spectrum disorders.* [Thesis fully internal (DIV), University of Groningen]. University of Groningen. https://doi.org/10.33612/diss.156108872

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 27-05-2024

CHAPTER 7

Summary, general discussion and future perspectives

SUMMARY

Phenotypic heterogeneity within disorders and phenotypic similarities across disorders are some of the main challenges in the current traditional classification of mental disorders, including schizophrenia spectrum disorders. This can be partly attributed to the absence of objective diagnostic criteria, and high comorbidity with other psychiatric and non-psychiatric diseases. This thesis aimed to dissect the phenotypic heterogeneity of schizophrenia spectrum disorders using data-driven approaches within the framework of the Genetic Risk and Outcome of Psychosis (GROUP) project, a naturalistic, longitudinal cohort study in the Dutch population. GROUP enables a comparison between patients with maximum susceptibility for schizophrenia spectrum disorders (N = 1,119), their unaffected siblings who share genetic and environmental risk factors with patients (N = 1,059), and control subjects who have baseline risk (N = 586). This thesis also aimed to investigate the role of sociodemographic and clinical risk factors along with cardiometabolic and genetic risk factors (as measured by polygenic risk score of schizophrenia (PRS_{SCZ}), and type 2 diabetes (PRS_{T2D})). **Chapters 2** to **5** found that positive, negative and cognitive symptoms are highly heterogeneous, constituting up to six subtypes with variable trajectories over time. Additionally, several sociodemographic and clinical factors were associated with the course of these symptoms in participants. We found weak evidence that genetic risk influences symptom course. **Chapter 6** showed that metabolic dysregulation, as measured by glycated hemoglobin (HbA1c), was associated with late age of illness onset in patients with schizophrenia.

Chapter 2 (1) describes a systematic review of 34 cross-sectional and 19 longitudinal data-driven studies that assessed clusters and trajectories of positive, negative and cognitive symptoms in patients, siblings and healthy controls. I showed that cross-sectional studies reported two to five clusters and longitudinal studies reported two to six trajectories. Out of 58 factors studied, the most common identified factors associated with symptomatic clusters and/or trajectories included sociodemographic factors, such as male gender, older age, low educational status, and having a non-Caucasian ethnicity. Additionally, clinical factors, such as late age of illness onset, severe positive and negative symptoms, low cognitive function, having comorbid general psychopathology, presence of depressive symptoms, and experiencing poor premorbid and global functioning, and poor quality of life were found to be predictive of clusters and/or trajectories. Moreover, this review

highlighted methodological limitations across previous cluster- and trajectory-based studies, including the lack of model validation, the use of different tools to assess similar symptom dimensions, lack of fit-to-purpose study design, insufficient data analyses and absence of guidelines to publish data-driven studies. The heterogeneity in the clinical course of symptoms and associated factors is evident despite the observed methodological limitations across studies. Defining symptoms subgroups and identifying their predictors might help to precisely allocate patients to one homogeneous group, which may help to predict their clinical and functional outcomes and response to interventions. Collectively, this knowledge may contribute to developing a model to predict disease risk or treatment outcome, and eventually to the implementation of personalized care.

Chapter 3 (under review) combined sub-phenotyping, polygenic risk scoring, and data-driven approaches for the first time to investigate the six-year clinical course of positive and negative symptoms, and identify underlying genetic and non-genetic factors in patients, unaffected siblings and healthy controls. This study found three trajectories of positive and negative symptoms in patients and controls, and four trajectories in siblings, characterized by stable, decreasing, increasing and relapsing longitudinal patterns. This study also showed evidence of an association between PRS_{SCZ} and trajectories of positive and negative symptoms though attenuated after adjustment for confounders. As expected, poor premorbid adjustment, low health-related quality of life, and severe positive and negative symptoms at baseline were strong predictors. Generally, I have shown that both positive and negative symptoms are equally heterogeneous, and they follow a comparable course over time. Besides, low levels of positive and negative symptoms are related to good cognitive function.

Chapter 4 (2) examined the heterogeneity and stability of general cognition in patients and unaffected siblings. Additionally, to investigate the amount of shared familial genetic and environmental risk, this study attempted to predict the cognitive subtypes of siblings by using subtypes of their affected probands. I identified five and four stable cognitive trajectories, spanned from severely impaired to high cognitive performance in patients and siblings, respectively. The cognitive trajectory of probands significantly predicted the cognitive trajectory of siblings. Furthermore, patients and siblings with cognitive deficits significantly differed from those without cognitive deficits in baseline IQ, education, premorbid functioning, and positive and negative symptoms. The stability and predictability in unaffected siblings suggest

that cognitive deficits can be a suitable endophenotype for schizophrenia and could be subjected into future genetic studies.

Chapter 5 (3) investigated the relation between PRS_{SCZ} and cognitive deficits in patients, unaffected siblings, healthy controls and all samples combined. Five cognitive subtypes with variable trajectories were observed in patients, four in siblings and controls, and six in all samples combined. Furthermore, PRS_{SCZ} significantly predicted severe cognitive deficits in the combined sample. These findings indicated the heterogenic character of cognitive impairments that can be observed in the majority of participants. Besides, the result indicates that PRS_{SCZ} can be used to disentangle the subtypes of cognitive deficits. These results support the premise that cognitive deficit is a suitable endophenotype for schizophrenia and strengthen the evidence found in **Chapter 4**.

Chapter 6 (4) describes the association between PRS_{SCZ} and HbA1c in patients with non-affective psychosis. I found no evidence for an association between high HbA1c level and increased PRS_{SCZ}, indicating the genetic risk for schizophrenia appears to not influence the risk for metabolic disturbances. Nevertheless, late age of onset of first psychosis was associated with a high HbA1c level. These findings suggest the mechanisms of hyperglycemia or diabetes are at least partly independent from genetic predisposition to SCZ, rather it may be linked to PRS_{T2D}, late age of illness onset, male gender, increased body mass index, and high diastolic blood pressure.

GENERAL DISCUSSION

Clinical course of schizophrenia

While positive and negative symptoms are recognized in the DSM-5 as the main symptoms of schizophrenia spectrum disorders, cognitive impairments are also pertinent manifestations of schizophrenia that lead to poor clinical and functional outcomes. Previous efforts to understand the development of cognitive deficits have brought a wide body of literature, however longitudinal studies are still lacking. In the last decade, only one study investigated the trajectory of cognitive deficit in patients, while 17 longitudinal studies have been conducted on positive and/or negative symptoms.(1) Moreover, previous studies on the long-term trajectories of positive and negative symptoms neither included healthy controls nor investigated

the whole spectrum of potential predictive factors of positive and negative symptoms trajectories. Recently emerging evidence showed the interrelatedness of positive, negative and cognitive symptoms. For example, while positive, negative and cognitive symptoms are distinct phenotypes (5), they are positively associated with each other (5-7) and follow an analogous course.(8) Likewise, **Chapters 3** to **5** showed a temporal relationship between these symptoms and several common identified risk factors suggesting a shared underlying pathophysiology. In unaffected siblings and control subjects, as **Chapters 2** to **5** showed, subclinical forms of symptomatic trajectories also existed that can be attributed to shared and unique determinants with probands. This may elucidate the disease mechanisms before the disease onset and may be helpful to predict transition to psychosis in yet unaffected individuals. Bearing this in mind, the early recognition and treatment of subtle psychotic symptoms will improve outcomes, and may prevent development of schizophrenia.(9) Generally, the current knowledge gained from my thesis confirms the existence of trajectories both at the preclinical and clinical phase and can reveal the course of schizophrenia in patients and vulnerability in unaffected siblings and healthy controls.

Chapter 6 showed the existence of glycemic dysregulation in patients with schizophrenia spectrum disorders that was strongly predicted by late age of illness onset and at least partly linked to genetic liability. Similarly, previous studies have shown the occurrence of cardiometabolic risk factors, including hyperglycemia and cardiometabolic diseases in patients related to unique or shared risk factors. (10) Mostly antipsychotics are held responsible for cardiometabolic alterations, while there is also evidence of a relation with negative and cognitive symptoms. Previous studies in patients with early-onset or chronic schizophrenia showed that severity of negative symptoms is associated with insulin resistance and increased triglyceride levels.(11,12) Moreover, approximately two-thirds of patients with schizophrenia spectrum disorders had physical diseases multimorbidity and the risk of mortality was further increased compared to those with no or a single physical illness.(13)

Several genetic and non-genetic factors are implicated in the development of schizophrenia and its symptoms. Regarding non-genetic factors, **Chapters 3** and **4** showed that poor premorbid adjustment, low health-related quality of life, severe positive and negative symptoms, low educational status, and low IQ are among others related to long-term trajectories of positive, negative and cognitive symptoms.

This finding is in line with previous reports.(1) From the genetic perspective, contemporary evidence shows both schizophrenia and its symptoms are heritable (14-16), and their genetic association has been observed in cross-sectional studies. Of note, none of the previous studies in the last decade investigated the association of genetic susceptibility for schizophrenia (PRS_{SCZ}) with symptom trajectories and yet, it is unknown to what extent this genetic susceptibility is shared. In response to this shortcoming, in **Chapters 3** and **5** we investigated the role of PRS_{SCZ} in six years trajectories of positive, negative and cognitive symptoms in patients, siblings and healthy controls. **Chapter 3** showed for the first time PRS_{SCZ} is linked with the baseline and six years clinical trajectories of positive and negative symptoms, though the evidence was not strong. This finding agrees with previous result from a population-based cohort study.(17) In **Chapter 5**, PRS_{SCZ} is strongly associated with long-term trajectories of severe cognitive impairments in all combined samples. This evidence at least partly shows the PRS_{SCZ} constructed from samples mainly in academic research settings would be useful in actual clinical practice (18,19) to disentangle clinically relevant patient subtypes given that patients in the GROUP cohort are recruited from mental health care institutions and university medical centers. For common physical disorders, such as type 2 diabetes, coronary artery disease, and breast cancer, PRS scores have shown potential clinical utility. Hopefully, this will also apply for psychiatric disorders including schizophrenia as collaborative efforts continue and sample size grows. This way, PRS_{SCZ} may identify a subset of individuals with poor clinical prognoses (20) and the use of PRS is essential though finding strong evidence is a big challenge. There are of course many unique challenges in translational psychiatry research, but the studies in this thesis provide support to use PRSs and endophenotypes in real clinical settings. Furthermore, compared to positive and negative symptoms, PRS_{SCZ} showed a stronger yet modest connection with the development of cognitive deficits (**Chapters 4** and **5**). This implies that cognition may be more strongly predicted by genetic background than positive and negative symptoms. This is consistent with the notion that cognition is a highly heritable phenotype of schizophrenia. It has been suggested that endophenotypes, such as cognition, have a simpler genetic architecture than clinical syndromes and thus provide better signal-to-noise ratios and greater statistical power, which can be detectible in smaller sample sizes.(21)

FUTURE PERSPECTIVES

Many efforts, including the current thesis, have been devoted to understanding the pathophysiology of schizophrenia and its symptoms over time. However, the cause-effect relationship and the pathway of the association of symptoms trajectories with each other as well as with functional outcomes in schizophrenia have not been utterly investigated. To elucidate the pathophysiology of schizophrenia, further research on the interrelatedness and distinctiveness of positive, negative and cognitive symptoms is needed.(6) It is also recommended to investigate the role of genetic and nongenetic factors (e.g., cardiometabolic disturbances) using network path analysis to unravel the intertwined pathophysiology of schizophrenia. Deep cognitive endophenotyping (e.g., attention, verbal learning, and memory subdomains) using data-driven methods may give additional insight into the heterogeneity of cognitive deficits. Unfortunately, the GROUP cohort used in this thesis, lacks data on inflammatory biomarkers and physical activity levels, and cardiometabolic data from siblings and controls. The cardiometabolic data from healthy siblings and controls could have a particular importance to understand pathophysiology of somatic comorbidities that occur before or concomitantly with schizophrenia.(22) Inflammation is also an important factor that plays a role in the bidirectional association between several physical illness and schizophrenia spectrum disorders.(22) Finally, further research on genes, molecules, cells, circuits and behavior level needs to be conducted simultaneously using big data from patients, their parents and siblings, and the general population.

The use of PRS, which is a measure of cumulative genetic susceptibility to symptoms or diseases, is one of the common genetic approaches in recent years to study biological and molecular mechanisms of developments of schizophrenia and its symptoms.(23) There are different methods to use PRS_{SCZ} in statistical modeling in schizophrenia research. Typically in the original schizophrenia GWAS (16), up to 12 PRSs could be constructed using several p-value thresholds and used separately to compare the explained variance and strength of associations with a particular phenotype. The other approach is performing principal component analysis on the resulting set of PRSs and using the first PRS principal component in statistical modeling.(24) Future gains from using the PRS approach may be greater if used for examining the association with schizophrenia symptoms, endophenotypes, biological substrates and metabolites in large multi-national consortia using system biological approaches.(25) This leads to identification of symptoms that have a

stronger genetic liability, provides an understanding of the underlying causal model specific for a clinical subtypes or symptom dimensions, and eventually may improve performance of risk prediction and efficacy of treatments.(18,23,26-28) Importantly, the PRS_{SCZ} should also be cautiously implemented and interpreted given that there is evidence that PRS_{SCZ} is also linked with ancestry, drop-out during follow-up, and several psychiatric and non-psychiatric conditions.(25,29,30)

In addition to PRS, endophenotypes are one of the relevant biological biomarkers in schizophrenia spectrum disorders.(31) Endophenotypes or intermediate phenotypes are stable and heritable quantitative neuropsychological or biological traits that are associated with the disorder, at least in part due to shared underlying genetic influences.(32) Endophenotype studies linearly connect different levels of biology – distinct genes code for proteins distinctly influencing brain structure, circuit function, cognitive and behavioral patterns, and ultimately risk for clinical diagnoses. However, endophenotype research has yet to deliver clinical innovation in psychiatry, while other areas of medicine have seen greater success in leveraging genetic insights into better treatments. Thus, endophenotype studies should continue from interdisciplinary domains to address knowledge gaps and to build endophenotype studies to their full potential and deliver clinically applicable insights.(21) More research is needed on the co-occurrence of endophenotypes within and among psychotic disorders, and the genetic link between schizophrenia spectrum disorders and several potential endophenotypes.(31) Besides, before using endophenotypes in clinical practice, it is recommended to evaluate the underlying assumptions of linearity and parsimony, validity, genetic complexity and neurodevelopmental context.(21)

Big data and data-driven methods in schizophrenia research

One of the major challenges of working in collaboration is the complexity of the data as big data emerges. Besides, the outcomes of data-driven models are heavily dependent on the structure of the input data.(33,34) Therefore, it is difficult to know how different identified subgroups relate to each other and which are the most relevant for clinical decision-making. Also, when applying data-driven methods, it needs to be considered that some classes may be unmanageably small or not well defined, some individuals may not belong to any class, and individuals in the same identified groups (latent class) may not be the same and equally respond to treatment.(35) Future efforts must move on with enriching data-driven methods by

developing richer clustering models, using a combination of model-fit statistics, and clearly defining research questions and interpreting results in a translatable way. (33,35) Moreover, applying data-driven methods using a combination of data, such as symptom scores, polygenic risk scores, cardiometabolic parameters and functional measurements is warranted. This approach has shown to be successful to identify subtypes of major depressive disorder and providing clinically useful information. (36) Furthermore, quantitative comparisons between different study cohorts and ensuring clinical validity are important.

Patients with schizophrenia spectrum disorders may not clearly fall into discrete classes as presented in the DSM, rather, they may fall along a continuum of symptoms. Traditionally distinct disorders (e.g., schizophrenia, schizoaffective disorder and bipolar disorder with psychotic features) share common genetic susceptibility, neurobiological changes, clinical symptoms (i.e., positive, negative and cognitive symptoms), neuroimaging findings, and treatment regimens. In clinical practice, it is also common that patients with a similar diagnosis often have undergone patho-physiologically distinct processes preceding disease onset and follow a different disease course. Consequently, misdiagnosis or misclassification of a patient can occur that may lead to suboptimal disease management and treatment efficacy or treatment non-responsiveness. This calls for a re-examination of disease diagnostic approaches and the need for big data at the molecular, cellular, tissue, and whole-organism levels to understand the patho-physiologic processes of the disease and develop objective disease-specific diagnostic criteria.

The opportunities for using big data have grown enormously with improvements in our ability to measure biomarkers (i.e., clinical laboratory, genetic, proteomic, metabolomics measurements), collect high dimensional neuroimaging data, instrument patients with personal devices, and electronically store or preserve all these data. Additionally, invention of novel computational and statistical methods, policies for a secure free and rapid sharing of data and a shift in the research culture toward a consortium approach facilitates the utilization of big data.(37,38) As a result, the landscape of psychiatric research has taken a major turn in the last decade and the ability to explore heterogeneity and biological drivers of schizophrenia and other psychotic disorders increased to an extraordinary scale and power.(39) Hence, the molecular classification and objective diagnosis of schizophrenia spectrum disorders are closer to reality than in the past.

Towards personalized psychiatry

All previous efforts shall hopefully continue to reach into a unified theoretical framework that accounts for the causal inference underlying the disease at cellular, endophenotypical, preclinical, and clinical levels. This may potentially surpass unitary diagnostic categories but could also allow coverage of comorbidities and the continuum of symptoms in conjunction with an understanding of fundamental biological processes. The thesis showed a continuum of positive, negative and cognitive symptoms across patients, siblings and healthy controls despite the difference in assessment instruments for positive and negative symptoms in healthy and diseased populations. The current efforts could also pave the way towards a paradigm shift, in which we can utilize evidence-based, multidisciplinary knowledge to diagnose and treat patients based on a truly personalized treatment plan.(37) Furthermore, it may help for optimizing the effectiveness and efficacy of currently available treatment, and the development of novel treatments and prevention strategies for schizophrenia spectrum disorders. Based on the idea of therapy as a process of change, continuous monitoring of the individual symptom course on different levels and dimensions could facilitate the consequential re-adjustment of therapeutic interventions. In this aspect, the current thesis shows the long-term clinical course of schizophrenia symptoms and at least partly contributes to further personalized care in schizophrenia spectrum disorders. Personalized psychiatry should not be restricted to individualized patient profiles and risk scores, allowing for the assignment of a specific therapeutic intervention, but should be extended to a rather dynamic understanding.

CONCLUSIONS

This thesis showed that schizophrenia constitutes of two to six data-driven subgroups of symptom severity that are characterized by stable, increasing, decreasing and relapsing trajectories over time. These subgroups are distinguished by different sociodemographic, genetic, metabolic and clinical factors. In this thesis, the use of cognitive endophenotypes to identify subgroups of patients with schizophrenia spectrum disorders may advance precision psychiatry.(31) Data-driven methods can dissect schizophrenia spectrum disorders compiling all symptoms domains across healthy and affected populations, which may help to design targeted evidence-based interventions. The identified subgroups may help to guide treatment selection

to improve treatment efficacy and to minimize costs and prevent unnecessary antipsychotic side effects, such as cardiometabolic dysfunction.(40) In addition, these findings may be useful in the design of future trials or the retroactive reanalysis of previous trials and may guide clinicians to better detect disease heterogeneity.(39) Moreover, in this era where there are no objective diagnostic criteria for schizophrenia, the use of data-driven methods for big data analysis is relevant and the evidence in this thesis may add insight to the accurate prediction and diagnosis of schizophrenia. Finally, the findings in my thesis may be a wake-up call for developing DSM-6 by characterizing disorders, not by categories, but based on a collection of symptoms along the continuum taken the course of the illness into account.

References

(1) Habtewold TD, Rodijk LH, Liemburg EJ, Sidorenkov G, Boezen HM, Bruggeman R, et al. A systematic review and narrative synthesis of data-driven studies in schizophrenia symptoms and cognitive deficits. Translational Psychiatry 2020;10(1):1-24.

(2) Islam MA, Habtewold T, van Es F, Quee P, van den Heuvel E, Alizadeh B, et al. Long term cognitive trajectories and heterogeneity in patients with schizophrenia and their unaffected siblings. Acta Psychiatr Scand 2018;138(6):591-604.

(3) Habtewold TD, Liemburg EJ, Islam MA, de Zwarte SMC, Boezen HM, Luykx JJ, et al. Association of schizophrenia polygenic risk score with data-driven cognitive subtypes: A six-year longitudinal study in patients, siblings and controls. Schizophr Res 2020; S0920-9964.

(4) Habtewold TD, Islam MA, Liemburg EJ, Bartels-Velthuis AAA, van Beveren NJ, Cahn W, et al. Polygenic risk score for schizophrenia was not associated with glycemic level (HbA1c) in patients with non-affective psychosis: Genetic Risk and Outcome of Psychosis (GROUP) cohort study. J Psychosom Res 2020 May 2020;132:109968.

(5) Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr Bull 2006;32(2):250-258.

(6) Eack SM, Keshavan MS. Cognition, negative symptoms, and functional outcome in psychosis. Schizophr Res 2020; S0920-9964.

(7) Chen L, Johnston JA, Kinon BJ, Stauffer V, Succop P, Marques TR, et al. The longitudinal interplay between negative and positive symptom trajectories in patients under antipsychotic treatment: A post hoc analysis of data from a randomized, 1-year pragmatic trial. BMC Psychiatry 2013;13.

(8) Carrà G, Crocamo C, Angermeyer M, Brugha T, Toumi M, Bebbington P. Positive and negative symptoms in schizophrenia: A longitudinal analysis using latent variable structural equation modelling. Schizophr Res 2019;204:58-64.

(9) van Os J, Guloksuz S. A critique of the "ultrahigh risk" and "transition" paradigm. World Psychiatry 2017;16(2):200-206.

(10) Vancampfort D, Wampers M, Mitchell AJ, Correll CU, De Herdt A, Probst M, et al. A meta analysis of cardiometabolic abnormalities in drug naïve, firstepisode and multiepisode patients with schizophrenia versus general population controls. World Psychiatry 2013;12(3):240-250.

(11) Wedervang-Resell K, Friis S, Lonning V, Smelror RE, Johannessen C, Agartz I, et al. Lipid alterations in adolescents with early-onset psychosis may be independent of antipsychotic medication. Schizophr Res 2020;216:295-301.

(12) Soontornniyomkij V, Lee EE, Jin H, Martin AS, Daly RE, Liu J, et al. Clinical Correlates of Insulin Resistance in Chronic Schizophrenia: Relationship to Negative Symptoms. Frontiers in psychiatry 2019;10:251.

(13) Kugathasan P, Wu H, Gaughran F, Nielsen RE, Pritchard M, Dobson R, et al. Association of physical health multimorbidity with mortality in people with schizophrenia spectrum disorders: Using a novel semantic search system that captures physical diseases in electronic patient records. Schizophr Res 2020;216:408-415.

(14) Ronald A, Pain O. A systematic review of genome-wide research on psychotic experiences and negative symptom traits: new revelations and implications for psychiatry. Hum Mol Genet 2018;27(R2):R136-R152.

(15) Trampush J, Yang M, Yu J, Knowles E, Davies G, Liewald D, et al. GWAS meta-analysis reveals novel loci and genetic correlates for general cognitive function: a report from the COGENT consortium. Mol Psychiatry 2017;22(3):336.

(16) Ripke S, Neale BM, Corvin A, Walters JTR, Farh K, Holmans PA, et al. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511(7510):421-7.

(17) Docherty AR, Shabalin AA, Adkins DE, Mann F, Krueger RF, Bacanu S, et al. Molecular Genetic Risk for Psychosis Is Associated With Psychosis Risk Symptoms in a Population-Based UK Cohort: Findings From Generation Scotland. Schizophr Bull 2020; ;46:1045-1052.

(18) Binder EB. Polygenic risk scores in schizophrenia: Ready for the real world? Am J Psychiatry 2019; 176:783-784.

(19) Zheutlin AB, Dennis J, Karlsson Linnér R, Moscati A, Restrepo N, Straub P, et al. Penetrance and pleiotropy of polygenic risk scores for schizophrenia in 106,160 patients across four health care systems. Am J Psychiatry 2019;176(10):846-855.

(20) Jonas KG, Lencz T, Li K, Malhotra AK, Perlman G, Fochtmann LJ, et al. Schizophrenia polygenic risk score and 20-year course of illness in psychotic disorders. Translational psychiatry 2019;9(1):1-8.

(21) Roffman JL. Endophenotype Research in Psychiatry—The Grasshopper Grows Up. Jama Psychiatry 2019;76(12):1230-1231.

(22) Chen Y, Pan C, Chang C, Chen P, Chang H, Tai M, et al. Physical Illnesses Before Diagnosed as Schizophrenia: A Nationwide Case-Control Study. Schizophr Bull 2020.

(23) Jones HJ, Heron J, Hammerton G, Stochl J, Jones PB, Cannon M, et al. Investigating the genetic architecture of general and specific psychopathology in adolescence. Translational psychiatry 2018;8(1):1-11.

(24) Coombes BJ, Ploner A, Bergen SE, Biernacka JM. A principal component approach to improve association testing with polygenic risk scores. Genet Epidemiol 2020; 44: 676-686.

(25) Mistry S, Harrison JR, Smith DJ, Escott-Price V, Zammit S. The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review. Schizophr Res 2018;197:2-8.

(26) Janssens ACJ. Validity of polygenic risk scores: are we measuring what we think we are? Hum Mol Genet 2019;28(R2):R143-R150.

(27) Bigdeli T, Peterson R, Ripke S, Bacanu S, Amdur R, Gejman P, et al. Genome-wide Association Study of Clinical Features in the Schizophrenia Psychiatric Genomics Consortium: Confirmation of Polygenic Effect on Negative Symptoms. bioRxiv 2017:161349.

(28) Fanous A, Kendler K. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. Mol Psychiatry 2005;10(1):6-13.

(29) Curtis D. Polygenic risk score for schizophrenia is more strongly associated with ancestry than with schizophrenia. Psychiatr Genet 2018;28(5):85-89.

(30) Martin J, Tilling K, Hubbard L, Stergiakouli E, Thapar A, Davey Smith G, et al. Association of genetic risk for schizophrenia with nonparticipation over time in a population-based cohort study. Am J Epidemiol 2016;183(12):1149-1158.

(31) Donati FL, D'Agostino A, Ferrarelli F. Neurocognitive and neurophysiological endophenotypes in Schizophrenia: an overview. Biomarkers in Neuropsychiatry 2020:100017.

(32) Miller GA, Rockstroh BS. Progress and prospects for endophenotypes for schizophrenia in the time of genomics, epigenetics, oscillatory brain dynamics, and the Research Domain Criteria. The neurobiology of schizophrenia: Elsevier; 2016. p. 17-38.

(33) van der Nest G, Lima Passos V, Candel MJJM, van Breukelen GJP. An overview of mixture modelling for latent evolutions in longitudinal data: Modelling approaches, fit statistics and software. Advances in Life Course Research 2020 March 2020;43:100323.

(34) Twisk J, Hoekstra T. Classifying developmental trajectories over time should be done with great caution: a comparison between methods. J Clin Epidemiol 2012 October 2012;65(10):1078-1087.

(35) Marquand AF, Wolfers T, Mennes M, Buitelaar J, Beckmann CF. Beyond Lumping and Splitting: A Review of Computational Approaches for Stratifying Psychiatric Disorders. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2016 September 2016;1(5):433-447.

(36) Beijers L, Wardenaar KJ, van Loo HM, Schoevers RA. Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. Mol Psychiatry 2019;24(6):888-900.

(37) Keck ME, Kappelmann N, Kopf-Beck J. Translational research as prerequisite for personalized psychiatry. Eur Arch Psychiatry Clin Neurosci 2018; 268(3): 215-217.

(38) Senthil G, Lehner T. Schizophrenia research in the era of Team Science and big data. Schizophr Res 2020 March 2020;217:13-16.

(39) Altman RB, Ashley EA. Using "big data" to dissect clinical heterogeneity. Circulation 2015; 131(3):232-3.

(40) Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. Br Med Bull 2015;114(1):169-179.