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

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CHAPTER 1

General Introduction

Schizophrenia

Schizophrenia spectrum disorders are highly heterogeneous clinical syndrome, which are all characterized by positive and negative symptoms. Schizophrenia is the most severe and chronic form of the schizophrenia spectrum disorders. The clinical diagnosis of schizophrenia is made based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (**Box 1**).(1) The first-episode of schizophrenia spectrum disorders usually occurs in late adolescence or early adulthood. The incidence is 15 and 10 per 100,000 individuals in men and women, respectively. The lifetime prevalence of schizophrenia is approximately 1%, although it varies across race or ethnicity, sex, location, and geographical origin for immigrants and their children.(2) The 2016 Global Burden of Disease study showed that the global age-standardized point prevalence of schizophrenia was estimated to be 0.28% (Figure 1).(3) The report also showed that the prevalence of schizophrenia in the Netherlands (i.e., 0.36%) was higher than the global estimate and other West European countries. Globally, the prevalence rose from 13.1 million in 1990 to 20.9 million in 2016.(3)

Schizophrenia results in a large health care burden given that it has typically an early adulthood onset that lead to long-term impairments in social and occupational functioning. Schizophrenia contributes 13.4 million years of life lived with disability (YLDs) (**Box 2**) to the global burden of disease.(3) As a lifelong disease, it conveys exploitation, poverty, victimization, and premature mortality. Yet, a small proportion of patients may fully recover. Individuals with schizophrenia has about 15 to 25 years shorter mean life expectancy than the general population related to psychiatric (e.g., suicide) and non-psychiatric (e.g., cardiometabolic diseases) complications.(4)

Individuals can already have an increased risk to develop schizophrenia from the time of conception. Schizophrenia risk groups can be classified as clinical high-risk and familial high-risk. The clinical high-risk group are those who already developed sub-clinical or prodromal symptoms of schizophrenia, such as changes in belief, thought and perception, before onset of illness. They are at risk due to exposure to various environmental factors. The familial high-risk group are relatives (i.e., siblings and parents) of patients with schizophrenia and they are at risk of developing psychosis due to their genetic relatedness with their probands. It is known that unaffected siblings of patients with schizophrenia may develop psychotic-like-experiences or sub-clinical psychotic symptoms, which may later convert to full-blown episode of

psychosis over time.(5) During the past decades, several large-scale epidemiological and genetic studies have been conducted to identify the environmental and genetic risk factors of schizophrenia as well as their interaction effects and to unravel the pathophysiology of schizophrenia.

Risk factors of schizophrenia

Environmental factors

The pathogenesis of schizophrenia may have its onset at conception, although disease manifestation often occurs in early adulthood. During pregnancy, maternal infection, stress and nutritional deficiencies, abnormal fetal growth and development (i.e., low birthweight, congenital malformations, intrauterine growth retardation) and pregnancy complications (i.e., bleeding, diabetes, ischemic injury, rhesus incompatibility) have been associated with schizophrenia. During birth, obstetric complications (i.e., preterm birth, preeclampsia), delivery complications (i.e., asphyxia, hypoxia, emergency caesarean), season of birth (i.e., winter) and place of birth have been associated with schizophrenia.(2,6) During childhood, mild cognitive and motor impairments, and childhood adversity (e.g., bullying or child abuse) also increase the risk of schizophrenia. Other risk factors are racial/ethnic minority, socioeconomic status, cannabis use, poor social and cognitive functioning, parental age, immigration, urbanicity and negative life events (e.g., trauma, loss of significant others).(2) Similarly, in relatives of patients with schizophrenia, paternal age, season of birth, cannabis use, urbanicity, childhood adversity, and obstetric and perinatal complications have been associated with schizophrenia.(7)

Several pathophysiologic mechanisms have been implicated in the course of development of schizophrenia. For example, early- and later-life environmental risk factors exert their influence to our body via aberrant reactions within the amygdala and frontal cortex stress-response circuit, which are thought to lead to sensitization of the subcortical dopamine system (Figure 2).(4) Additionally, early-life experiences, such as bullying or child abuse may lead to cognitive biases resulting from the hostile acts of others and delusional beliefs, as a result.(4) Even though, subcortical dopamine dysregulation is the most widely known pathway, GABA/glutamate pathway alteration that increase pruning of dendritic cells in the prefrontal cortex has also a role in the development of schizophrenia.(8)

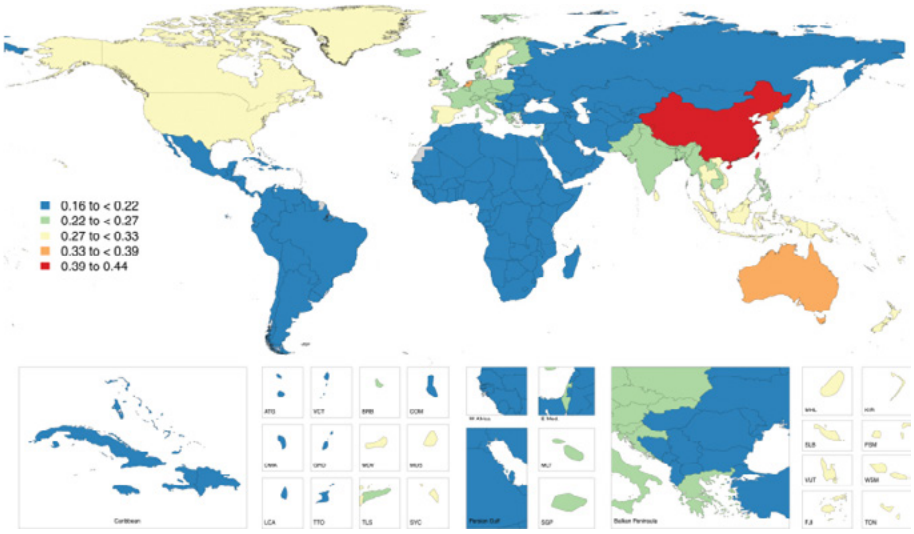

Figure 1: Map of age-standardized point prevalence of schizophrenia by country in 2016. (3) (Reprinted with permission from Charlson et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr Bull. 2018; 44:1195-203)

Genetic factors

Schizophrenia is a polygenic psychotic disorder with a heritability estimate of 50% to 80% based on single-nucleotide polymorphisms (SNP)- and family-based studies. (9) Since 2006, when the first schizophrenia genome-wide association studies (GWAS) was conducted, there has been an increasing discovery of candidate genes and SNPs. In recent years, GWASs have made huge progress to identify multiple common variants that associated with schizophrenia, each with only small effects. The latest GWAS to date using 11,260 cases and 24,542 controls, identified 145 loci that are associated with schizophrenia.(10) In addition, there are copy-number variants found in 2% to 3% of cases of schizophrenia and involved in deletion/ duplication of genes. The development of GWAS has also enabled the construction of polygenic risk scores (PRS), which provide a composite estimation of genetic liability to a particular disease (e.g., schizophrenia). It has been well recognized that PRS is a good predictor of case-control status. Schizophrenia has also shared heritability with several psychiatric disorders (e.g., bipolar disorder, autism spectrum disorder, attention deficit hyperactivity disorder, negative symptoms, and depressive

symptoms), physical disorders (e.g., type 2 diabetes, coronary artery diseases, hypertension, rheumatoid arthritis, Crohn's disease) and quantitative traits (e.g., IQ, general cognitive ability, negative symptoms score).(11)

Gene expression analyses, mappings of GWAS onto neuronal gene expression profiles and postmortem studies results implicate that schizophrenia risk genetic variants are involved in the regulation of the postsynaptic membrane, synaptic transmission and voltage-gated potassium channels. Additionally, these genes may affect the hippocampal pyramidal cells, medium spiny neurons and cortical interneurons. They may also disrupt microglial complement-mediated synaptic elimination and lower levels of synaptic proteins, dendritic spines, and gamma-aminobutyric acid (GABA)–ergic and glutamatergic markers.(4) Furthermore, risk genes could affect the development of symptoms in schizophrenia in at least two ways. First, allelic variation in disease susceptibility genes themselves might predispose to illness and influence the development of symptoms. Second, modifier genes might directly influence the development of symptoms without increasing disease susceptibility.

Gene-environment interaction

Schizophrenia is a complex disorder with multiple symptoms and interacting risk factors. The pairwise concordance for schizophrenia is approximately 50% among identical twins leaving 50% not explained by genetic liability.(9) This indicates the importance of environmental factors and their interactions with genetic factors to influence the risk of schizophrenia. For example, the risk for schizophrenia explained by PRSs was five times higher in those who had perinatal complications, while the PRSs did not differentiate case-control status in those who did not experience any obstetric complications.(12) Overall, research suggests the genetic and early-life environmental risk factors alter neurodevelopment that lead to prodromal symptoms and predispose to schizophrenia.

Clinical manifestations of schizophrenia

Positive symptoms

Positive symptoms include delusion, hallucination, and disorganized thinking, speech and motor behavior. Delusion is characterized by fixed beliefs that are not

amenable to change considering conflicting evidence and can be persecutory, referential, erotomaniac, nihilistic, somatic, religious, or grandiose. Hallucination is vivid and clear perception-like experiences that occur without an external stimulus and are not under voluntary control. Auditory hallucination is the most common in schizophrenia, though hallucination may occur in any sensory modality. Disorganized behavior is characterized by lack of associations during speech, abnormal motor behavior and substantial decrement in reactivity to the environment. Psychosocial stressors, psychological factors and subcortical dopamine dysfunction most frequently lead to the onset of positive symptoms.(4) Positive symptoms are often the reason that the patient presents to the clinician and attract most attention nowadays. These symptoms lead to difficulties in performing activities of daily living. Positive symptoms are characterized by relapses and remission (Figure 2), and they often respond well to antipsychotic treatment because they are caused by alteration of striatal dopamine signaling, which is also part of the mechanism of action of the antipsychotic drugs.

Negative symptoms

Negative symptoms are pertinent manifestation of schizophrenia with cluster of symptoms, including diminished emotional expression, avolition, alogia, anhedonia, and asociality (see **Box 2** for definition). Diminished emotional expression includes reduced facial expression, eye contact, intonation of speech, and movements of the hand, head, and face. Avolition is a decrease in motivated, self-initiated and purposeful social activities. Negative symptoms occur in up to 60% of patients with schizophrenia spectrum disorders and is responsible for the long-term disability and poor functional outcomes, such as poor social functioning, occupational and academic performance, quality of life and household integration.(13) About 73% of patients could have negative symptoms before the onset of positive symptoms, while 20% of them develop during the same time with positive symptoms.(13) Regarding the course and pathophysiology, negative symptoms are more chronic and steadier (Figure 2), and most likely result from the disruption of glutamatergic/GABAergic cortical circuits, dopaminergic functioning, cortical excitatory-inhibitorybalance, and cortico-striatal or frontocortico-temporal neural networks that may be attributed to prenatal events, poor premorbid adjustment and genetic contributions. Impaired cognitive function (e.g., executive function, memory) may also contribute to the development of negative symptoms. Negative symptoms show no or little improvement with antipsychotic treatment.(4)

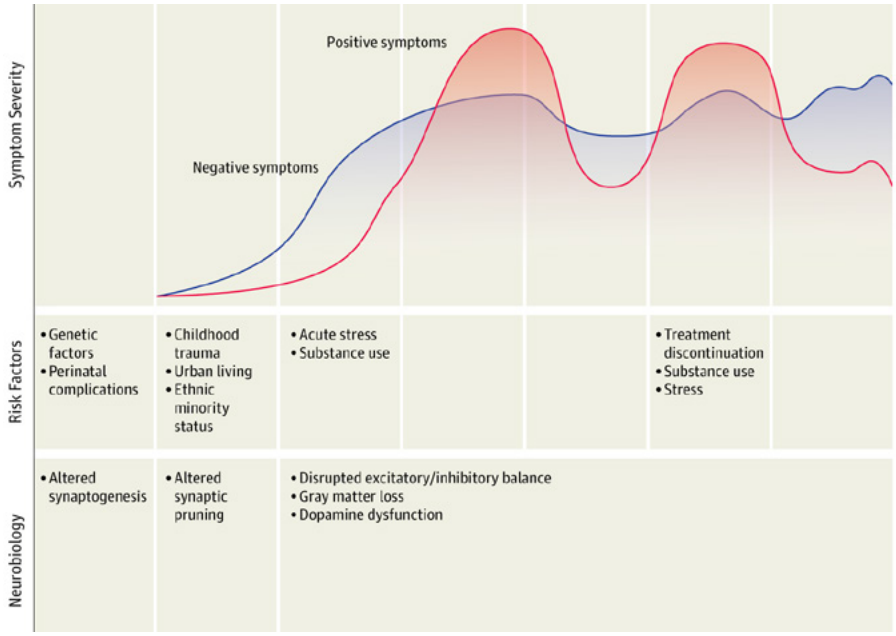

Figure 2: Risk factors and clinical course of positive and negative symptoms.(4) (Reprinted with permission from McCutcheon RA, Marques TR, Howes OD. Schizophrenia—an overview. JAMA Psychiatry. 2020; 77: 201-210)

Cognitive deficits

As shown in **Box 1**, cognitive symptoms are not part of DSM criteria to diagnose schizophrenia, yet they may have long-term consequences. Mild to severe general or domain specific cognitive deficits affect more than 90% of patients with schizophrenia, while some patients have intact cognitive function.(14) Memory, attention, verbal fluency, executive function, problem-solving, and processing speed are the most affected cognitive domains in schizophrenia.(15) Social cognitive impairment have also been seen in patients with schizophrenia.

Similar to negative symptoms, cognitive deficits may also occur before the onset of schizophrenia and they can be responsible for a large proportion of morbidity associated with schizophrenia. Cognitive deficits are stable over time compared to positive and negative symptoms (Figure 3).(13) Reductions in gray matter volume during adolescence and early adulthood, cortical excitatory-inhibitory imbalance and disruption of both structural and functional brain networks may lead to widespread impairments in neural communication, which may in turn results in cognitive deficits. (4)

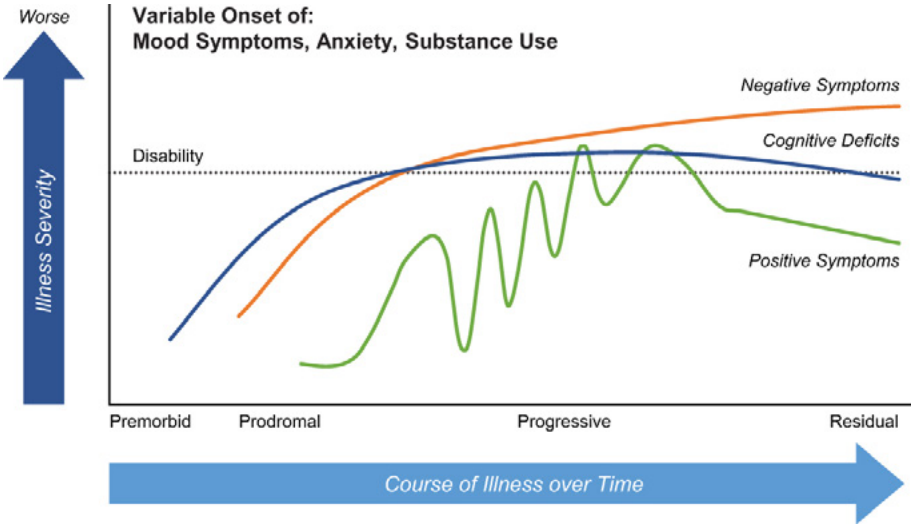

Figure 3: Clinical course of cognitive symptoms in relation to positive and negative symptoms. (13) (Adapted from Correll CU, Schooler NR. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. Neuropsychiatr Dis Treat. 2020; 16: 519–534)

Cognitive impairments in schizophrenia have also been associated with shared risk genes, comorbid physical diseases, cannabis use, and positive and negative symptoms.(16,17) Moreover, cognitive impairment can occur in unaffected first-degree relatives of patients with schizophrenia, but to a lesser degree compare to patients, which indicates the presence of genetic overlap between schizophrenia and cognitive phenotypes. Cognitive endophenotypes are up to 50% heritable.(18) A recent report from the Cognitive Genomics Consortium also showed that the PRS_{SCZ} has been associated with low general cognitive ability and SNPs nominally associated with cognitive impairment have been associated with schizophrenia.(18) On the contrary, individuals who are carrier of some schizophrenia risk genes have a better cognitive performance, particularly processing speed.(19) Like negative symptoms, cognitive symptoms show little to no improvement with antipsychotic treatment.(4)

Diagnosis of schizophrenia

The diagnosis of schizophrenia solely depends on the DSM criteria (**Box 1**). However, DSM criteria have been criticized because of overreliance on positive

symptoms, negligence of affective, negative and cognitive symptom dimensions, and incompetency in overcoming heterogeneity.(20) Misdiagnoses of schizophrenia can occur in approximately 50% of cases with only 65% diagnostic stability across a lifetime.(22) To date, evaluating the level of severity of symptoms and diagnosis entirely depend on subjective interviewing of patients using neuropsychological assessment questionnaires given that there is no objective test (e.g., blood test) for diagnosing schizophrenia. Attempts to develop blood tests for schizophrenia have been made ever since the establishment of questionnaire-based clinical diagnosis tools. Current blood test approaches include genetic (i.e., derived from genome-wide association studies), proteomic (focusing on a plethora of proteins) and immunological (e.g., autoantibodies in cerebrospinal fluid) tests. Yet, none of them are successful because of methodological problems, professional fears and conceptual contradictions.(23) Thus, the pathophysiology of schizophrenia is yet far from understanding and creating reliable diagnostic tests is still a challenge. The schedules for clinical assessment for neuropsychiatry (SCAN) and comprehensive assessment of symptoms and history (CASH) interview are used for diagnosing schizophrenia, whereas the positive and negative syndrome scale (PANSS), scale for the assessment of negative symptoms (SANS) and scale for the assessment of positive symptoms (SAPS) are used for assessing the level of symptom severity. When valid and specific measures are not available or readily accessible to ascertain disease etiology, checklist-based diagnostic criteria still can guide treatment planning, prognostic decision making, generate high quality throughput data, and promote research on pathophysiological mechanisms.(20)

Cardiometabolic outcomes in schizophrenia

Besides the symptoms charactering the illness, patients with schizophrenia spectrum disorders often experience medical complications. As a result, their life expectancy is reduced by 15-30 years compared to the general population. Shared risk factors such as shared genes, inflammation, poor fetal development, neuroendocrine dysfunction and poverty have been associated with physical comorbidity (Figure 4).(25,26) In addition, medication use and poor lifestyle (e.g., cigarette smoking and poor diet) may play a significant role.(24) Type 2 diabetes mellitus (T2D) is the most common comorbidity in schizophrenia spectrum disorders (Figure 4).(26) A meta-analysis showed that the worldwide prevalence of T2D among patients with schizophrenia

is 10.8%.(27) T2D is also a risk factor for several cardiovascular diseases and causes micro- and macro-vascular complications that can leads to brain dysfunction, cognitive decline and increased mortality risk. Other physical comorbidities includes cardiometabolic abnormalities, hypertension, cerebrovascular diseases, circulatory system diseases and immunological diseases that can be related to dysregulation of the cardiometabolic, immune and central nervous system.(28)

In addition to the disease itself, several physical illnesses show correlation with positive, negative and cognitive symptoms. Current evidence suggests negative symptoms are associated with insulin resistance that precedes well known risk factors, such as the use of antipsychotic medications, smoking and development of obesity.(29) Poor engagement in health maintenance behaviors (e.g., cancer screening, physical exercise) related to negative symptoms and cognitive impairment also increase the risk of chronic physical illness in schizophrenia. Moreover, impairments in several cognitive domains have been associated with diabetes mellitus, hypertension, dyslipidemia and obesity.(30) Diabetes mellitus has been associated with processing speed and visual memory impairment, hypertension with verbal memory deficit, dyslipidemia with executive function, verbal memory and attention deficit, and obesity with impairment in processing speed.(31) Interestingly, the severity of positive symptoms was negatively related to insulin resistance in antipsychotic-naïve first-episode patients with schizophrenia spectrum disorders.(32) Another study showed no association between positive and negative symptoms and obesity, which commonly precedes serval physical illness.

Heterogeneity and data-driven approaches in schizophrenia

Schizophrenia can be seen as a clinically and genetically heterogeneous syndrome with several symptom clusters and sub-clusters. For example, negative symptoms include amotivation, anhedonia, affective flattening and poverty of expression that most frequently co-occur and cluster together. Similar patterns may be observed for positive symptoms. Consequently, individual patients may differ markedly in their symptom profiles and treatment response. Diagnostic categories therefore often do not map cleanly onto either biology or outcome, which forms a major barrier to understanding disease mechanisms and developing more effective treatments.

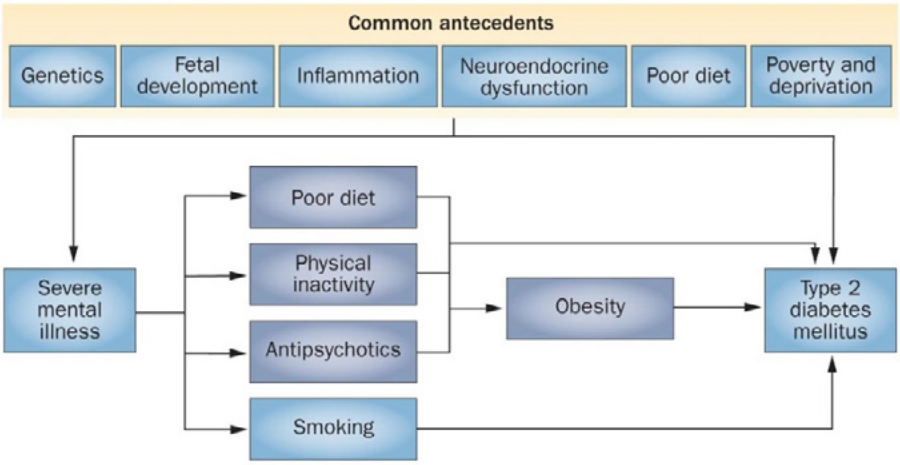

Figure 4: The pathophysiology of the association between physical comorbidities (e.g. type 2 diabetes mellitus) and severe mental illness (e.g., schizophrenia).(26) (Adapted from Holt RI, Mitchell AJ. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. Nat. Rev. Endocrinol. 2015; 11: 79-89)

Additionally, each symptom should be present for a significant portion of time during a one-month period (or less if successfully treated). This criterion generates heterogeneity that allows variable choices by different clinicians that theoretically leads to hundreds of different symptom combinations for a similar diagnosis – schizophrenia.(21) Moreover, diagnoses of psychiatric disorders, including schizophrenia are dependent on the cultural and social context in which they are applied and provides additional sources of heterogeneity.(20)

Heterogeneity can be observed at disease, symptom or biological level. A review of DSM-5 showed four forms of heterogeneity occurred within specific diagnostic criteria (e.g., schizophrenia): the difference in the standards to which symptoms are compared (e.g., comparisons with prior experience, comparison with socially expected responses, no comparators), duration of symptoms (e.g., minimum duration, no duration, discrete episodes), identifiers of severity, and perspective from which distress is assessed.(21) In psychiatry, diagnostic heterogeneity is a common problem in both research and clinical practice. The absence of objective diagnostic tests, longstanding focus on diagnostic categories over specific symptoms and inconsistencies in previous study reports increases disease heterogeneity that may obscure to draw sustainable conclusions on disease prediction, diagnosis and personalized drug treatment and psychological therapies.

In response to the longstanding debate and criticism over the diagnostic categories and high disease heterogeneity, disease classifications are revised with every new edition of DSM diagnostic manuals and move towards a dimensional approach.(1,33,34) Focusing on the underlying specific symptoms or symptom clusters and their relationship with each other is the current approach to address heterogeneity. The DSM-5 favors dimensional concepts over categorical approaches in the diagnosis of schizophrenia and recommends to identify intermediate categories.(1) Consequently, dimensional constructs based on positive, negative and cognitive symptoms have been proposed and they have been found to be predict clinical and functional outcomes, severity of illness, and treatment response. From both clinical and theoretical perspectives, there is a need for a multi-dimensional approach that can be combined with DSM diagnostic criteria. Such an approach incorporates varieties of symptoms within an individual – differential severity of individual symptoms as measured by intensity, duration, or number of symptoms, along with other features such as type and severity of disabilities, and helps to identify more homogeneous groups, which may help with treatment planning, prognostic decision-making, and research on pathophysiological mechanisms.(1) A dimensional approach depends primarily on an individual's subjective reports of symptom experiences along with the clinician's interpretation. The symptom dimension concept in DSM-5 is also complemented by the development of Research Domain Criteria (RDC) (35) by the National Institute of Mental Health in the USA and the Roadmap for Mental Health Research (ROAMER) (36) in Europe.

The use of data-driven methods to stratify psychiatric disorders is another response to tackle heterogeneity in the past decades aiming to find more homogeneous subgroups on the basis of multidimensional data. Recently, data-driven approaches have received renewed interest after the development of DSM-5 and the research initiatives of RDC and ROAMER that emphasize finding stratifications based on biological systems. As a result, the number of data-driven studies based on symptoms, neuropsychologic scores and neuroimaging measures has increased. Additionally, the advent of technologies for measuring many aspects of diseases biology – neuroimaging and omics data, advances in statistical and machine learning data analytic approaches to extract information from complex and high-dimensional biological data, and increasing emphasis on precision medicine have increased the interest of using data-driven methods.(37,38) Overall, the use of data-driven methods

can lead to a biologically grounded understanding of disease heterogeneity and ultimately to more effective and personalized treatments.

Clustering and finite mixture models (FMMs) are commonly used unsupervised data-driven methods to automatically identify subgroups based on structures within the data and heuristics used by each algorithm. K-means, Ward's method and community detection are known clustering methods. Gaussian mixture models, group-based trajectory modeling, latent class cluster analysis, growth mixture modeling, latent class growth analysis and factor mixture modeling are commonly known FMMs.(39) Even though they all have similar objectives, these methods have slightly different assumptions. Clustering methods are frequently used for cross-sectional data analysis, whereas FMMs are used for longitudinal data-analysis. Semi-supervised method, hybrid methods that combine supervised learning with clustering, manifold learning techniques, novelty detection algorithms and disease mapping with normative modeling are also widely known data-driven methods in literature.(39) Several software packages exist for the estimation of clusters and longitudinal FMMs. Some of the popular packages to apply data-driven methods are SAS, Stata, Mplus, LatentGOLD and R. These software packages vary considerably in their capabilities to run the various models, ability to extend beyond standard and default specifications – varying covariance structures and the inclusion of random effects, standard model fit criteria output and default model specifications. It is up to the user to decide which is best suited for their purposes, bearing in mind their own model's underlying assumptions, flexibility, and limitations.(40,41)

The long-standing disease heterogeneity combined with comorbidity with physical diseases makes the treatment and prediction of outcome of schizophrenia spectrum disorders difficult and complex. This urges the need for further investigation using previously published literature and large-scale cohort-based studies that encompass data on both genetic and environmental factors. Previous epidemiological studies on schizophrenia spectrum disorders are hampered by the demographic heterogeneity of study participants, limited sample size, limited access to genetic data, short duration of follow-up, and financial constraint particularly to extract genetic data.(42) Moreover, studies on positive, negative and cognitive symptoms of schizophrenia report inconsistent results, perhaps due to high heterogeneity of symptoms themselves. Of interest, there is no study that comprehensively examined the underlying structure and heterogeneity of positive, negative and cognitive

symptoms, and underlying genetic and non-genetic factors in patients, unaffected siblings and controls using a combination of data-driven, polygenic risk scoring and (sub)phenotyping approaches. Thus, the long-term variation in schizophrenia symptoms and cognitive function conditioned on genetic and non-genetic factors is still an unanswered question.

Aim of the thesis

The main aim of this thesis was to investigate heterogeneity, comorbidity and underlying factors in patients with schizophrenia spectrum disorders, unaffected siblings and controls (Figure 5). Firstly, this thesis aimed to dissect the heterogeneity of positive, negative and cognitive symptoms using data-driven approach. Secondly, this thesis investigated underlying genetic, sociodemographic, metabolic and clinical factors that determine heterogeneity. Thirdly, this thesis assessed glycemic dysregulation in schizophrenia. To achieve these objectives, published evidence and primary data from a large national Dutch cohort was used. This thesis may create opportunity to compare findings, advance the understanding of the clinical course of schizophrenia and underlying pathophysiology, and guide clinicians to provide personalized evidence-based intervention.

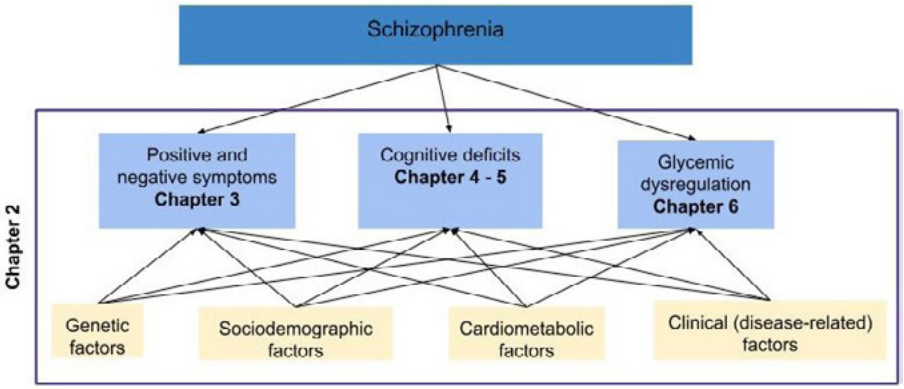

Figure 5: Overview of my thesis.

Cohort studied in this thesis

Data were extracted from the Genetic Risk and Outcome of Psychosis (GROUP) cohort (data release 7.00), a six-year naturalistic, longitudinal cohort study conducted by a consortium of four university psychiatric centers (University Medical Center Amsterdam, University Medical Center Groningen, University Medical Center Maastricht and University Medical Center Utrecht) and their affiliated mental health care institutions in the Netherlands, covering a population of more than 7.5 million individuals. At baseline, 1,119 patients with a schizophrenia spectrum disorder, 1,059 unaffected first-degree siblings and 586 unrelated healthy controls were eligible for inclusion. Outpatients or inpatients presenting at mental health service centers were consecutively recruited. Patients with an age range of 16 to 50 years, a diagnosis of non-affective psychosis (i.e., 96.6% diagnosed with schizophrenia) based on DSM4 criteria, good command of the Dutch language, and who gave written informed consent were included. The age range was chosen because psychosis is presumed to be prevalent in this age range, while minimizing the effect of age-related cognitive decline. Similar criteria, except a diagnosis of psychosis, were applied to the siblings (more than one per family was allowed). Controls were included if they had no known lifetime psychotic disorder and no first-degree family member with a lifetime psychotic disorder. Sociodemographic, diseases-related, symptomatic and behavioral data were collected at baseline, the third year and sixth year using various standard tools by psychiatrists, psychologists, research assistants, nurses and PhD students. Genotype data were collected at baseline and cardiometabolic data were collected at the third year. Details on GROUP project structure, recruitment of participants, sample size estimation and data collection has been published elsewhere.(43)

Outline of the thesis

In **Chapter 2**, a systematic review of cross-sectional and longitudinal data-driven studies was performed to explore the clinical heterogeneity of schizophrenia and identify sociodemographic, metabolic and clinical factors that determine heterogeneity and poor clinical outcomes. Common methodological limitations also assessed in the reviewed studies and future directions are forwarded to optimize evidence from data-driven studies.

In **Chapter 3**, the trajectories of positive and negative symptoms was explored using group-based trajectory modeling. The genetic, sociodemographic and clinical factors associated with these long-term trajectories were also elucidated.

In **Chapter 4,** the heterogeneity and stability of general cognition examined in patients and their unaffected siblings. Sociodemographic and clinical factors that are associated with the cognitive subtypes were assessed, and the cognitive subtypes of siblings predicted using their probands cognitive subtypes.

In **Chapter 5**, data-driven cognitive subtypes in patients, siblings, healthy subjects and all groups combined were identified, and the association with the genetic susceptibility for schizophrenia (as measured by PRS_{SCZ}) and phenotypical factors were assessed.

In **Chapter 6,** the relationship between glycated hemoglobin levels and PRS_{SCZ} in patients was investigated while adjusting for polygenic risk score of T2D (PRS_{T2D}), and clinical and sociodemographic covariables.

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