Investigation of predictors of Psychosocial function in Schizophrenia

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"Investigation of predictors of Psychosocial function in Schizophrenia"

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Andrew T. Olagunju

Dedication

This work is dedicated to my beloved wife, Tinuke Oluwasefunmi Olagunju, my sweet daughters, Oluwatomi, Oluwatosin and Oluwatoni Olagunju, my parents, siblings, and the rest of my family. I am grateful for your support, love, patience and input into my life.

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List of Abbreviations

AIMS- Abnormal Involuntary Movement Scale

ALFA- Assessment of Lifespan Functioning Attainment

AOM- Aripiprazole Once Monthly

BARS-Barnes Akathisia Scale

BAS-Burden Assessment Scale

BC -Before Christ

BDNF- Brain-Derived Neurotrophic Factor

BP-Bodily Pain

BPRS-Brief Psychiatric Rating Scale

BSI-Brief Symptom Index

CBT-Cognitive Behavioural Therapy

CDS-Calgary Depression Scale

CGI-S- Clinical Global Impression-Scales

CGI-S-SCA-Clinical Global Impression of Severity for Schizoaffective Disorder

CHR-Clinical High Risk

CI-Confidence Interval

CIAS-Cognitive Impairment Associated with Schizophrenia

CINAHL- Cumulative Index to Nursing and Allied Health Literature

COA-Common Objects and Activities

CoFAMS-Cognitive Function and Mood Study

CoFAPSS-Cognitive and Functional Assessment of Psychosis Stratification Study

Cogtest= Cognitive Battery Test

CR- Cognitive Remediation

CRP- C-Reactive Protein

C-SSRS-Columbia-Suicide Severity Rating Scale

CTQ-Childhood Trauma Questionnaire

DAFS-Direct Assessment of Functional Status

DAI-Drug Attitude Inventory

DALYs-Disability Adjusted Life-Years

DIA-Data Independent Acquisition

DIEPSS-Drug-Induced Extrapyramidal Symptoms Scale

DNA= Deoxyribonucleic Acid,

DSM-IV- Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition

DSM-5- Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition

DSQ-Deliberate Self-harm Questionnaire

EuroQoL-European Quality of Life Scale

eQTL-expression Quantitative Trait Loci

FAST-Function Assessment Short Test

FFR-Full Functional Recovery

FILE-Family Inventory of Life Events

GAF-Global Assessment of Function

GH-General Perception of Health

GWASs-Genome-Wide Association Studies

HAM-A-Hamilton Anxiety Scale

HAM-D-Hamilton Depression Scale

HC-Healthy Controls

5HT2A-5-Hydroxy-Tryptamine (subtype 2A)

IAQ- Investigator's Assessment Questionnaire

ICD-11- International Classification of Diseases, Eleventh Edition

IF-Intrapsychic Foundation

IR-Instrumental Roles

ITT-Intention To Treat

JART-Japanese Adult Reading Test

LAI- Long Acting Injectables

LAI-A- Long-Acting Injectable Atypical Antipsychotics

LC-MS/MS-Liquid Chromatography-tandem Mass Spectrometry

LOFS-Strauss-Carpenter Levels of Functioning Scale

LPTR-The Lifetime Psychotropic Treatment Response Scale

LSM- Last Square Mean

MASC-Maryland Assessment of Social Competence

MCS-Mental Component Summary

MD-Mean Differences

MDD- Major Depressive Disorder

MH-Mental Health

MHF-Mental Health Functioning

MINI-Mini-International Neuropsychiatric Interview

MLDL-Munich Life Dimension List

MMN-Mismatch Negativity

MRM- Multiple Reaction Monitoring

MSQ- Medication Satisfaction Questionnaire

NAMES-New Antipsychotics Metabolic Evaluation Scale

PANSS- Positive and Negative Symptom Scale

PDQ-5-Perceived Deficit Questionnaire-five item

PEBL-Psychology Experiment Building Language

PF-Physical Functioning

PGI- Patient Global Impression Scale

PGS-Polygenic Scores

PICOS- Population, Intervention, Comparison, Outcomes, and Setting

POM-Preference of Medicine Questionnaire

PP- Paliperidone Palmitate

PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSP-Personal and Social Performance Scale

PSS-Perceived Stress Scale

QLS- Heinrichs-Carpenter Quality of Life Scale

QoL- Quality of Life

QWBS-Quality of Well-Being Scale

RAH-Royal Adelaide Hospital

RBANS-Repeatable Battery for the Assessment of Neuropsychological Status

RCTs-Randomized Controlled Trials

RNA- Ribonucleic Acid

ROC-AUC-Receiver Operating Curve- Area Under Curve

RP-Role limitation due to Physical Problems

RSQ-Relationship Style Questionnaire

RTP-Research Training Program

SADS-L-Schedule for Affective Disorders and Schizophrenia Lifetime

SANS-Scale for Assessment of Negative Symptoms

SARS-Simpson–Angus Rating Scale

SAS- Social Adjustment Scale

SCT- Social Cognition Training

SCWT-Stroop Colour Word Test

SD-Standard Deviations

SDS-Schedule for Deficit Syndrome

SECT-Social Emotional Cognition Task

SF-Social Functioning

SF-36-Short Form Health Survey-36 items

SIGH-AD- Structured Interview Guide of the Hamilton Anxiety and Depression Scale

SLOF-Specific Level of Functioning

SMD-Standardized Mean Difference

SOF- Scale of Functioning

SOFAS-Social and Occupational Functioning Assessment Scale

SQLS-R4- Schizophrenia Quality-of Life Scale Revision 4

SSPA-Social Skills Performance Assessment

SVAS-Sleep Visual Analog Scale

SVL-Supported Vector Learning

SWN-S-Subjective Well-being Under Neuroleptic Treatment-short version

TAAR-Trace Amine–Associated Receptors

TAU- Treatment As Usual

TMS- Trans Magnet Stimulation

TOS-Test of Significance

TRS-Treatment-Resistant Schizophrenia

TSQM-Treatment Satisfaction Questionnaire for Medication

UCSDUPSA-B-University of California San Diego Performance-Based Skills Assessment-Brief

WAIS-IV-ACS-Wechsler Adult Intelligence Scale Advanced Clinical Solutions Package

WGCNA-Weighted Gene Co-expression Network Analysis

W-QOLI-Wisconsin Quality of Life Index

Chapter 1

Introduction and Thesis Outline

Historical perspective on schizophrenia

A historical perspective is presented on schizophrenia to provide a background on the diagnosis, treatment, and psychosocial outcome of the illness. With the description of the historical evolution of the illness, we hope to improve the understanding of the origin and scientific progress that are related to the pathogenesis, treatment and outcome of the disorder, and how major definitions or ideas about the illness (especially those related to functional outcome) have emerged.[1] For example, the knowledge about diagnosis, pathogenesis and treatment of schizophrenia is important to provide appropriate contexts for understanding deficits in psychosocial function and the progress made to understand the factors that impede or promote improvement in psychosocial function (recovery) in people with schizophrenia.

The term "schizophrenia" was coined from two Greek root words — "schizo" (split) and "phrene" (mind) — in 1911 by a Swiss psychiatrist called Eugen Bleuler to capture the fragmented thinking that is characteristic of people with schizophrenia.[1-4] However, schizophrenia is generally thought to be as old as humans.[1] Prior to Bleuler's description of "schizophrenias" as a group of disorders that are defined by *basic* (i.e., loosening of associations, ambivalence, and autism) and *accessory* (i.e., hallucination and delusions) symptoms, people with a similar pattern of illness were categorized by Emil Kraepelin (a German psychiatrist, 1856-1926) as suffering from *"dementia preacox"*, characterised by severe cognitive and behavioural decline based on longitudinal observations of several patients.[3,4,5] Existing records also showed that psychotic disorder with features similar to schizophrenia was described in written documents in the old Pharaonic Egypt, as far back as the second millennium before Christ.[1,2] Other ancient reports including the Yellow Emperor's Classic of Internal Medicine (a popular Chinese text) written approximately 1000 BC, the Atharva Veda (one of the four Hindu Vedas) dated around 1400 BC and the Book of Hearts, which is part of the Eber papyrus (an Egyptian medical papyrus of herbal knowledge dating to circa 1550 BC) contained a description of symptoms, treatment and outcome of mental disorders similar to schizophrenia.[1]

In ancient times, mental disorders were poorly understood, and the aetiology, as well as the treatment of schizophrenia, was not well differentiated from other forms of mental illnesses,[6] much of which were adjudged to be supernatural in origin resulting from demonic or evil-spirit possession, punishment from the gods for sins and other related spiritual phenomena.[1-2]

Treatment during this ancient time was for the most part based on spiritual healing, exorcism, and sometimes trepanation as a means of letting evil spirits out.[2-3]

Since the beginning of the modern psychiatry era in the nineteenth century, the description of the symptoms, treatment and understanding of the clinical course of schizophrenia have improved as knowledge of the illness expanded. The identification and diagnostic classification of schizophrenia (and other mental disorders) improved with a deeper knowledge of the pathogenesis, phenomenology, and treatment of the illness.[1-3] Several major milestones regarding the evolvement of the concept of schizophrenia since the nineteenth century are described to better highlight the developments in the field. In addition to describing schizophrenia as a distinct disorder, Bleuler acknowledged the presence of clinical subgroups of schizophrenia, including paranoid, catatonia, hebephrenia, and simple.[5] During the decades ensuing the Bleulerian contributions to the understanding of schizophrenia, experts in clinical psychiatry proposed sub-nosological categories of schizophrenia, including schizoaffective disorder,[7] schizophreniform psychoses,[8] process-nonprocess,[9] and paranoid–nonparanoid schizophrenia to capture the heterogenous phenotypes in individuals diagnosed with schizophrenia.

In the 1950s, Kurt Schneider highlighted a group of nine psychotic symptoms called “first rank symptoms” as having decisive weight in the diagnosis of schizophrenia. On account of the reliability of eliciting these first-ranked symptoms, they were incorporated into diagnostic schedules and the Research Diagnostic Criteria to promote diagnosis.[10] However, subsequent evidence reported that these symptoms were not predictive of the severe deterioration in psychosocial function and cognitive deficits observed in individuals with schizophrenia.[5] In fact deficit in psychosocial function and efforts to promote recovery are major issues that have garnered much scientific attention across the history of the illness.[5]

Functional recovery became an important goal for treatment, a target for assessing the effectiveness of treatment and the drive for proposing the recovery model for people with schizophrenia.[3-5,8,11] The recovery model underscored the need for a subjective experience of hope, optimism, empowerment, and support for functioning and interpersonal relationships in people with schizophrenia through the creation of positive and recovery-oriented services.

Clinical diagnosis of schizophrenia and epidemiology

Currently, schizophrenia is described as a complex mental illness characterized by a constellation of features, including positive (i.e., delusions, hallucinations, and disorganized behaviour) and negative (blunted affect, alogia, avolition, asociality, and anhedonia) symptoms, albeit there is a wide variation in the expression of symptoms and signs.[11,12] Moreover, several iterations of the diagnostic manuals (Diagnostic and Statistical Manual of Mental Disorder [DSM] and International Classification of Diseases [ICD] now in fifth and eleventh editions respectively) have been developed and revised based on contemporary knowledge to allow structured classification and reliable diagnosis of mental disorders, including schizophrenia.[13, 14]

According to the Diagnostic and Statistical Manual of Mental Disorder, fifth edition (DSM-5), schizophrenia is "defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behaviour (including catatonia), and negative symptoms".[13] Similarly, the International Classification of Diseases, eleventh edition (ICD-11) indicated that schizophrenia disorder is characterized by significant impairments in reality testing and behaviour changes as manifested by symptoms such as delusions, formal thought disorder, hallucinations, and disorganized behaviour.[14] Other common features documented include abnormal motor behaviour, and cognitive impairment.[13,15] Compared to earlier versions, the dimensional classification was proposed in DSM-5 and ICD-11 to describe schizophrenia as a spectrum disorder, highlighting the variability in symptom severity along a continuum in patients.[16]

The prevalence rate of schizophrenia varies across settings due to clinical and methodological factors, such as an overlap in its clinical features with other mental disorders, and the variability in diagnostic criteria.[13,14, 17] However, there is consensus that the prevalence rate of schizophrenia approaches about one per cent internationally, and slightly higher in males compared to female.[14, 18] The modal age of onset is between 18 to 25 and 25 to 35 years in males and females respectively.[18] While evidence from previous studies suggests a more favourable prognosis in females compared to males,[19-21]schizophrenia is among the top 15 causes of disability globally.[24] See Table 1 below for some epidemiological indices on schizophrenia derived from literature and a recent estimate of the global burden of diseases.[16, 24]

The clinical management of schizophrenia is life-long, often requiring maintenance treatment to prevent relapse, sustain symptom remission and enhance recovery.[25, 26] Embedded in the clinical guidelines for the treatment of schizophrenia is an emphasis on correct diagnosis, symptom remission (defined as the absence or presence of mild severity of any of the central clinical symptoms, including positive, negative, and disorganized symptoms of the illness), rational use of medications to minimize side effects, and the promotion of optimal recovery of social function.[27, 28] The treatment modalities for people with schizophrenia can be broadly grouped into pharmacotherapy, psychosocial therapy and cognitive therapy. These treatment modalities are optimised and a combination of these treatments can be indicated in many cases to enhance functional recovery. [27-31.] The goal of treatment in people living with schizophrenia has shifted from a paradigm that is focused on "symptomatic remission" to a more patient-centric meaningful goal of "recovery".[29-32] Recovery is construed as the achievement or restoration of independent living, vocational or educational activities, and satisfying interpersonal relationships.[30-32]

Types of treatment for people with schizophrenia

Treatment of schizophrenia is often multimodal including:

Pharmacotherapy: Individuals with schizophrenia are treated with antipsychotic medications, broadly classified into first- (typical) and second-generation (atypical) antipsychotic medications.[27-34] The mechanism of action of typical (e.g., chlorpromazine, haloperidol, and fluphenazine among others) antipsychotics is mainly via anti-dopaminergic (D2) receptor blockage, while the atypical (e.g., olanzapine, risperidone, paliperidone, and aripiprazole) act on other receptors (e.g., serotonergic) in addition to D2 receptors to cause their antipsychotic effects.[29-33] Antipsychotic medications, especially the second-generation antipsychotics are recognized as first-line treatments for people with schizophrenia.[27-31] While the typical antipsychotic medications (e.g., chlorpromazine, haloperidol, and fluphenazine among others) have proven efficacy and are used for the treatment of schizophrenia, their use is now less common due to side effects, particularly extrapyramidal side effects.[23, 28] The biological basis of the beneficial effects of pharmacotherapy on psychosocial function is not fully understood,

however, antipsychotics are thought to be neuroprotective against the cytotoxic effects of active psychosis.[33] Moreover, psychosocial function worsens with a longer duration of untreated psychosis and frequent relapses. Additionally, performance-based skills decline with the disruption of social relationships, unemployment and institutionalisation resulting from relapses or chronic illness.[32-34]

Taking all these points together, adherence to antipsychotics through relapse prevention can confer functional recovery. The efficacy of long-acting antipsychotics for symptom remission and relapse prevention is thought to be the core explanation for their benefits on functional outcomes, albeit more research (including naturalistic and trial studies) is needed to better understand the longitudinal effects of antipsychotics on psychosocial function.[32-35] The effects of antipsychotics on psychosocial function in individuals with poor response to treatment also require further exploration.

Psychosocial therapy: Psychosocial interventions (such as psychosocial rehabilitation, illness self-management training, and family support) are recommended as adjunct treatments in clinical practice guidelines to enhance recovery.[27-35] Psychosocial treatment and social skills training are currently in use as adjunct strategies with pharmacotherapy to improve functional outcomes.[27-31] These therapies are particularly important among individuals with poor response to the trial of antipsychotics, especially those with a degree of diminished cortical reserve that limits their margin for response to treatment.

Cognitive therapy: Several treatment modalities, including cognitive behavioural therapy (CBT), cognitive remediation (CR), and social cognition training (SCT) are currently in use as adjunct strategies to improve outcomes.[28-30] In cognitive behavioural therapy sessions, unwanted feelings or problematic behaviours are targeted by teaching strategies to modify and respond to them differently.[36] Furthermore, therapy sessions can be designed to help people with schizophrenia develop better social and problem-solving skills, reduce the severity of symptoms, and reduce the risk of relapse.[30,36] In their paper, Laws et al.[36]reported that cognitive behavioural therapy showed therapeutic benefits on functional outcomes and distress in people with schizophrenia at the completion of the included trials. Compared to CBT, cognitive remediation is “a behavioural training-based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goals of durability and

generalization".[37,38] On the other hand, SCT aims to ameliorate deficits in social interaction to improve functioning through practising with social stimuli (e.g., pictures) and the use of learning strategies to cope with these deficits (e.g., verbalizing salient emotional features). Optimally, SCT is aimed to improve the cognitive processes involved in understanding social situations and other people.[39]

In addition to the effective use of the above-mentioned treatment modalities, some important concepts in the care of people with schizophrenia include early intervention, treatment of physical health, cultural considerations, and improvement of vocational-psychosocial outcomes.[27-31] All of these are directed at achieving recovery that entails optimal management of symptoms towards achieving remission and regaining of psychosocial function, lasting for a sustained period (some authors have suggested a period of two to five years) depending on the studies[39-42]

Psychosocial functional outcome of schizophrenia

The efficacy of antipsychotic treatment to cause symptom remission is well established in people with schizophrenia, however, recovery of psychosocial function is still variable.[28-33] Impairments in psychosocial function in patients with schizophrenia have been linked with an array of deficits in socio-occupational and personal function, leading to different degrees of disability. [10,12, 20] Economically, these deficits in psychosocial function are attributed to direct (related to treatment) and indirect (related to loss in productivity) costs of schizophrenia, estimated to be worth billions of dollars in an annual estimate in Australia (1.44 billion Australian Dollars), United States (62.7 billion United States Dollars), Canada (2 billion Canadian Dollars) and United Kingdom (2.6 billion Great Britain Pounds).[41-45]

Multiple factors (e.g., cognitive deficits, illness symptoms, psychological events, medications, number of episodes, and neural circuit deficits) have been linked with psychosocial deficits in schizophrenia.[46-49] Importantly, converging lines of evidence have highlighted cognitive deficits as a central determinant of treatment response and functional outcome in people with schizophrenia.[46-48] In addition to cognition, clinical or illness-related, socio-economic and biological factors have been correlated with functional outcome.[48, 49] Notably, these factors individually were not accountable for a major proportion of variance in functional outcomes in patients with schizophrenia.[46,49,50] A succinct overview of the relationship between functional

outcome and some of these identifiable factors (cognition, clinical and biological) are provided below (See Figure 2 for a multivariate model).[51-53]

Cognition: Cognitive dysfunctions across multiple domains have been described in people with schizophrenia, and linked with poor functional recovery despite treatment and clinical remission.[51,52] Recent explanatory models consider cognitive dysfunctions as a feature of psychosis, which could predate the hallmark clinical symptoms and psychosocial outcome.[53-55] Cognitive deficits may be present from the early phase of schizophrenia and linger through the course of the illness, impacting functional status and response to treatment.[55] Majorly, deficits in executive functions, working memory, planning, processing time, social cognition and abstract reason have been reported in severe psychosis with various degrees, shades and combinations of these deficits previously fielded in different studies.[55-57] These deficits in cognition have provided some of the best evidence for the inability of people with psychosis to attain 'normal' landmarks in productivity, residence, personal or self-care, occupational roles and social functioning after the onset of illness.[47, 58,59] In fact, previous works have described the contributions of cognition to global function across a variety of measures, including Global assessment of function (GAF), Clinical Global Impression-scales (CGI-S), Specific Level of Functioning (SLOF) and Assessment of Lifespan Functioning Attainment (ALFA) among others.[46, 48, 58-60] Notwithstanding, there is a need for better knowledge on the relationship of cognition with specific aspects of functional deficits to promote targeted intervention. In recognition of this, there is emerging evidence of targeted metacognitive therapy to address specific aspects of function using novel approaches and technology.[61-64]

Clinical factors: Several clinical factors including illness symptoms, psychological events, medications, number of episodes and length of untreated illness among others have been correlated with functional outcome in schizophrenia.[46,55,60] Earlier studies indicated that atypical antipsychotics, a lower dose of medications, and lesser symptom severity were predictive of improved functional outcome in cohorts with schizophrenia. However, few of these studies reported that clinical factors alone could not account for a large percentage of the variance observed in the outcome.[46,55,57,65] In a multivariate analysis conducted by Joseph et al.,[46] exploring the relationships between individual clinical symptoms and functional status, only 11% of the variance in functional outcome was explained by clinical factors. Further, other findings

include a stronger link between illness symptoms and cognitive functions with social function[46,55, 66] and a history of psychoactive drug use correlated with poor functional outcome.[46,67]

Biological factors: While this is outside the scope of this thesis, it is suffice to note that there is a body of evidence linking neurodevelopmental and neural circuit deficits in the cortical regions of the brain with impairment in cognitive and psychosocial function in people with schizophrenia.[57,68] For example, biological markers, including blood-based markers (such as brain-derived neurotrophic factor [BDNF], and C-reactive protein [CRP] etc.) and electrophysiology markers are increasingly used to explain the neurobiological processes underpinning functional outcome in psychosis.[55,69] Electrophysiological markers including TMS-induced neuroplasticity and Event- Related Potentials (including Mismatch negativity [MMN], N100, N400, P3a, and P300) have been shown to have promising explanatory roles for the pathophysiology underpinning response to treatment and prognosticating functional outcome. In particular, established correlations, as well as mediating effects, have been shown between measures of early auditory information processing (including MMN, P3a and reorienting nativity) and functional outcome in schizophrenia.[70,71] For example, Lee et al., [70] found MMN to be a stronger predictor of functioning than neurocognition in a sample of patients with schizophrenia. Further, blood and electrophysiological markers are gaining traction in studies aimed at validating the existing biological signature of treatment response and functioning.[53,67,69] In fact, changes in brain connectivity, synaptic neurotransmission, level of biomarkers (BDNF or CRP) and neuroplasticity are thought to play a role in treatment response, functional outcome and constitute common targets for novel treatments.[70,71] It is therefore not surprising that increasing attention is currently paid to investigating the roles of electrophysiological markers in explaining the relationship between cognitive and functional outcome.

Multi-variate explanatory models for functional outcome: Several clinical, neurocognitive, and biological factors have been highlighted as correlates of functional outcome in psychotic disorders, including schizophrenia,[53, 68] and some of these factors are identified as candidate predictors with prognostic utility in modelling.[68, 71-73] However, observational studies focusing on such individual predictors have yielded results with small effect sizes, thus validating the need for multivariate modelling.[53,68,70] In their study, Schubert, Clark & Baune[53] demonstrated the

benefits of a putative model for predicting functional outcome and illness trajectory using the combination of multimodal predictors in patients with schizophrenia (See Figure 1). The model proposed that the combination of data on multiple predictors (e.g., clinical, demographic, structural and functional imaging, electrophysiological and cognitive) compared to a single predictor may better inform the prediction of distinct illness trajectories and functional outcome clusters that were previously described in many long-term follow-up studies (summarized into four groups A, B, C, D).[53] In the model, group A were individuals who experience full functional recovery (FFR) and remained stable in the long term after a period of a psychotic episode. Group B are individuals with multiple exacerbations of their psychotic illness and/or poor functioning over the course of the illness, but achieve FFR in between these illness episodes. In group C are individuals who demonstrated recurrent exacerbations and some enduring functional deficits between their illness episodes. Individuals in group D are characterized by severe and enduring functional impairment early around the onset of their illness.[53] The translation of such a model on predictors of functional outcome in schizophrenia can enhance better clinical decisions and individualization of care. Hence, we applied the foundational principle proposed in the above work[53] in this thesis, investigating the relationship of clinical, sociodemographic and cognitive factors with psychosocial function utilizing primary data from people with schizophrenia. The analyses and data presented in the original work are also informed by the findings in two meta-analytic reviews. For example, we tested the relationship between psychosocial function and cognitive function and illness severity in the empirical studies considering that the two reviews highlighted them as predictors of psychosocial function.

Structure and outline of the thesis

We recognize that extant literature has indicated limitations in addressing functional impairments associated with schizophrenia. Such that, a significant proportion of patients with schizophrenia contend with functional deficits despite recovery from clinical symptoms.[29,30,35] Closely linked is that global functional outcome has been correlated with several factors (including clinical, demographic and cognitive) but largely unpredictable as findings on current individual factors could not account for a large percentage of the variance in functioning in schizophrenia.[46,61,63] Hence, this thesis examined functional status in patients with schizophrenia using a multi-

dimensional construct of psychosocial function (that includes multiple domains of basic-daily function, socio-occupational function, interpersonal relationships, adaptive function, life satisfaction and subjective wellbeing/quality of life) to generate a comprehensive information on specific patterns of psychosocial deficits in patients and promote evidence-informed personalized care. Furthermore, we investigated the predictors (focusing on socio-demographic, clinical and cognitive factors) of functional outcome which in turn could translate into better clinical assessments and evidence-guided treatment. Individuals with schizophrenia were compared with those with major depression and healthy controls to improve the robustness of the analysis and explore the potential of transdiagnostic application of the findings on functional status and its predictors.

Specifically, we pursued a thesis by publication format taking into consideration the contributions of two published meta-analytic papers, a methodological publication on the Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS)[74] and two empirical studies (in pre-publication paper format) prepared from the cross-sectional analysis of data collected on individuals with schizophrenia or schizoaffective disorder from CoFAPSS. We completed two meta-analytic syntheses of existing literature, assessing the impacts of treatments on functional outcome in people with schizophrenia, and presented the predictors of functional outcome that were reported from gold standard clinical trials in schizophrenia. The information from these two meta-analytic studies was utilized to refine the aims and analysis conducted in two original clinical studies that are included in this thesis. The clinical studies utilized primary data from CoFAPSS to assess and describe the links between symptoms, cognition and functional status/quality of life (QoL) in schizophrenia compared to individuals with major depressive disorder (MDD) and healthy controls (HC). Data on MDD and healthy controls are derived from the Cognitive Function and Mood Study (CoFAMS)[75], a sister study that shared similar measures and methods with CoFAPPS. Specifically, we contrast the commonalities and differences in psychosocial function in schizophrenia versus MDD and HC. In chapters 5 and 6 a novel transformation of general symptom severity was conducted to allow comparison of illness severity (a measure of symptom load) across these disorders-schizophrenia and major depression.

Importantly, the thesis is divided into seven chapters. **Chapter 1** provides a background to the thesis and included the historical evolution of schizophrenia, and a general description of clinical diagnosis, treatment, and psychosocial outcome, outlining the central importance of multi-dimensional function. This chapter provides a broad introduction for the rationale and subsequent chapters of the thesis. In **Chapter 2,** we presented findings from a systematic review and meta-analysis of clinical trials to pool the benefits of long-acting antipsychotic medications compared to placebo and oral medications on functional outcome in patients with schizophrenia. The study presented findings on the longitudinal effects of long-acting atypical antipsychotics on measures of psychosocial function compared with placebo or oral antipsychotic medications among people with schizophrenia. We also consider the predictors of change in psychosocial function included in the primary studies. Importantly, we operationalised psychosocial function using a multi-dimensional construct (that includes multiple domains of basic-daily function, socio-occupational function, interpersonal relationships, adaptive function, life satisfaction and subjective well-being/quality of life) and described predictors of functional outcome described in the trials. Notably, this chapter describes the benefits of long-acting injectables (LAI) in the care of patients with schizophrenia. In particular, depot medications confer functional recovery through relapse prevention via better adherence.[9] Furthermore, atypical LAIs have been linked to good subjective well-being and life satisfaction, which can in turn enhance social adaptation, autonomy, and psychosocial function.[30,31] Atypical LAIs are also recommended in practice guidelines as the first-line choice for maintenance treatment in non-adherent patients with schizophrenia, an important clinical group.[31] There was high variability in measures used but we found that atypical LAIs are effective with moderate effect size over placebo to improve function but with only a small effect size over oral antipsychotics. This small difference is associated with variability in treatment as usual in some of the trials. The predictors of poor function in the studies included in the review were severe symptoms, cognitive impairment, and poor insight.

Chapter 3 represents a replication of the methodology implemented in Chapter 2 focusing on patients with treatment-resistant schizophrenia (TRS) who were on clozapine therapy. Importantly, patients with treatment-resistant schizophrenia are an important clinical sub-group that often experiences severe psychosocial impairment and disability. The use of the multidimensional construct of psychosocial function allowed the inclusion of composite measures of patient's personal experience, supporting such construct as more reliable, valid,

comprehensive and holistic indicators of functional status.[43] We systematically reviewed the literature to complete a meta-analytic synthesis of the findings in clozapine clinical trial reports on functional outcome in schizophrenia compared to other medications. Notably, the paper reported a limited improvement in psychosocial function in individuals with TRS in clozapine trial studies. In addition, a comprehensive description of the predictors of psychosocial function in patients treated with clozapine was provided. The predictors associated with poor functional outcomes for clozapine treatment included the severity of illness, illicit drug use, extrapyramidal side effects, gender and cognition can help predict those who may benefit from clozapine coupled with intensive psychosocial therapies. These meta-analytic chapters provided the necessary scientific evidence on current evidence in the field to refine the hypothesis tested in the empirical studies.

This is followed by **Chapter 4** where the description and rationale of the Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS) were provided. The chapter provided comprehensive information on the methodology of the naturalistic study that provided the data on patients with schizophrenia analysed in the empirical studies contained in the following two chapters**.** The CoFAPSS study was specifically designed to identify predictors of functional outcome in psychotic illness.[74]

In **Chapter 5,** we presented a case-control study, exploring commonalities and differences in the range and nature of functional deficits in patients with schizophrenia compared with MDD and healthy controls (HC). This comparison is premised on the knowledge that impairment in psychosocial function is also common in mood disorders, especially MDD. We hope that the comparative analyses of deficits in psychosocial function between schizophrenia and MDD can help improve current knowledge on the differences and overlap in the pattern and variability in impaired functions in individuals with schizophrenia compared with individuals with MDD. To allow this comparative analysis, a novel method was implemented to standardize symptom burden by generating illness severity in patients with schizophrenia and MDD adapting the method previously described by Leucht et al[74,75] In this chapter, we compared multiple aspects of functional status and quality of life in patients with schizophrenia with MDD and healthy control considering variability in illness severity, age, years of education and sex. In recognition of the importance of cognitive process in psychosocial function, **Chapter 6** expands on the analysis of

chapter 5, focusing on the variation due to multiple aspects of cognitive deficits across schizophrenia, MDD and controls. Importantly, the chapter examined the main and mediation effects of multiple aspects of cognition on the relationship between illness severity and functional outcome/QoL trans-diagnostically. We found that individuals with schizophrenia showed the most severe form of deficits across all the measured aspects of cognitive function, functional status and QoL followed by patients with MDD compared to HC. Furthermore, while there was main effect of attention on QoL, deficits in multiple aspects of cognition showed an indirect effect on psychosocial function, mediating the effects of illness severity on functional status and QoL.

Lastly, **Chapter 7** concluded this thesis with a general discussion of our findings and study limitations. The thesis was concluded with a discussion of future perspectives and recommendations to inform novel research to extend the field. For example, we highlighted the need for standardized measurement and reporting of psychosocial function using an optimum construct, preferably one that is multidimensional and evidence-based. This will enhance comparative analysis in future meta-analyses or network meta-analyses. Similarly, drug discovery research to develop a more effective treatment for people with schizophrenia remains a critical area of scientific enquiry. Effective treatment should be informed by the evidence on the predictors of good response and functional outcome. In this regard, recent advancements in computer and data science provide opportunities to combine markers in novel ways to address the current limitations of prediction models. Finally, there is a need for policy actions and scalable programs to support social integration and functional recovery of individuals with schizophrenia

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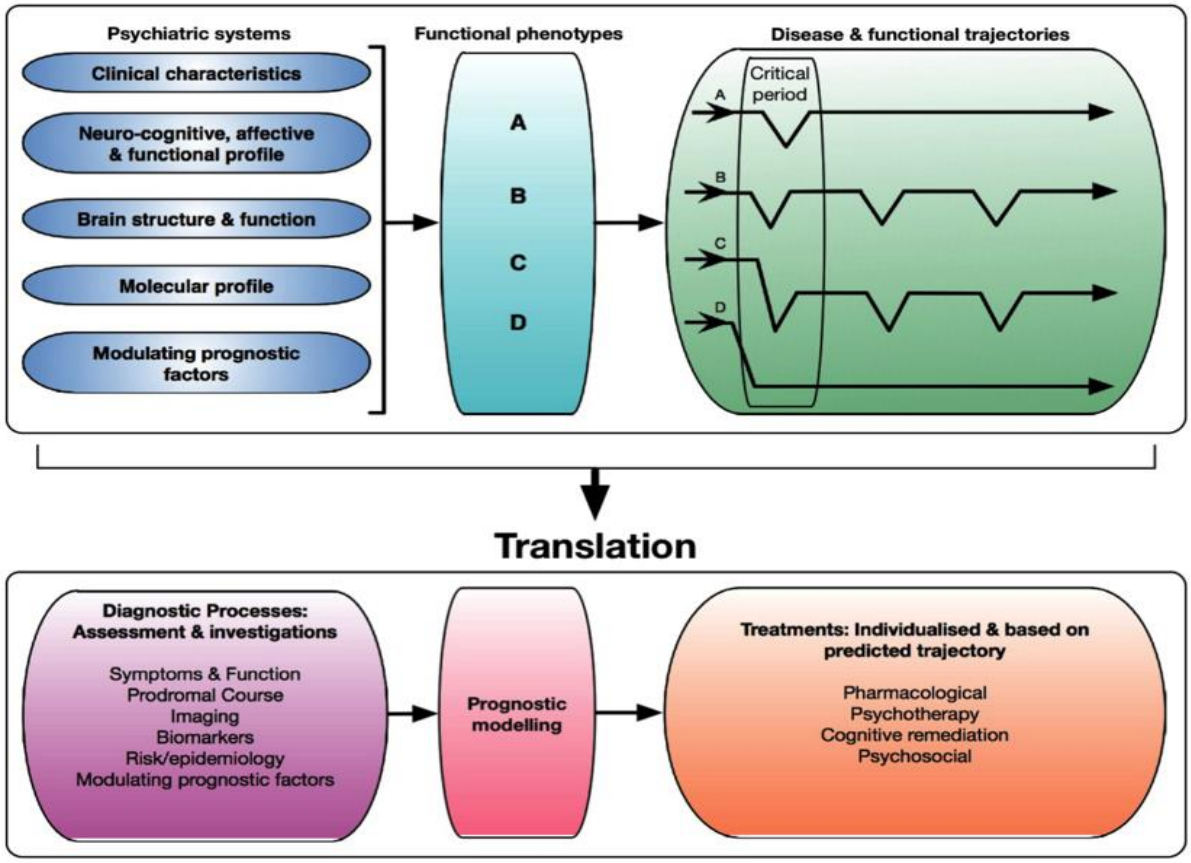
Table 1: Epidemiological indices on schizophrenia

Epidemiological indices	Values/Rates	Male versus Female
Incidence (Global)	1 289 832[24]	699 770 versus 590 062[24]
Prevalence (Global)	≈24million[12,13,24]/≈1%[31]	12 393 169 versus 11 203 877[24]
	23 597 047 individuals	
Life-time prevalence	4-7/1000 individuals[16, 23]	1.4 versus 1[25]
Life-time risk	7.2/1,000 individuals	30–40% higher in males[25]
Disability Adjusted Life Years	15 107 248 [24]	8 030 432 versus 7 076 815[24]

Incidence, prevalence and disability adusted life years (DALYs) data are represented per millions

Figure 1: Diagrammatic representation of multimodal modelling of outcome in Psychosis.



(Schubert, Clark & Baune[53])

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Overall percentage (%)	70%		
Certification:	This paper reports on the meta-analytic research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Chapter 2

Long-acting atypical antipsychotics in schizophrenia: A systematic review and meta-analyses of effects on functional outcome

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Abstract

Objective: Impairment in psychosocial function is common in schizophrenia. Long-acting injectable atypical antipsychotics (LAI-A) are thought to enhance psychosocial function by boosting adherence. However, no systematic review has examined the effects of LAI-A on psychosocial function in clinical trials.

Methods: We searched major databases including Medline/PubMed, PsychINFO, EMBASE, CINAHL, Scopus, Web of Science, Cochrane Central Register of controlled trials and clinical trial registries for randomised controlled trials that compared LAI-A to placebo, oral antipsychotic medications or LAI-A for all years till 2018, with no language limits. We performed a systematic review of findings on change in psychosocial function and its predictors in the included reports. Data on change in psychosocial functioning were meta-analysed using a random effects model.

Results: Twenty-six studies were included in systematic review, and nineteen studies with 8616 adults, 68.1% males were meta-analysed. LAI-A were superior to placebo (standardized mean difference [SMD] =0.39, 95% Confidence Interval [CI] =0.32, 0.47; $p<0.001$; $I2=0\%$, nine studies) and oral antipsychotic medications (SMD= 0.16; 95% CI= 0.01, 0.31; $p=0.04$; $I2=77\%$, ten studies) for improved psychosocial function and superiority was maintained in short and long trials. Poor psychosocial function was predicted by longer treatment duration, severe symptoms, poor cognition, and poor insight. Functioning was assessed by either a single or a combination of measures, but was not the primary outcome in most studies. Other sources of bias include poor blinding and reporting of randomization.

Conclusion: LAI-A are beneficial for recovery of psychosocial function in comparison to placebo, but the magnitude of superiority over oral antipsychotic treatment was small. Severe psychopathology at baseline predicted poor psychosocial function. Future effectiveness trials in which post-randomization involvement is kept to a minimum, and psychosocial function is included as primary outcome a priori are needed to capture the real-world impact of LAI-A and to address methodological biases**.**

Introduction

Functional impairment is a major problem in schizophrenia. Globally, the disorder was estimated to account for 222·3 million disability adjusted life-years [DALYs] in 2016.[1,2] Functional deficit is a core feature in the diagnosis and course of schizophrenia which can persist beyond hallmark clinical symptoms and impact negatively on prognosis.[3,4] While there is strong evidence for the efficacy of antipsychotic medications in treating psychotic symptoms, functional improvement is more variable and does not necessarily require complete symptom remission.[5]

Medication adherence is key to symptomatic and functional recovery,[6] and relapse rates are high following cessation of oral antipsychotics or partial adherence.[7,8] Non-adherence is, however, common in schizophrenia, with discontinuation rates ranging from 44% within one year after first episode,[9] and as high as 74% over longer periods.[10,11]

Long-acting injectable [LAI] antipsychotic formulations are effective in reducing the rate of antipsychotic discontinuation,[12] and significantly lower the risk of relapse and rehospitalization.[13, 14] However, extrapyramidal side-effects and poor tolerability of conventional LAIs have limited their use and led to the development of second-generation LAI to improve adherence.[15] Since the introduction of LAI-Risperidone in 2003, several other long acting injectable atypical [LAI-A] formulations (including olanzapine, paliperidone, and aripiprazole) have been developed with differences in dosing flexibility, costs, pharmacodynamics-kinetics and side-effect profile.[16] Several theories have been proposed to explain the potential advantages of broader and early use of LAIs for schizophrenia. First, LAI use facilitates close monitoring of adherence which is particularly important in the early phases of psychotic illness.[12] Second, patients may prefer the longer dosing interval, and third, single dosing prevents the risk of self-medication and harmful use that can occur with oral preparations.[17, 18] Lastly, due to higher bioavailability and lower fluctuations in serum level,[19] the pharmacokinetics of LAIs may promote lower effective dosing to improve tolerability. However, evidence from clinical studies suggests that for most LAIs discontinuation rates due to side effects are similar to oral dosing.[20]

Although psychosocial function as a term is widely used in literature, there has been a lack of uniformity in its construct. The patient's wellbeing/quality of life (QoL) is not measured in some studies. More recently a multi-dimensional construct that includes both measures of daily function and subjective well-being/QoL is gaining support as a more reliable, valid,

comprehensive and holistic indicator.[21-26] Thus, in this present study we used a multi-dimensional construct of psychosocial function that includes multiple domains of basic-daily function, socio-occupational function, interpersonal relationships, adaptive function, life-satisfaction and subjective well-being/QoL.

The biological basis of psychosocial function is yet to be well understood, however antipsychotics are thought to be neuroprotective against the cytotoxic effects of active psychosis.[27, 28] Psychosocial function is known to worsen with frequent relapses or longer duration of untreated psychosis. In addition, performance-based skills decline with the disruption of social relationships, unemployment and institutionalization following relapses or chronic illness.[29] LAI-A may therefore confer functional recovery through relapse prevention via better adherence.[9] Further, LAI-A have been linked to good subjective wellbeing and life satisfaction, which can in turn enhance social adaptation, autonomy, and psychosocial function.[30,31] Atypical LAIs are now recommended in practice guidelines as first-line choice for maintenance treatment in non-adherent patients.[32-34]

While the efficacy of LAI-A for symptom remission and relapse prevention is well established, the functional benefit of these treatments has not been interpreted across clinical trials. The majority of comparative effectiveness trials of LAI-A versus oral medications are modelled on proxy indices of functional outcome including relapse rates and rehospitalization. These proxy endpoints are thought to be reliable to ascertain real-world functioning.[35] and have good face validity, however, hospitalization as an outcome translates poorly between differing healthcare contexts, does not capture patient's personalized experience and can be a negative therapeutic goal to end-users.[36]

The results of randomized controlled trials (RCTs) of LAIs versus orals for relapse and rehospitalization are mixed. Compared to RCTs, naturalistic studies are consistent in reporting LAI superiority, although they are not flaw-proof.[37] The impact of these study biases on functional outcome measures need to be considered individually for all studies (RCT and observational) to appropriately interpret the benefits of LAI over oral treatment. In addition, experts have recommended effectiveness trials, in which post-randomization involvement (manipulation of trial-related factors including adherence such that the performance of intervention reflects ideal or well-controlled circumstances) would be kept to a minimum to

better reflect routine practice.[38, 39] Such novel trials can be informed by an analysis of study quality in existing trials using psychosocial function measures.

To summarize and interpret the impact of LAI-A on function, we conducted a systematic review and meta-analysis using a multidimensional construct for function ("psychosocial function") that includes multiple domains of basic-daily function, socio-occupational function, interpersonal relationships, adaptive function, life-satisfaction and subjective wellbeing/QoL.[25, 26] Critical appraisal of all included reports was performed to assess the quality of the implementation of standardized measures of psychosocial function. We also systematically reviewed factors predictive of improvement in function with LAI-A treatment to identify characteristics that could be used to guide the decision to commence LAIs. Our specific aims were to:

- Investigate the longitudinal effects of LAI-A on measures of psychosocial function among people with schizophrenia or schizoaffective disorders
- Compare the effects of LAI-A on measures of psychosocial function with placebo or oral antipsychotic medications
- Describe the predictors of change in psychosocial function included in primary studies
- Appraise the quality of measures of psychosocial function.

Methods

Materials and methods

Inclusion criteria

This systematic review was conducted in accordance with Cochrane collaboration guideline and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guideline.[40, 41] All literature till March 2018, with no language limits was searched for randomized controlled trials (RCTs) that compared LAI-A with placebo or active controls in people with schizophrenia or schizoaffective disorders. Eligible studies included adults 18 years or older of either gender that provided information on measures of psychosocial function. We included reports on placebo-controlled trials and open label active-controlled RCTs to improve

study power and to allow a comprehensive appraisal of the quality of psychosocial function measurement. Studies with flexible or fixed doses of LAI-A within the recommended therapeutic range for clinical efficacy were shortlisted.[42] Non-randomised controlled studies, and single arm prospective experimental trials were excluded.[43] Data concerning the predictors of functional outcomes was not consistent across studies and is described as a systematic review alone.

Outcome parameters

The main outcome was longitudinal change in psychosocial function associated with LAI-A treatment as defined in primary studies in comparison to placebo or oral antipsychotic medications**.** We indexed psychosocial function with study-defined multidimensional measures of domains of basic-daily function, socio-occupational function, interpersonal relationship, adaptive function, life-satisfaction and subjective wellbeing/QoL. The composite scores of the psychosocial function scales in the included studies were used. LAI-A controlled trials, designed to compare the efficacy of different LAI-A or of different doses of the same LAI-A were included only in systematic review. Further, we collected data on factors that predicted change in psychosocial function from the included studies.

Database search

We searched Medline/PubMed, PsychINFO, EMBASE, CINAHL, Scopus, Web of Science, Cochrane Central Register of controlled trials and clinical trial registries (http://clinicaltrials.gov/) for all studies (published and unpublished) to avoid publication bias. In case of PubMed, the terms used as string in combination to search in titles, abstract and as MeSH terms included (1) "Antipsychotic Agents" "Pharmacological Action", "antipsychotic" (2) "schizophren" OR "schizo" (3) "inject" OR "depot" OR "long acting" OR "delayed-action preparations" (4) "Quality of life" OR "Function". An additional search was done with the names and standard abbreviations of scales used to measure psychosocial function and QoL. The scales included; "global assessment of function", "Heinrichs-Carpenter QoL scale", "Short Form-36 Health Survey", "Personal and Social Performance scale", "Strauss-Carpenter Levels of Functioning" and "Social and Occupational Functioning Assessment". The clinical trial registration number was used to identify all published reports on each of the clinical trials for comprehensive extraction of data. References of included studies and relevant reviews were

snowball searched for additional studies. Authors of studies with missing data were contacted for further information.

ATO screened titles and abstracts of 1104 articles to produce a shortlist of 98 potential articles. The full texts of the selected articles were reviewed by ATO for eligibility as per the a priori criteria.

Data extraction and management

Data extraction was done by ATO independently using piloted forms based on the PRISMA guidelines, and included the PICOS data items (population, intervention, comparison, outcomes, and setting). Data extraction forms collected the following data: first author, funding source, study design; study country or sites, participants characteristics (age range, total number, gender, diagnosis and treatment setting), trial duration, antipsychotics (LAI-A versus controls), dosage, trial arms, measures of psychosocial function, clinical scales, findings on psychosocial function (baseline, endpoint and mean change), and identified predictors with statistical significance. During data collection, discrepancies were resolved through consultation with the senior author, BTB where necessary.

Assessment of quality of studies with risk of bias tool

We assessed the risk of bias within individual studies using the Cochrane Collaboration's methods for assessing bias in controlled clinical trials.[43] Bias assessments were conducted at both the study and the outcome levels, and included items as random sequence generation, allocation concealment, blinding of personnel, blinding of outcome assessment, incomplete data reporting, selective reporting and other sources of bias. The presence of possible publication bias was visually assessed from funnel graphs and included Egger's test.[43, 44]

Results synthesis and meta-analytic calculation

We performed both qualitative and quantitative analyses of psychosocial function but could only complete qualitative analyses for predictor variables. We compared LAI-A with placebo or oral antipsychotic medications on change in psychosocial function using standardized mean difference as the primary effect size. Analysis was conducted considering all time points, with data for the last outcome time point in each study used to calculate change from baseline. All

calculations were performed using Rev. Manager 5 software,[45] and meta-regression was done with STATA.[46] A p-value <0.05 (two-tailed) was considered statistically significant. Given the heterogeneity in the measures of psychosocial function, we used the generic inverse variance model and random effects to estimate the pooled standardized mean differences (SMD) of the included studies. If change score was not available, endpoint value was subtracted from baseline. We merged data from multi-arm trials using formula for combining groups and online calculators in Rev. Manager.[43] Missing standard deviations were estimated from test statistics and useable data from published scales based on Cochrane methodology.[47,48] Study heterogeneity was investigated using the sensitivity test and the chi-square test of homogeneity (p-value <0.05) together with the I^2-statistic. We considered values of 50% heterogeneity or higher non-negligible and looked for explanations in the included studies.[43, 49]

Subgroup analyses and meta-regression.

We conducted subgroup analyses for duration of trial, however analyses were limited due to one short-term oral-controlled trial. To check the effects of trial duration, we categorized studies into short term for trials not beyond three months and those greater than three months were grouped as long term.[50] We also performed subgroup analysis to assess any difference in functional outcomes for trials that used treatment as usual (TAU) with oral antipsychotics in comparison to LAI-A. We conducted meta-regression to check effects of study settings (outpatient versus in-patient), trial design, year of publication, industry sponsorship, baseline symptom severity and inclusion of psychosocial function as primary outcome in included trials.[51]

Results

Study selection

A total of 1631 publications were retrieved from all sources and 527 duplicates were removed. Abstracts and titles of the remaining 1104 reports were screened, and 98 full-text was shortlisted for review. Of these 98 full texts, 25 (containing 26 studies) were included while 73 were excluded due to non-RCT studies (n=46), duplicate data (n=16), absence of a validated functional measure (n=19), and wrong medications-antipsychotics (n=21). We used main reports where many articles published findings on same RCT (details of reports used for data extraction are included in supplementary S1). Overall, findings in 26 primary studies (one report contained

two RCT studies) were included in systematic review, 19 studies from both placebo and oral controlled trials were meta-analysed, and seven studies with information on predictors were systematically reviewed. Figure 1 presents a PRISMA- flow diagram.[40]

Study characteristics

The study characteristics are shown in Table 1 and supplemental table S2. All twenty-six studies were conducted from 2003 to 2016, and included 11097 participants with 67.1% males. Data on two trials were obtained solely from clinical trial registry [NCT00604279; NCT00992407] because there were no publications indexed to them. Thirteen studies reported double-blind RCTs including all the eight placebo-controlled studies, three LAI-A controlled studies and two oral-controlled study. Open label studies were mostly oral-controlled (n=8), and three studies were LAI-controlled. The mean trial duration was 53.52 (±9·05) weeks and ranged from eight to 130 weeks. Of the nine placebo-controlled studies, five were short term (duration ranged from 8-12weeks), while the remaining were long term (duration ranged from 14 to 52weeks). There were eleven oral-controlled trials, one[32] was short trial (12 weeks) and ten were long trials (duration ranged from 52 to 130 weeks). Concerning oral controlled trials, LAI-A were compared with oral atypical antipsychotics in eight trials, in two of which the choice of atypical was at investigator discretion.[52,53] Three trials compared LAI-A with treatment as usual (oral antipsychotic medications as per investigator discretion).[54-56] All six LAI-A-controlled (duration ranged from 24 to 52 weeks) studies were long term and compared LAI-A to different LAI-A (n=4) or different LAI-A doses (n=2). Out of twenty-six trials, one Korean, Japanese and Taiwanese trial each were single centre. Of the twenty-three multicentre studies, sixteen took place across several international centres and five solely in US centres.

Diagnoses of schizophrenia and schizoaffective disorder were based on DSM-IV criteria in all twenty-six studies. Most studies recruited participants with diagnosis of schizophrenia (n=16) compared to either schizophrenia or schizoaffective disorder (n=9) and only schizoaffective disorder in one study.[57] Most of studies enrolled both inpatients and outpatients (n=13) compared to studies with either out-patients (n=11) or in-patients (n=2) alone. In addition to DSM-IV diagnostic scales, thirty-seven other clinical scales were used to measure predictors of psychosocial function, including assessment of severity of illness using Clinical Global Impression scale (CGI) in twenty-four studies, the Positive and Negative Symptom Scale

(PANSS) in twenty studies and the Brief Psychiatric Rating Scale (BPRS) in two studies.[53,58] Extra-pyramidal side effects were assessed using both Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Scale (BARS) in nine studies, Simpson–Angus Rating Scale (SARS) in seven studies and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) in one study. A cognitive test battery (Cogtest) was assessed in four studies.

In twelve studies, LAI-Risperidone was compared with placebo (n=2), oral comparators (n= 7), and other LAI-A (n=3). LAI-Paliperidone was compared with placebo in four studies, and two each with orals and other LAI-A. Two studies compared LAI-Aripiprazole with placebo while one study each compared it with oral aripiprazole and with LAI-Paliperidone. One study each compared LAI-Olanzapine with placebo and oral olanzapine.

Seventeen different measures of psychosocial function were used across studies. Thirteen studies each used single and multiple scales. Personal and Social performance scale [PSP] was used in seventeen studies, Short Form Health Survey in six studies, Heinrichs-Carpenter QoL scale [QLS] in five studies, EuroQoL- in two studies, Global Assessment of Function [GAF] in three studies, University of California San Diego (USCD)-Performance-Based Skills Assessment-Brief [UPSA-B] and Social and Occupational Functioning Assessment Scale (SOFAS) in one study each. Only three studies assessed psychosocial function as primary study objective a priori. All the included studies were industry sponsored except two. [See Table 1a, b and c]

Assessment of quality of studies with risk of bias tool

The findings on study quality using the risk of bias tool are presented in figures 2 and S3. We included thirteen double-blind RCTs studies, eleven open labelled and two rater-blinder studies. All twenty-six studies were randomised but only eleven studies described the process of sequence generation for randomization including seven that used interactive web software, three that allocated by randomly permuted blocks, and one study by stratified lot. All participants were aware of treatment allocation in two studies. There was no confirmation of effectiveness of blinding in any of the twenty-six studies. While selective reporting was low in twenty-four studies, it was high and unclear in one study each. Incomplete outcome data was high in six studies due to early withdrawal, drop out from relapse and lack of efficacy, and low in the remaining twenty trials. Other bias was high in three studies, low in one study and unclear in the remaining trials. [See Figure 2]

Findings on outcome

Qualitative description of effects of LAI-A across studies on psychosocial function

Qualitative findings on effects of LAI-A on psychosocial function are presented in table 1. All the twenty six studies reported positive effects of LAI-A on longitudinal change in psychosocial function except three.[59-61] LAI-A superiority was reported in three oral-controlled and eight-placebo-controlled trials. Head-to-head comparisons of LAI-A were reported in six trials, and showed mixed results.[62-66] Data showing the clinical significance of LAI-A benefits on psychosocial function were reported in few placebo and oral-controlled trials. Findings varied across studies and between LAI-A and comparators. For example, in one study patients treated with LAI-Paliperidone with good functioning (PSP score >70) increased from 57.9% at baseline to 59.0% at endpoint, whereas there was reduction in the proportion of placebo-treated subjects with good functioning from 50.6% at baseline to 41.1% at trial endpoint. The difference between LAI-A versus placebo was significant.[57] In one oral-controlled trial, the proportion of patients treated with LAI-Paliperidone with good functioning (PSP score >70) increased from 6.4% at baseline to 36.7% at endpoint while those on oral antipsychotics with good functioning increased from 6.5% to 34.6% at endpoint.[56] Similarly, 19.2% of LAI-Olanzapine treated patients had a good level of functioning (QLS score ≥84.5) at baseline, which increased to 27.5% ($P<0.05$), while the figures for oral olanzapine were 14.2% and 24.5%, respectively.[6] In terms of clinically meaningful data, Rouillon et al.,[68] reported a five point increased in mean SOFAS score in patients treated with LAI- Risperidone. At trial endpoint, while SOFAS scores continued to represent serious impairment for patients treated with oral quetiapine, the scores improved from serious impairment at baseline to moderate functional difficulty at endpoint for patients on LAI-Risperidone.

Effects of LAI-A on psychosocial function compared to placebo

Figures 3-5 showed overall effects of LAI-A compared to placebo on psychosocial function. When the nine included studies were pooled, LAI-A treatment showed significant superiority in functional measures over placebo [SMD=0·39; 95% CI= 0·32, 0·47; $p<0.001$; nine studies, n=2862; I^2=0%]. Both short-term [SMD=0·39; 95% CI=0·28, 0·50; $p<0·001$; five studies, n=1430; I^2=0%] and long-term studies [SMD=0.40; 95% CI= 0·29, 0·50; $p<0·001$; four studies,

n= 1421; I^2=0%) showed consistent superiority of LAI-A over placebo with respect to improving psychosocial function. [See Figures 3, 4, and 5]

Effects of LAI-A on psychosocial function compared to oral antipsychotic medications

LAI-A superiority in total score on functional outcomes was reported in three oral-controlled trials.[53,54,6] Seven trials, Ascher-Svanum et al.,[67] Bai et al.,[32] Fleischhacker et al.,[60] NCT00992407, Rosenheck et al.,[55] Schreiner et al.,[56] and Wykes et al.,[52] reported no statistically significant difference in total functional improvement between LAI-A and orals. However, pooled effects of all the ten oral-controlled studies showed that LAI-A treated patients displayed a small but significantly greater improvement in functional outcomes compared to oral antipsychotic medications [SMD=0·16; 95% CI= 0·01, 0·31; p=0·04; ten studies, n=3540; I^2=77%], and this small advantage was maintained in all long-term trials when the short-term trial (Bai et al., 2016) was excluded [SMD=0.17; 95% CI=0.01, 0.33; p=0·03; nine studies; n=3490; I^2=79%] (See figure 6).

Effects of LAI-A across subdomains of the psychosocial scales

The majority of the studies did not report on subdomains of the functional scales used. Four studies reported positive change in QLS total scores among LAI-A and also published sub-domain data.[55,58,64,67] Compared to placebo, LAI-A showed significant improvement in three domains of QLS including intrapsychic functioning (adaptive function and life-satisfaction) instrumental roles (socio-occupational function) and interpersonal roles (interpersonal relationship) but no difference in common objects and activities (basic-daily function).[58] LAI-A Paliperidone and oral olanzapine treatment showed similar improvements in the subdomains of occupational activities, psychological well-being and symptoms/outlook based on the WQoLI.[69] Individual studies suggested improvements for LAI-A over oral antipsychotics in the social function scale of the SF-36[32] and illness and activities of daily living scales of the AQoL.[52] Details are included in table 1.

Investigation of heterogeneity and meta-regression

Heterogeneity was present in the oral-controlled trials [Chi^2 = 39·08, df = 9, (p = 0·0001); I^2 = 77%]. All the ten oral-controlled studies were long term except one, and open-labelled except two that were double-blind.[55, 60] Visual inspection showed that heterogeneity effects were due to

Alphs et al.,[54] that showed superiority of LAI-Paliperidone over oral antipsychotic medications [SMD=0.56; 95% CI= 0.36, 0.77; p<0.00001; n=388] and two studies including Buckley et al.,[55] and Rouillon et al.,[68] that demonstrated significant superiority of LAI-Risperidone over oral antipsychotic medications [SMD = 0·43; 95% CI= 0·20, 0·66; p= 0·0002; n=305] and [SMD= 0·35; 95% CI= 0·19, 0·51; p< 0·0001; n=593) respectively. In addition to open-blind design, these studies allowed flexibility in the choice and dosage of oral antipsychotic medications, and included only intermittent telephone monitoring of compliance, resulting in high variability in treatment. When all four oral TAU comparator trials were excluded,[54,56,60] heterogeneity was reduced but functional outcome still favoured LAI-A over oral atypical antipsychotic medications [SMD=0·16; 95% CI= 0·07, 0·24; p=0·0003; seven studies; I^2=69%].

Meta regression did not show trial effects of study settings (outpatient versus in-patient), trial design, year of publication, industry sponsorship, baseline symptom severity and inclusion of psychosocial function as primary outcome. Egger's test was not significant for publication bias considering all studies (intercept, 0. 22, 95% CI- -0.122; 0.563; p=0.790), and when placebo-controlled trials (intercept, 0.785; 95% CI= 0.176; 1.39; p=0.168) and oral-controlled trials (intercept, 0.193; 95% CI= -0.247; 0.635) were considered alone. [Details included in supplementary S2-5].

Predictors of change in psychosocial function

Predictors of psychosocial function are presented in table 2. Considering the seven studies that addressed predictors, poor psychosocial function outcome was predicted by baseline factors including high general psychopathology in one study,[58] high negative symptoms in four studies,[58,62,70,71] and severe illness based on poor CGI-S.[72] Further, positive change in insight, longer duration of treatment, lesser disorganised thoughts and higher cognitive performance predicted better psychosocial function.[70,71] Witte et al.[58] reported that high baseline general psychopathology predicted poorer instrumental role, intrapsychic foundations, common objects and activities, interpersonal relations and overall function. More severe negative symptoms predicted poorer recreational and prosocial functioning with medium effect size.[62] In Gharabaw et al.,[70] a combination of predictive factors explained larger variability (27%) in psychosocial function compared to the 2·1% explained by insight, 10·3% by negative symptoms, and 1·6% explained by duration of treatment alone. [See Table 2]

Discussion

To our knowledge, this systematic review and meta-analyses is the first to analyse the effects and predictors of LAI-A on psychosocial function compared with placebo or oral antipsychotics. We were able to review evidence from twenty-six studies, including 11097 participants treated with second generation LAIs where psychosocial function was indexed by a wide range of measures including QoL.[26]

We found that LAI-A were superior to placebo in improving psychosocial function with a medium effect size of SMD=0·39, consistent over short and long-term trials. LAI-A also demonstrated a small but significant benefit (SMD=0.16) compared to oral antipsychotic medications for functional outcome in long term clinical trials. While there was clear evidence of clinically meaningful benefit for LAI-A treatment over placebo, where reported absolute differences between oral and LAI-A treatment in terms of percentage of patients achieving good function was small. This benefit is smaller than that reported in mirror-image and some large cohort studies, potentially due to higher levels of oral adherence and under representation of non-compliant patients in selective and closely monitored clinical trials.[12,37,38] Thus, there is need for true effectiveness trials, in which post-randomization involvement would be kept to a minimum to better reflect routine practice.[38,39] Non-adherence with oral antipsychotic medication is associated with high rates of relapse and poor functional outcomes.[14] Adherence is affected by many factors including insight, side effects, patient treatment goals, attitude to treatment and the effectiveness of the treatment itself.[73] Depot treatments can reduce day to day fluctuations in compliance that occur with oral dosing and allow clear monitoring of adherence, leading to early psychoeducation and intervention.

Systematic review of predictors in seven studies showed that patients with more severe symptoms,[58,62,66,67] cognitive impairment,[71] and poor insight[66] at decision to trial LAI-A were less likely to improve in psychosocial function. Our findings are consistent with the existing evidence of a clear association between cognitive impairment, severity of psychopathology and poor insight with poor functional recovery.[74] This association is complex but modifiable, such that adherence, less severe psychopathology and functional recovery is associated with better insight, while insight is cognition-dependent, particularly on executive performance and working memory.[75-78]. Evidence suggests that insight[79] and cognition can be improved by a wide range of

interventions including cognitive behavioural therapy, assertive community treatment and cognitive remediation. These interventions are recommended for the promotion of functional recovery and in combination with pharmacotherapy lead to the best psychosocial outcomes.[33,80,81] Further research is required to predict poor functional outcomes and fully personalise the selection of medications and interventions.[82] More fundamentally, there is a need to develop better understanding of the pathophysiology of functional decline and studies of the biological basis of function are ongoing.[83,84]

On a different note, our findings underscore the impact of antipsychotics on overall outcome, and by extension support the benefits of maintenance antipsychotics in patients with schizophrenia. Several studies have reported decline in functional recovery and increased relapse rates with cessation of maintenance antipsychotic treatment.[85] Notwithstanding the small advantage of LAI-A over oral antipsychotic medications on psychosocial function, careful interpretation of this finding is required. The choice of antipsychotic formulation for individual patient should entail a balanced consideration of clinical factors, patient attributes and evidence from clinical guidelines through a shared-decision process.[86]

There are several limitations to this study. Firstly, in all but two included studies, psychosocial function was not the primary outcome measure. While some trials reported statistical corrections to address potential effects of this limitation on findings, the quality of evidence would be much improved if cofounding effects and study power were considered in relation to psychosocial function a priori.[87] Given the increasing burden of mental illness related disability and the emerging understanding that symptomatic improvement is not prerequisite nor necessarily sufficient for improved function, there is a need to consider functional measures as primary outcomes in studies of antipsychotic efficacy.[1,88] In keeping with a broad composite concept of psychosocial function, 50% of the studies reviewed considered both QoL and general functional measures. Standardization of these approaches will make future trials of depot efficacy more comparable.

Similar to previous systematic reviews of the literature, we found poor reporting of the randomization process, concealment and sequence generation was common.[14] We used a random effects model to address heterogeneity in psychosocial function scales, and grouped trials into clinical meaningful groups placebo-controlled versus oral controlled during analyses and

sensitivity analyses. The oral-controlled data showed heterogeneity of 77%, accounted for by three studies that showed superiority of LAI-Paliperidone and LAI-Risperidone over orals.[53,54,68] The oral arms of these trials were not well standardised or monitored. For example, LAI-A were not necessarily compared to the same atypical oral, however, recommended dosing was generally implemented. The outcome of meta-analysis was not changed when studies using a TAU oral comparator were excluded.

Only two non-industry trials could be included suggesting risk of industry sponsored bias.[53,62] Studies varied in active comparators and drug dosage, however, all trials used doses within the recommended ranges. Trial length did not appear to influence functional outcome in depot over placebo treatment, suggesting a ceiling effect as optimal function was met within the first 3 months.[89,90] Most of trials did not look at predictors of psychosocial function and useable data was poorly reported.

Conclusion

We conclude that LAI-A improve psychosocial function, but in clinical trials the magnitude of effect is small when compared to oral antipsychotic medications. Patients with more severe symptoms and cognitive impairment at decision to trial were less likely to improve in psychosocial function and may benefit from more intensive psychosocial therapies in adjunct to pharmacological treatment. Consideration of baseline attributes at diagnosis could help to stratify patients who may benefit from early adjunct interventions. Further analysis of predictors of long-term function is needed, potentially leading to trials of indicated psychosocial intervention. Future clinical trials should improve on the quality of reporting and design, and include composite psychosocial function as a measure of efficacy a priori.

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Figure 1: Flow diagram of study selection

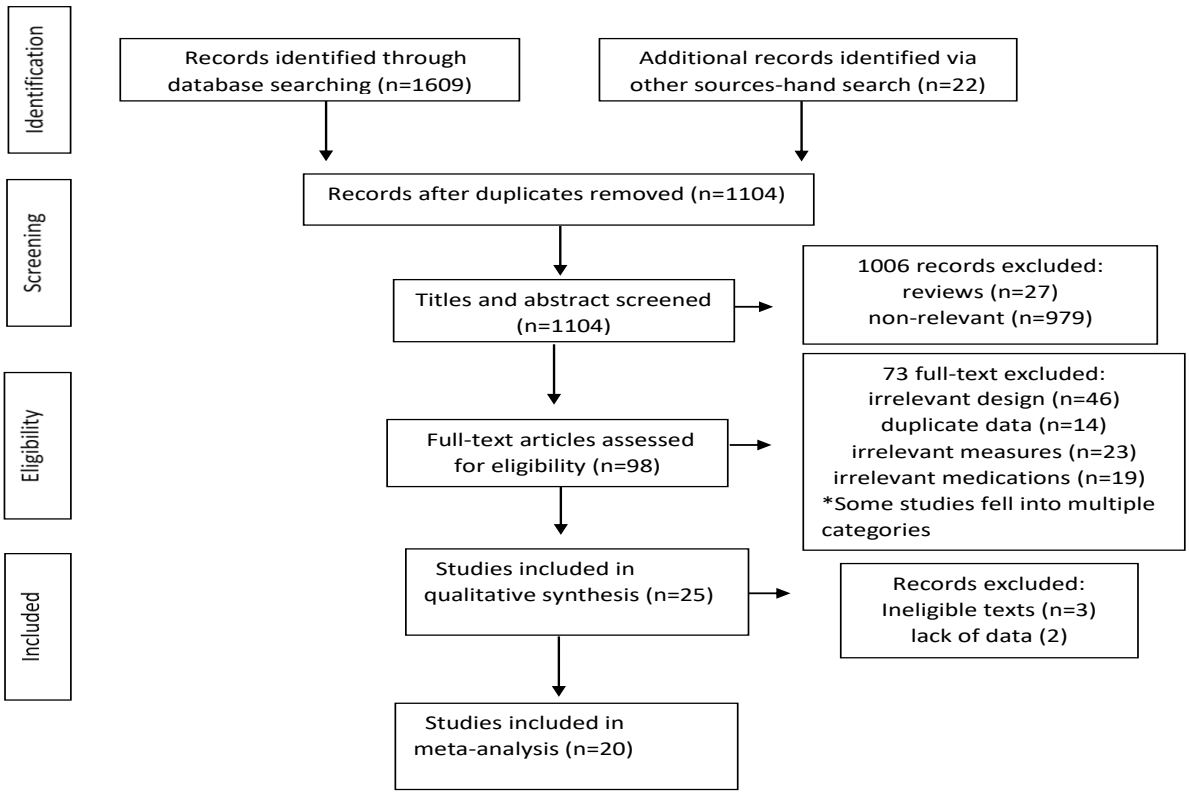


Table 1a: Characteristics of studies on LAI-A versus Placebo

Study	Design	Sample (N) Gender (%)	LAI-A /dosage	Functional measures	Clinical scales	Findings on Psychosocial Function and Statistics
Berwaerts et al., (2015)[$]	RCT double-blind Ratio=1:1 LAI-A Vs placebo	N=305 M=75%	Paliperidone 175, 263, 350 525 mg eq/3m	PSP	DSM-IV-TR, CGI-S, PANSS	**PSP:** There was decline in function on both formulations, although worse in placebo -4.2(±9.70) compared to LAI-A -0.5 (±6.63). No statistical analysis was done.
Fleischhacker et al., (2014)[$]	RCT double-blind Ratio: 2:1 LAI-A Vs placebo	N=403 M=59·8%	Aripiprazole 400mg/m	PSP	DSM-IV-TR, CGI	PSP: significant difference in change in score between LAI-A and placebo, indicating greater functional deterioration with placebo (p< 0·001). LAI-A mean (±SD) baseline to endpoint =68·0(±0·76) to 66·6(±0·89). Placebo- mean (SD) baseline to endpoint= 69·4(±0·97) to 63·2(±1·37).
Fu et al., (2015)[$]	RCT double-blind Ratio 1:1 LAI-A Vs placebo	N=334 M=50·6%	Paliperidone 78 mg/m 117 mg/m 156 mg/m 234 mg/m	PSP	DSM-IV PANSS, HAM-D-21, YMRS, SCID, CGI-S-SCA, MSQ	**PSP:** Significant difference (increase) in LAI-A versus placebo at endpoint. LS means difference = 3·3 (95% CI, 0·68 to 5·95) Participants with good function improved from 57·9% to 59% in LAI-A compared to placebo where participants with good function decreased from 50·6% to 41·1% (p=0·002).
Hough et al., (2010)	RCT double-blind Ratio1: 1 LAI-A Vs placebo	N= 410 M=55%	Paliperidone 25, 50, or 100 mg eq,)/m flexibly-dosed	PSP	DSM-IV, PANSS, CGI-S, PSP, EPS (SAS), AIMS, BARS	**PSP**: Significant difference in longitudinal change in score (decrease) between LAI-A and placebo, indicating greater functional deterioration with placebo (P < 0·001). Least-squares mean difference of change in scores from baseline was placebo= − 7·2 (13·03) versus LAI-A= − 1·5 (11·53).
Isitt et al., (2016)	RCT double-blind Ratio 1:1 LAI-A Vs placebo	N=337 M=76·6%	Risperidone (RBP-700) 90mg/m 120mg/m	EuroQol EQ-5D-5L, SWN-S	DSM-IV-TR, C-SSRS, SAS, AIMS, BARS, MSQ, CGI-S, POM, PANSS	**EQ-5D-5L:** Significant difference in longitudinal change in score (increase) between LAI-A compared to placebo indicating improved functioning in LAI-A. Change from baseline mean score for LAI-A Vs placebo was 8.184 versus 3·295, p= 0·0212. **SWN-S:** Significantly greater improvements in LAI-A in the following scores compared to placebo: physical functioning (2·086 versus 0·750, p = 0·0093), social integration (2·868 versus 1·765, p = 0·0368) and total score (10·951 versus 6·942, p = 0·0395). Significant improvement in LAI-A relative to placebo was recorded in those on 120mg/m dose compared to 90mg/m

Study	Design	Sample (N) Gender (%)	LAI-A /dosage	Functional measures	Clinical scales	Findings on Psychosocial Function and Statistics
Kane et al., (2003)	RCT double-blind Ratio: 1:1 LAI-A Vs placebo	N=400 M=75·3%	Risperidone 25mg/bw, 50 mg/bw,75 mg/bw	SF-36	DSM-IV, PANSS, CGI, EPSRS	**SF-36:** There was significant difference (increase) in scores (improvement from baseline) across multiple domains (BP, GH, SF, RE, MH) in favour of all the LAI-A dose group compared to placebos (p<0·05). MC showed largest improvement after 12 weeks (2·37 Vs -0·27 placebo).
Kane et al., (2014)	RCT double-blind Ratio 1:1 LAI-A Vs placebo	N=340 M=79·1%	Aripiprazole 120mg/m	PSP	DSM-IV-TR, MINI, BARS PANSS, SAS CGI-I, CGI-S,TEAE, AIMS	**PSP**: LS mean (SE) change from baseline in PSP total score was significantly greater with LAI-A versus placebo at endpoint (12·3 [1·2] vs 5·2 [1·2], respectively; P <0·0001) and at week 12 (13·0 [1·2] vs 5·5 [1·2]; P < 0·0001
Padina et al., (2010)	RCT double-blind Ratio: 1:1 LAI-A Vs Placebo	N=652 M=67.5%	Paliperidone 25,100, or150 mg/m	PSP	DSM-IV, PANSS, CGI-S	**PSP**: A dose-related improvement in LAI-A treatment groups including, compared to placebo, which was significant for the 100 mg eq (p=0.007) and 150 (p <0.001)mg eq groups.
Witte et al., (2012)	RCT double-blind Ratio=1:1:1:1 LAI-A Vs placebo	N= 404 M=70·5%	Olanzapine 210 mg/bw 300 mg/bw 405 mg/bw	QLS, SF-36	DSM-IV or DSM-IV-TR, BPRS, PANSS	**QLS**: Significant difference (increase) in total score in LAI-A compared to placebo (p<0·05). Scores on IF, IPR & IR were significantly higher in LAI-A compared to placebo but no difference in COA domain (p<0·05). **SF-36:** Significant difference (increase) in MCS & MHF domain in LAI-A compared to placebo

Table 1b: Characteristics of studies on LAI-A versus Oral antipsychotic medications

Study	Design	Sample (N) Gender (%)	LAI-A /dosage	Functional measures	Clinical scales	Findings on Psychosocial Function and Statistics
Alphs et al., (2015)	RCT open-label Ratio: 1:1 LAI-A Vs Oral[x]	N= 444 M=86.3%	Paliperidone 78- 234 mg/m Flexible-dosed	PSP	DSM-IV, CGI-S, MINI	**PSP**: Both formulations improved function and no significant between-group differences were observed in mean change in PSP total scores (P =0 .689).
Ascher-Svanum et al., (2014)	RCTs open-label Ratio=1:1 LAI-A Vs Oral[o]	N=1182 M=66·8%	Olanzapine 150-600 mg/m	QLS, SF-36; EuroQol	DSM-IV, DSM-IV-TR, MSQ, PANSS,CGIS,	**QLS**: Significant change (increase) in total score from baseline to endpoint in LAI-A, mean (±SD) $_{BL}$=64·0 (±21·2) and mean (±SD)$_{EP}$=70·8 (±22·9). No significant difference in total scores, COA, IF, IPR and IR for LAI-A versus Orals (p>0.05).
Bai et al., (2006)	RCT single-blind Ratio=1: 1 LAI-A Vs Oral[r]	N=50 M=48%	Risperidone Max 50mg/bw	GAF; SF-36	DSM-IV, SAS, PANSS, CGI, UKS, AIMS, BARS	**GA**F: Both formulations improved general function and there was no significant difference in change of score from baseline to the endpoint between LAI-A (0.8 ± 8.1) versus oral (1.6±9.4). **SF-36:** No significant difference between LAI-A and orals across all domains except in social function where LAI-A was superior to oral (p = 0.017).
Buckley et al., (2015)	RCT open label, Ratio 1: 1 LAI-A Vs Oral[w]	N=305 M=71%	Risperidone 12.5-50mg/bw	SOF	DSM-IV-TR, BPRS, SANS, CGI, BARS	**SOF**: No significant difference in total score at endpoint in LAI-A versus oral. Estimated mean (95% CI) = 42·7 (41·6 - 43·9) vs 42·1 (40·9 - 43·4); F=·34, df=9, 1420, p=0·96. **SOF global rating**: No difference in LAI-A versus Oral. Estimated mean is (95% CI) =3·0 (2·9 - 3·1) vs 3·0 (2·8 - 3·1); F=·90, df=9, 1430, p=0·53.
Fleischhacker et al., (2014)	RCTdouble-blind Ratio: 2:2 LAI-A Vs Oral[a]	N=662 M=61·3%	Aripiprazole 400mg/m	PSP	DSM-IV-TR, CGI	**PSP:** scores remained stable in LAI-A and oral groups. LAI-A mean(±SD) baseline to endpoint=65·3(±0·7) to 65·9(±0·8) Oral mean (±SD) baseline to endpoint =66·9(±0·75) to 66·8(±0·83).
Keks et al., (2007)[$]	RCT open label: Ratio: 1:1 LAI-A Vs Oral[o]	N= 547 M=56%	Risperidone 25 mg/m 50 mg/m	W-QOLI	DSM-IV, SCI-PANSS, CGI-S, SARS	**W-QOLI:** There was improvement from baseline to end-point on all sub-scale ratings. Clinically meaningful improvements (score changes >0·5 points) were seen in three domains in LAI-A and orals: occupational activities, psychological well-being and symptoms/outlook.

Study	Design	Sample (N) Gender (%)	LAI-A/dosage	Functional measures	Clinical scales	Findings on Psychosocial Function and Statistics
NCT00992407 (2014)	RCT open label Ratio=1:1 LAI-A Vs Oral[r]	N=41 M=60.9%	Risperidone Max 50mg/bw	PSP; SFS; GAF	DSM-IV, SAS PANSS, CGI-S, BDI, BARS, BAI, DAI, AIMS, Cogtest	**PSP:** There was improvement in both formulations from baseline to endpoint but no significant difference between LAI-A and oral (p= 0.859). **GAF:** There was improvement in both formulation from baseline to endpoint but no significant difference between LAI-A and oral (p= 0.957).
Rosenheck et al, (2011)	RCT double-blind Ratio 1:1 LAI-A Vs Oral[x]	N=369 M=90·5%	Risperidone 25-50 mg/bw	QLS; PSP; QWBS	DSM-IV, CGI, DAI, PANSS, BSI, ASI, SAS, BARS, AIMS	**QLS, PSP & QWBS**: Significant change (improvement) in scores from baseline to endpoint in LAI-A. No significant superiority of LAI-A over oral was observed on all the three scales (p>0·05). No difference between LAI-A versus Oral on QLS total scores, IF, IPR and IR (p>0.05).
Rouillon et al., (2013)	RCT open label Ratio 1:1 LAI-A Vs Oral[a q]	N=666 M=57·9%	Risperidone 25-50 mg/bw	SQLS-R4; SOFAS; SF-12	DSM-IV, ESRS, CGI-S	**SOFAS:** Mean change in scores from baseline to endpoint was significant for LAI-A for all assessment points and endpoint (p <0·001). Between-treatment differences in change in scores for LAI-A versus oral, respectively, were significant at treatment in 6month [6·1 (SD= 15·2) vs. 2·7 (SD=11·0); p= 0·02], 12month [9·5 (SD=11·2) vs. 6·1 (SD= 10·7); p= 0·009], and endpoint [6·6 (SD= 15·2) vs 1·1 (SD=16·1); p< 0·0001]
Schreiner et al., (2015)	RCT, open-label Ratio 1:1 LAI-A Vs Oral[x]	N=715 M=57·9%	Palliperidone-25-150mg/m	PSP; EQ-5D; SWN-S; SF-36	DSM-IV, SAS, BARS, PANSS, AIMS CGI-S, CGI-C, TSQM	**PSP**: Total score improved significantly from baseline to endpoint for LAI-A Vs Oral; (mean change= 9·8 versus 8·7); both within groups p<0·0001. **SF-36, EQ-5D, and SWN-S:** Significant improvement in scores in LAI and orals were observed. All scales showed similarity in LAI-A Vs oral (p>0·05).
Wykes, et al., (2013)	RCT open label Ratio 1:1 LAI-A Vs Oral[w]	N=50 M=72%	Risperidone 25mg/bw to 50mg/bw (flexible dose)	AQoL; PSP	DSM-IV-TR, WAI, PANSS, CGI-S, CGI-C	**AQoL**: significant change in LAI-A over time: QoL- illness (N = 36, z = −2·12, p = 0·034) and QoL- activities of daily living (N = 36, z = −2·82, p = 0·005). **PSP:** no change in score over time in LAI-A (N = 43 z = −1·08, p = 0·279). LAI-A was not significantly different from oral.

Table 1c: Characteristics of studies on LAI-A versus LAI-A

Study	Design	Sample (N) Gender (%)	LAI-A /dosage	Functional measures	Clinical scales	Findings on Psychosocial Function and Statistics
Koshikawa et al., (2016)[$]	RCT open label Ratio=1: 1 LAI-A Vs LAI-A	N=30 M=52·3%	Risperidone Max 50mg/bw Paliperidone[#] Max 150 mg/m	SFS; UPSA-B	DSM-IV-TR, PANSS, JART, SECT, Cogtest, DIEPSS	**SFS:** The two LAI-A groups showed improvement in scores from baseline, with LAI-P showing greater improvement in total score and two subscales: independence-competence and independence-performance, compared to the LAI-R group (total score: F = 5·03, df. = 1, 18, p = 0·038; competence: F = 14·04, df. = 1, 18, p = 0·001, and performance: F = 9·14, df. = 1, 18, p = 0·007), respectively. **UPSA-B**: Significant difference (increase) in total scores (improvement) for both LAI-A groups with greater improvement in LAI-P. Mean change(SD) LAI-R=1·36(13·85) Vs LAI-P= 5·78(8·79), and no significant difference in the two groups F=1·70; p=0·211
Meltzer et al., (2014)[$]	RCT double-blind Ratio 1:1 LAI-A Vs LAI-A	N=160 M=72·5%	Risperidone 50mg/bw Risperidone[#] 100mg/bw	GAF; PSP	DSM-IV-TR, PANSS. SAS, CGI-S, AIMS, BARS, cogtest	**GAF:** Significant change (increase) in scores from baseline (improvement) was reported in the two doses of LAI-A (p<0·05). Effect size for improved GAF scores was 1·67 and 1·94 for the 100 and 50 mg doses respectively. **PSP:** Significant change (increase) in scores from baseline (improvement) was reported in the two doses of LAI-A (p<0·05). The ES for improvement between baseline and 24 weeks was 1·29 and 1·10 for the 50 mg and100 mg dose groups, respectively. Improvement in function began at six weeks and was progressive but had plateaued by 24 weeks.
Naber et al., (2015)[$]	RCT single-blind Ratio 1:1 LAI-A Vs LAI-A	N=295 M=56·9%	Aripiprazole 400 mg/m Paliperidone[#] 50-150mg/m flexible dose	QLS; SWN-S TooL	DSM-IV-TR, CGI-S, IAG, SWN-S, TooL, WoRQ	**QLS:** Significant change (increase) in scores as measured with least square mean (LSM) treatment differences at week 28 favouring AOM 400 vs PP in patients ≤ 35 years on QLS (10·7, 95%CI: [0·70;20·7], p=0·037). No difference between AOM versus PP in COA, IPR and IR (p>0.05), but AOM was superior to PP in IF (p=0.039)
NCT00604279 (2013)[$]	RCT open-label Ratio=1:1 LAI-A Vs LAI-A	N= 452 M=40%	Paliperidone 50,100,150mg/m Risperidone[#] 25, 37.5 & 50mg/bw	PSP	DSM-IV, SVAS, PANSS, CGI-S	**PSP**: There was improvement in function in both LAI-A groups, mean change 16.8 (±14.76) versus 18.6 (±13.92). No between-group statistics

Study	Design	Sample (N) Gender (%)	LAI-A /dosage	Functional measures	Clinical scales	Findings on Psychosocial Function and Statistics
Padina et al., (2011)[$]	RCT double-blind Ratio 1:1 LAI-A Vs LAI-A	N= 1221 M=55%	Paliperidone 50-150mg/bw Risperidone[#] 25, 37.5, & 50 mg/bw flexibly-dosed	PSP	DSM-IV, PANSS, CGI-S, SDS	**PSP**: There was improvement in longitudinal change in score in both paliperidone, 8.5(±11.82) and Risperidone 8.8 (±11.65). No significant difference between the two drugs ($p>0.05$).
Simpson et al., (2006)[$]	RCT double-blind Ratio 1:1 LAI-A Vs LAI-A	N= 323 M= 62·3%	Risperidone-25mg/bw Risperidone[#] 50mg/bw	LOF, PSP; SQLS	DSM-IV, AIMS, PANSS, CGI-S, ESRS, Cogtest	**PSP:** Longitudinal change in scores (increase) was significantly different for both LAI-A doses. LAI-A-25mg mean $(SD)_{Baseline}$ to endpoint=61·8(±14·8) to 63·8(±15·0). LAI-A-50mg mean (SD) baseline to endpoint= 62·5(±13·5) to 64·4±(13·1). No difference in scores between both LAI-A treatment doses group.

#=comparator LAI-A; $= included in systematic review only; a=oral aripiprazole; o=oral olanzapine; p=oral paliperidone; r=oral risperidone; q=oral quetiapine; w= oral atypical at discretion of clinician; x=treatment as usual; AIMS=Abnormal Involuntary Movement Scale; AOM= Aripiprazole Once Monthly; AQoL=Assessment of Quality of Life; ASI=Addiction Severity Index; BARS= Barnes Akathisia Scale; BAS= Burden Assessment Scale; BPRS= Brief Psychiatric Rating Scale; BSI=Brief Symptom Index; COA=Common objects and activities; Cogtest= Cognitive battery test; C-SSRS=Columbia-Suicide Severity Rating Scale; CGI-S-SCA=Clinical Global Impression of Severity for Schizoaffective Disorder; DAI=Drug Attitude Inventory; DIEPSS= Drug-Induced Extrapyramidal Symptoms Scale; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders-fourth edition; ESRS=Extrapyramidal Symptom Rating Scale; GAF-=Global Assessment of Function; IAQ= Investigator's Assessment Questionnaire; IF= Intrapsychic foundation; IR=Instrumental Roles; IR=Interpersonal Roles; JART=Japanese Adult Reading Test; MCS=Mental Component Summary; MHF=Mental Health Functioning; MSQ= Medication Satisfaction Questionnaire; LAI-A= long acting injectable-atypical; LOF=Strauss-Carpenter Levels of Functioning; LSM= least square mean; mg/d= milligram per day; mg/bw= milligram per two weeks; mg/m=milligram per month; NAMES= New Antipsychotics Metabolic Evaluation Scale; nr= not reported; PANSS=Positive and negative symptoms scale; POM= Preference of Medicine Questionnaire; PP= Paliperidone Palmitate; PSP=Personal and Social Performance Scale; QLS= Heinrichs-Carpenter QoL scale; QoL=Quality of Life; QWBS= Quality of Well-Being scale; RCT-randomised controlled trials; RSQ= relationship style questionnaire; SANS=Scale for Assessment of Negative Symptoms; SAS=Simpson-Angus Scale; SDS=Schedule for Deficit Syndrome; SECT=Social Emotional Cognition Task; SF-36=36-Item Short Form Health Survey; SOF= Scale of Functioning; SOFAS=Social and Occupational Functioning Assessment Scale; SQLS-R4= Schizophrenia Quality-of Life Scale Revision 4; SWN-S=Subjective Well-being Under Neuroleptic Treatment-short version; TSQM=Treatment Satisfaction Questionnaire for Medication; UPSA-B= University of California San Diego (USCD)-Performance-Based Skills Assessment-Brief; SVAS= Sleep Visual Analog Scale; W-QOLI=Wisconsin Quality of Life Index.

Table 2: Predictors of change in functioning in LAI-A trials

Study	Predictors/correlates of change in functional outcome in LAI-A	Statistics (Mean difference, regression coefficient & effect size)
Gharabaw et al., (2007)	**Predictors of change in PSP scores**	**Contribution of predictors to variability in PSP scores**
	Change in insight (PANSS item G12)	Partial r^2 for insight =0·0224
	Change in Negative factors (PANSS negative factor)	Partial r^2 for Negative symptoms =0·1689
	Duration of treatment	Partial r^2 for duration of treatment (month)=0·0619
		R squared for model=0·2742
	Predictors of change in LOF scores	**Contribution of predictors to Variability in LOF scores**
	Change in insight (PANSS item G12)	Partial r^2 for insight =0·0021
	Change in Negative factors (PANSS negative factor)	Partial r^2 for Negative symptoms =0·1034
	Duration of treatment	Partial r^2 for duration of treatment (month)=0·0161
		R squared for model=0·1502
	Correlates of change in SQLS scores	**Correlation with SQLS**
	Change in insight correlated significantly with change in SQLS psychosocial subscale	Insight with SQLS psychosocial subscale r =0·149
Isitt et al., (2016)	Dose of LAI-A was linked with improvement as those on higher dose reported significant improvement	nr
Koshikawa et al., (2016)	**Correlates of change in SFS scores**	**Correlation coefficient (r) of PANSS negative score versus**
	PANSS negative symptoms	recreation: r = -0·46
	Significant negative correlations were found between negative symptoms assessed with PANSS and two subscales of the SFS (i.e. recreation p = 0·036, and prosocial p = 0·028)	prosocial: r = -0·48
Pandina, et al., (2013)	**Correlates of change in PSP scores**	nr
	Higher end point least-squares (LS) mean in cognitive composite scores (NCS T-scores) was associated with better functioning (p= 0·006)	
	Lower mean end point scores (i.e., improved) on PANSS total score, disorganized thoughts, and positive and negative factors was associated with better function (all, p< 0·0001)	

Table 2 continued

Study	Predictors/correlates of change in functional outcome in LAI-A	Statistics (Mean difference, regression coefficient & Effect size)
Peuskens et al., (2012)	**Predictors of change (improved) in QLS at 6 months** Higher PANSS positive scores at baseline Low CGI-S scores at baseline **Predictors of change (improved)in QLS at 12 months** High PANSS positive scores at baseline	**Regression coefficient, Odd ratio at 6 months** PANSS positive [OR =2·840; 95% [CI]=(1·834; 4·399); p<0·0001 CGI-S [OR]=0·619, 95% [CI]=(0·463; 0·828); p= 0·0012 **Regression coefficient, Odd ratio at 12 months** PANSS positive [OR]= 1·537; 95% [CI]=(1·129; 2·093); P= 0·0063
Potkin et al., (2017)	**Predictors of change (improvement) in QLS at 24 months** Type of LAI-A performed better in people aged below 35 years	The odds of improved function was greater in LAI-Aripiprazole compared to LAI Paliperidone in participants < 35 years (OR 10·7, 95%CI: [0·70;20·7], p=0·037) but there was no difference in patients > 35 years.
Witte et al., (2012)	**Correlates of change in QLS scores** Changes in PANSS total, PANSS negative, and PANSS general psychopathology scores showed significant negative correlations with QLS scores (p<0·0001)	**Correlation coefficient (r) of PANSS total score with:** QLS total= - 0·44 QLS Instrumental role=-0·23 QLS Intrapsychic Foundations=-0·43 QLS Common Objects and Activities =- 0·28 QLS Interpersonal Relations= - 0·37

Cogtest= Cognitive battery test; CGI-S-SCA=Clinical Global Impression of Severity for Schizoaffective Disorder; 95% CI=95% Confidence interval; LAI-A=Long acting injectable atypical antipsychotics; LOF=Strauss-Carpenter Levels of Functioning; nr=not reported; .

; PANSS=Positive and negative symptoms scale; PSP=Personal and Social Performance Scale; QLS= Heinrichs-Carpenter QoL scale; r= Correlation coefficient; SQLS-R4= Schizophrenia Quality-of Life Scale

Figure 2: Risk of bias

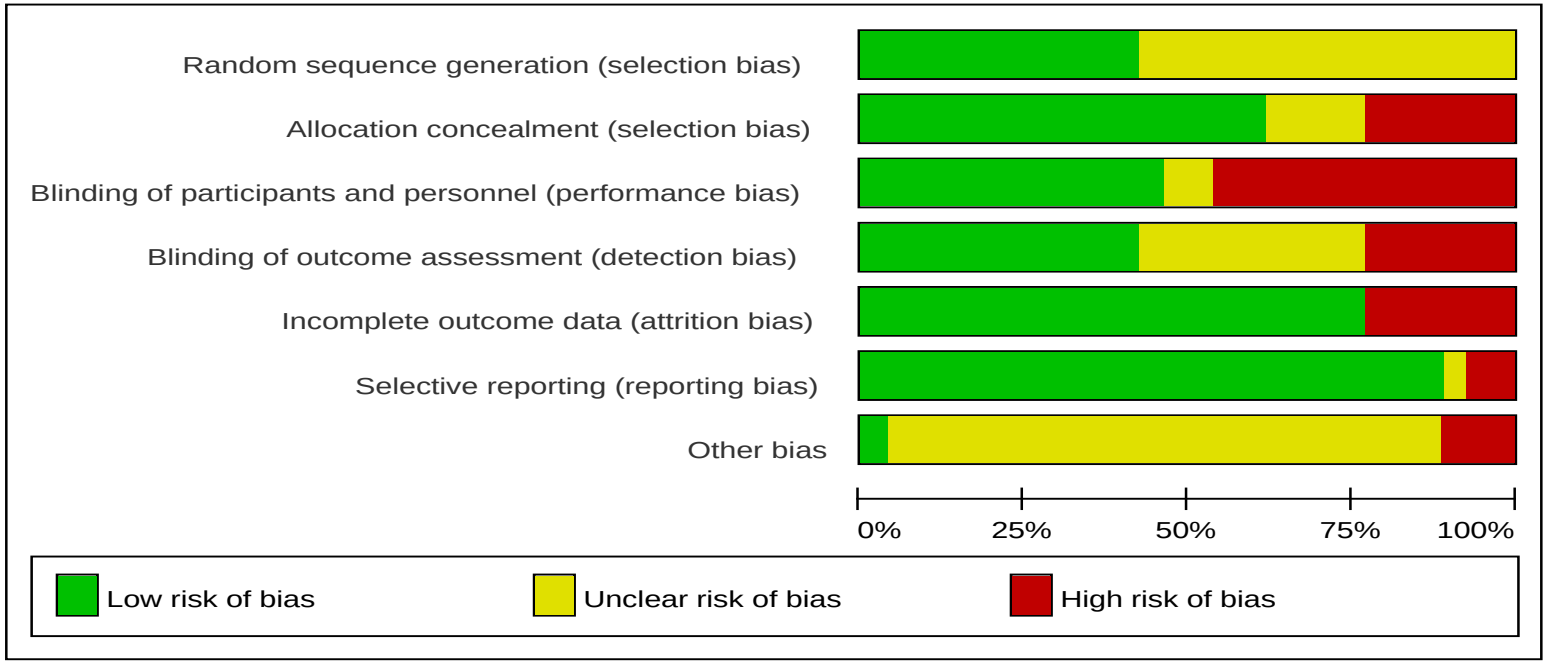


Figure 3: All LAI-A versus Placebo studies

Study or Subgroup	Std. Mean Difference	SE	LAI-A Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischhacker et al.,(2014) LAI-Aripiprazole	0.399	0.1094	258	127	16.3%	0.40 [0.18, 0.61]
Fu et al., (2015) LAI-Paliperidone	0.271	0.11	164	170	16.2%	0.27 [0.06, 0.49]
Hough et al., (2010) LAI-Paliperidone	0.4626	0.1003	205	203	19.5%	0.46 [0.27, 0.66]
Isitt et al., (2016) LAI-Risperidone	0.27	0.13	114	112	11.6%	0.27 [0.02, 0.52]
Kane et al., (2003) LAI-Risperidone	0.22	0.15	97	92	8.7%	0.22 [-0.07, 0.51]
Kane et al., (2014) LAI-Aripiprazole	0.45	0.11	168	172	16.2%	0.45 [0.23, 0.67]
Witte et al., (2012) LAI-Olanzapine	0.48	0.13	272	83	11.6%	0.48 [0.23, 0.73]
Total (95% CI)			**1278**	**959**	**100.0%**	**0.38 [0.29, 0.46]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.54$, df = 6 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 8.54 (P < 0.00001)

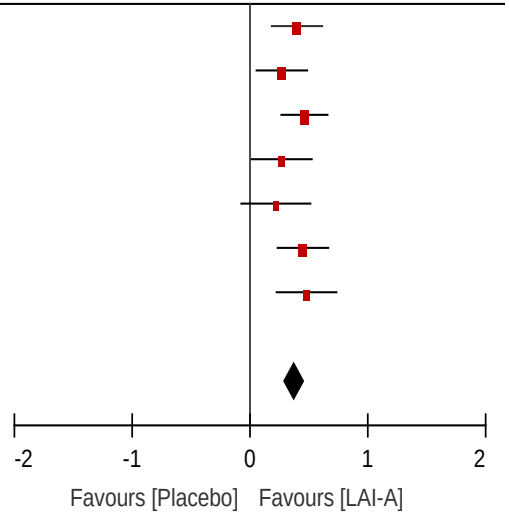


Figure 4: Short term trials of LAI-A versus Placebo

Study or Subgroup	Std. Mean Difference	SE	LAI-A Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Isitt et al., (2016) LAI-Risperidone	0.27	0.13	114	112	24.1%	0.27 [0.02, 0.52]
Kane et al., (2003) LAI-Risperidone	0.22	0.15	97	92	18.1%	0.22 [-0.07, 0.51]
Kane et al., (2014) LAI-Aripiprazole	0.45	0.11	168	172	33.7%	0.45 [0.23, 0.67]
Witte et al., (2012) LAI-Olanzapine	0.48	0.13	272	83	24.1%	0.48 [0.23, 0.73]
Total (95% CI)			**651**	**459**	**100.0%**	**0.37 [0.25, 0.50]**

Heterogeneity: Tau² = 0.00; Chi² = 2.84, df = 3 (P = 0.42); I² = 0%

Test for overall effect: Z = 5.83 (P < 0.00001)

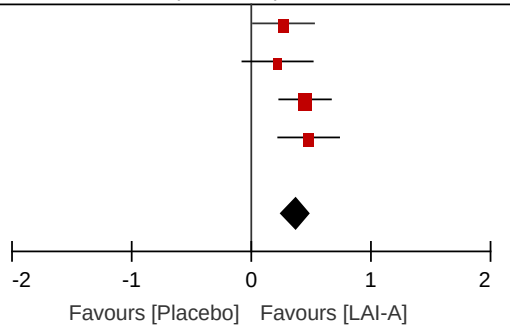


Figure 5:Long term trials of LAI-A versus Placebo

Study or Subgroup	Std. Mean Difference	SE	LAI-A Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischhacker et al.,(2014) LAI-Aripiprazole	0.399	0.1094	258	127	31.5%	0.40 [0.18, 0.61]
Fu et al., (2015) LAI-Paliperidone	0.271	0.11	164	170	31.1%	0.27 [0.06, 0.49]
Hough et al., (2010) LAI-Paliperidone	0.4626	0.1003	205	203	37.4%	0.46 [0.27, 0.66]
Total (95% CI)			**627**	**500**	**100.0%**	**0.38 [0.26, 0.50]**

Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 2 (P = 0.43); I² = 0%

Test for overall effect: Z = 6.24 (P < 0.00001)

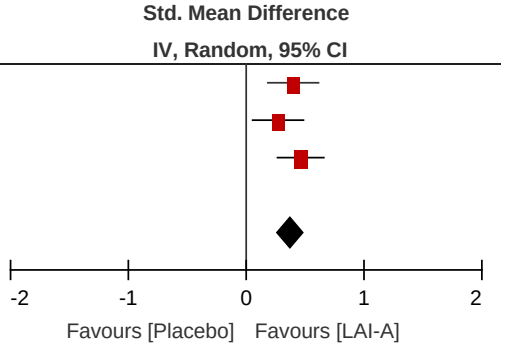
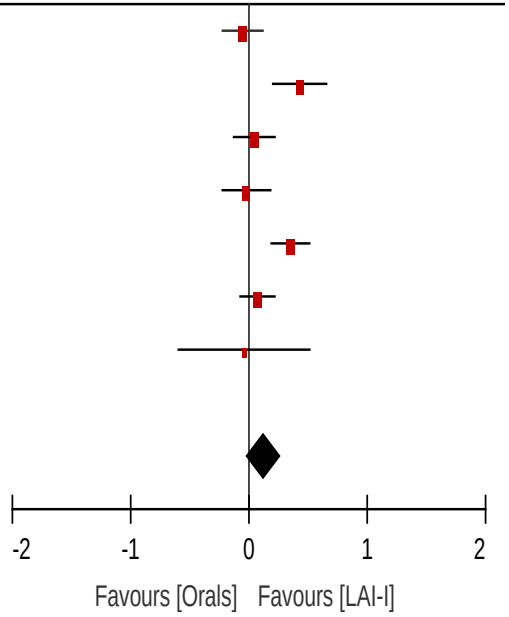


Figure 6: All LAI-A versus Orals studies

Study or Subgroup	Std. Mean Difference	SE	LAI-A Total	Orals Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ascher-Svanum et al., (2014) LAI-Olanzapine	-0.0529	0.0874	264	260	16.2%	-0.05 [-0.22, 0.12]
Buckley et al., (2015) LAI-Risperidone	0.4286	0.1158	153	152	13.8%	0.43 [0.20, 0.66]
Fleischhacker et al.,(2014) LAI-Aripiprazole	0.0454	0.089	257	248	16.1%	0.05 [-0.13, 0.22]
Rosenheck et al, (2011) LAI-Risperidone	-0.0208	0.1041	187	182	14.8%	-0.02 [-0.22, 0.18]
Rouillon et al., (2013) LAI-Risperidone	0.3509	0.0828	298	295	16.6%	0.35 [0.19, 0.51]
Shreiner et al., (2015) LAI-Paliperidone	0.0725	0.0748	352	363	17.3%	0.07 [-0.07, 0.22]
Wykes, et al., (2013) LAI-Risperidone	-0.0408	0.2831	26	24	5.1%	-0.04 [-0.60, 0.51]
Total (95% CI)			**1537**	**1524**	**100.0%**	**0.12 [-0.02, 0.27]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 22.05$, df = 6 (P = 0.001); $I^2 = 73\%$

Test for overall effect: Z = 1.69 (P = 0.09)



Supplementary S1: Additional information on studies

Study	Study locations	Participants details	Duration	Functioning was primary study outcome/Analyses	Industry sponsor/ Trial number
Alphs et al., (2015)	Multi-center: US Centers	Mean age= 38.1(±10·5) years; Diagnosis=Schizophrenia; Outpatients	65 weeks	No ITT	Yes NCT01157351
Ascher-Svanum et al., (2014)	Multi-center: International	Mean age= 40.9(±10.9) years; Diagnosis: Schizophrenia; Outpatients	104 weeks	No ITT	Yes NCT00320489
Bai, et al., (2006)	Single center: Taiwan	Mean age: 44.7(± 9.2) years; Diagnosis: Schizophrenia: out-patients	12 weeks	Yes ITT	Yes NCS932314B480002
Berwaerts et al., (2015)	Multi-center: International	Mean age: 37.8(±11.0) years Diagnosis: Schizophrenia; Inpatient or out-patients	60 weeks	No ITT	Yes NCT01529515
Buckley et al., (2015)	Multi-center: US centers	Mean age= 38·2(±12·1) years; Diagnosis: Schizoaffective or Schizophrenia; inpatients or outpatients	130 weeks	No ITT	No NCT00330863
Fleischhacker et al., (2014) 2RCTs	Multi-center: International	[1]Mean age=41·2(±10·4) years [2]Mean age =40.6(10.8) years Diagnosis: Schizophrenia outpatients	[1]38 weeks [2]52 weeks	No ITT	Yes [1]NCT00706654 [2]NCT00705783
Fu et al., (2015)	Multi-center: international	Mean age =38·6 (nr) years; Diagnosis: Schizoaffective; inpatients or outpatients	65 weeks	No ITT	Yes NCT01193153

Study	Study locations	Participants details	Duration	Functioning was primary study outcome/Analyses	Industry sponsor/ Trial number
Hough et al., (2010)	Multi-center: International	Mean age= 38·8(±11·4) years; Diagnosis: schizophrenia; out-patients	24 weeks	No ITT	Yes NCT00111189
Isitt et al., (2016)	Multi-center: US centers	Mean age=41·2 (±9·27) years; Diagnosis: Schizophrenia; in-patients	8 weeks	No ITT	Yes NCT02109562
Kane et al, (2003)	Multi-center: US centers	Mean age=37.7 (±9.8) years; Diagnosis: Schizophrenia; outpatients or inpatients	12 weeks	No ITT	Yes Ris-USA-121
Kane et al., (2014)	Multi-center: International	Mean age=42·1(±11·0) years; Diagnosis= Schizophrenia; in-patients or out-patients	12 weeks	No ITT	Yes NCT01663532
Koshikawa et al., (2016)	Single center: Osaka, Japan	Mean age=46·4(±10·3) years; Diagnosis: schizophrenia or schizoaffective; out-patients	26 weeks	Yes ITT	No UMIN000014470
Keks et al., (2007)	Multi-center: International	Mean age= 32·6(±10·4) years; Diagnosis= Schizophrenia or schizoaffective disorders; in- patients or out-patients	52 weeks	No ITT	Yes NCT00236457
Meltzer et al., (2014)	Multi-center: US centers	Mean age=41·0(±11·4) years; Diagnosis: schizophrenia or schizoaffective disorder; in-patients or out-patients	26 weeks	No ITT	Yes NCT00539071

Study	Study Locations	Participants details	Duration	Functioning was primary study outcome/Analyses	Industry sponsor/ Trial number
Nabar et al., (2015)	Multi-center: International	Mean age= 42·6 (±10·9) years; Diagnosis: Schizophrenia; in-patients or out-patients	28 weeks	Yes ITT	Yes NCT01795547
NCT00604279 (2013)	Multi-centre: China	Mean age: 31.7 (±10.88) years; Diagnosis: Schizophrenia outpatient	14 weeks	No Per-protocol	Yes NCT00604279
NCT00992407 (2014)	Single Centre: Korea	Mean age: 34.5 (±10.00) years Diagnosis: Schizophrenia or schizoaffective disorders outpatient	52 weeks	Yes Per-protocol	Yes NCT00992407
Padina et al., (2010)	Multi-center: International	Mean age: 39.3 (±10.55) years Diagnosis: Schizophrenia outpatient	13weeks	No ITT	Yes NCT00590577
Padina et al., (2011)	Multi-center: International	Mean age: 38.9 (±11.98) years; Diagnosis: Schizophrenia Outpatient or outpatients	13 weeks	No ITT	Yes NCT00589914

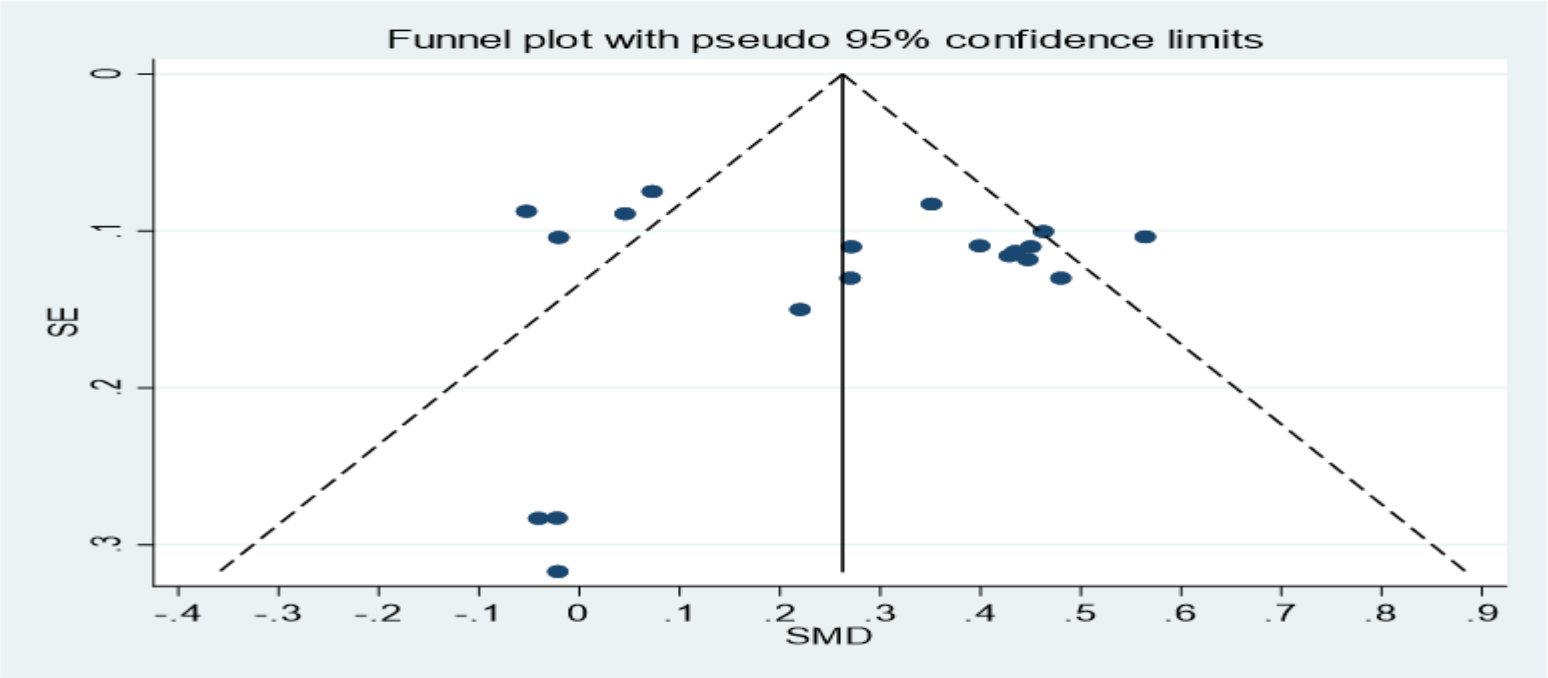
Study	Study Locations	Participants details	Duration	Functioning was primary study Outcome/Analyses	Industry Sponsor/ Trial umber
Rosenheck et al, (2011)	Multi-center: US centers	Mean age=50·9(± 9·3) years; Diagnosis: schizophrenia or schizoaffective disorder; inpatient or outpatient	104 weeks	No ITT	Yes NCT00132314
Rouillon et al., (2013)	Multi-center: International	Mean age= 41·6 (±12·8) years; Diagnosis: Schizophrenia or Schizoaffective in-patients or inpatient	104 weeks	No ITT	Yes NCT00216476
Schreiner et al., (2015)	Multi-center: International	Mean age= 32·6 (±10·7) years; Diagnosis: Schizophrenia; in-patients	104 weeks	No ITT	Yes NCT01081769
Simpson et al, (2006)	Multi-center: International	Mean age= 40·9(±11·0) years Diagnosis: Schizophrenia or Schizoaffective out-patients	52 weeks	No ITT	Yes NCT00297388
Witte et al., (2012)	Multi-center: International	Mean age= 40·8 (±11·2) years; Diagnosis: Schizophrenia; Inpatients or outpatients	8 weeks	No ITT	Yes NCT00088478
Wykes, et al., (2013)	Multi-center: International	Mean age: 36·8(±10·8) years; Diagnosis: Schizophrenia; in-patients or out-patients	104 weeks	No ITT	Yes NCT00256997

Supplementary S2: Meta-regression of predictors

Study Group (Placebo or Oral)	**Predictors**	**Comparison**	Coefficient (95% CI)	P value	**Egger's test p-value***
All studies					0.790
Oral studies only	Year of publication (continuous)		0.043 (-0.041, 0.126)	0.274	0.873
Oral studies only	Year of publication (binary)	≥ 2014 versus ≤2014	0.078 (-0.325,0.480)	0.668	
Oral studies only	Trial duration (continuous)		0.001 (-0.005, 0.007)	0.702	
Oral studies only	Study setting	Inpatient versus Outpatient	-0.106 (-0.688, 0.476)	0.680#	
		Both versus Outpatient	0.060 (-0.390, 0.510)	0.761	
Oral studies only	Functioning as primary outcome	Yes versus No	-0.202 (-0.827, 0.423)	0.477	
Oral studies only	Industry sponsorship	Yes versus No	-0.301 (-0.864, 0.263)	0.254	
Oral studies only	Study design	Blinded versus Open-label	-0.219 (-0.598,0.161)	0.220	
Oral studies only	Length of trial	Long versus Short	0.193 (-0.641, 1.027)	0.608	
Oral studies only	Baseline CGI-S for LAI-A group		0.031 (-0.130, 0.192)	0.664	
Placebo studies only	Year of publication (continuous)		0.002 (-0.026, 0.030)	0.893	0.168
Placebo studies only	Year of publication (binary)	≥2014 versus ≤2014	-0.049 (-0.235, 0.137)	0.554	
Placebo studies only	Trial duration (continuous)		-0.0001 (-0.005, 0.003)	0.711	
Placebo studies only	Study setting	Inpatient versus Outpatient	-0.164 (-0.516, 0.188)	0.298##	
Placebo studies only		Both versus Outpatient	-0.053 (-0.254, 0.148)	0.545	
Placebo studies only	Functioning as primary outcome	All			
Placebo studies only	Industry sponsorship	All			
Placebo studies only	Study design	All double-blind			
Placebo studies only	Length of trial	Long versus Short	0.009 (-0.175, 0.193)	0.908	
Placebo studies only	Baseline CGI-S for LAI-A group		-0.003 (-0.101,0.095)	0.850	

*Null hypothesis is no in small-study effects; #global p- value==0.8017; ##global P value=0.5376; CGI-S=Clinical global impression-severity; 95% CI= 95% Confidence Interval

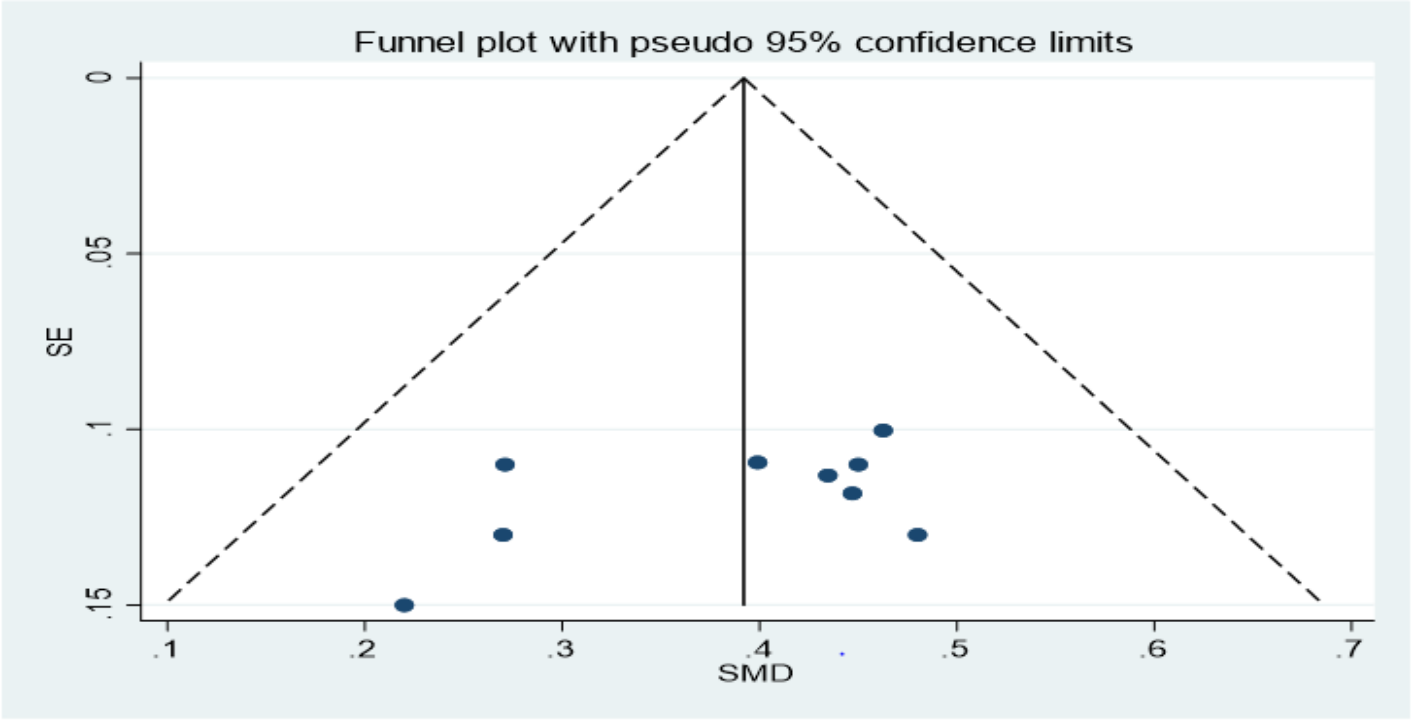
Supplementary S3: Funnel plot for all studies and Egger test



Egger test for all studies

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.220656	.1624294	1.36	0.192	-.12204	.5633521
bias	.3945513	1.461057	0.27	0.790	-2.68801	3.477112

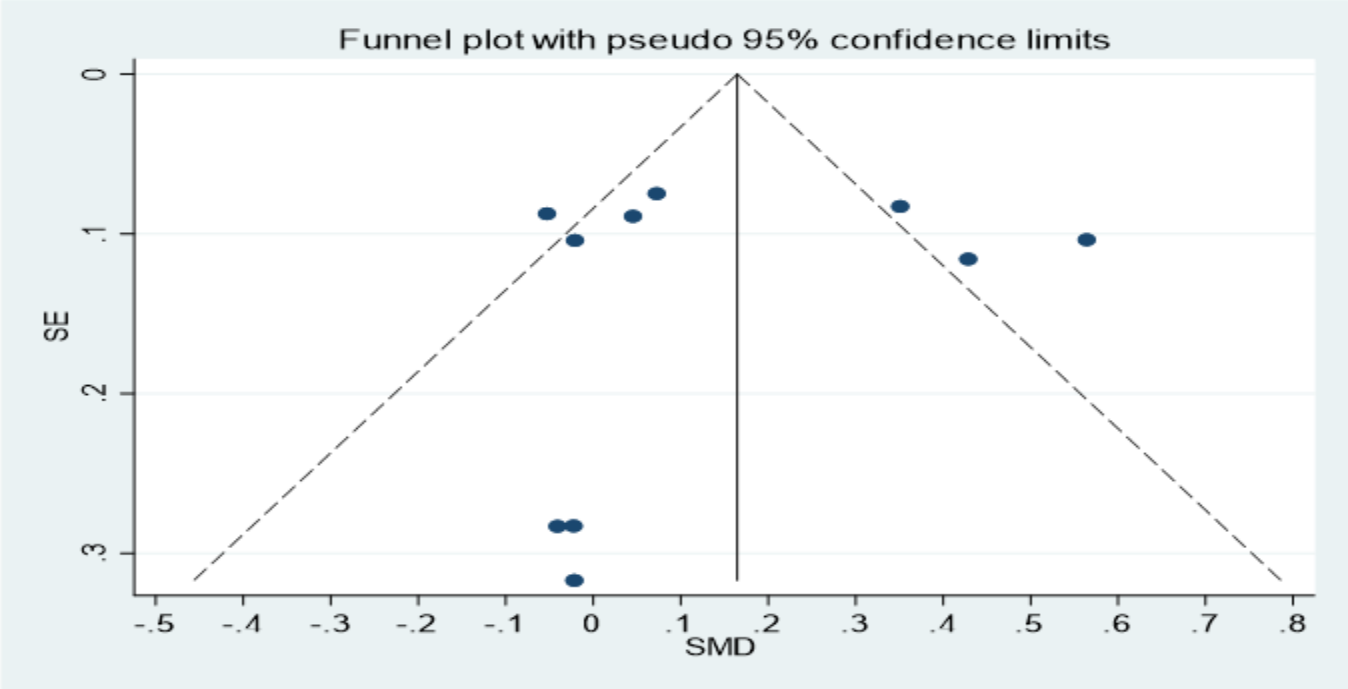
Supplementary S4: Funnel plot for placebo-controlled studies and Egger test.



Egger test for placebo-controlled trials

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.785327	.2575515	3.05	0.019	.1763146	1.394339
bias	-3.390889	2.20685	-1.54	0.168	-8.609261	1.827483

Supplementary S5: Funnel plot for oral-controlled studies and Egger test.



Egger test for oral-controlled trials

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1938582	.1913737	1.01	0.341	-.2474505	.6351668
bias	-.2954459	1.791686	-0.16	0.873	-4.427082	3.83619

Statement of Authorship

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Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Olagunju, A. T., Clark, S. R., & Baune, B. T. (2018). Clozapine and Psychosocial Function in Schizophrenia: A Systematic Review and Meta-Analysis. CNS drugs, 32(11), 1011–1023.

Principal Author

Name of Principal Author (Candidate)	Dr Andrew T. Olagunju		
Contribution to the Paper	Formulated the meta-analytic strategy/ methods, article selection, extraction of data, interpretation of results, drafting and revision of the manuscript.		
Overall percentage (%)	70%		
Certification:	This paper reports on the meta-analytic study I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24/02/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);
II. permission is granted for the candidate in include the publication in the thesis; and
III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	A/Professor Scott R. Clark		
Contribution to the Paper	Supervision, overall guidance of the project, and critical revision of the manuscript drafts.		
Signature		Date	24/02/2022

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Contribution to the Paper	Overall guidance of the project, supervision and critical review of the draft. Communicated with the journal as the corresponding author.		
Signature		Date	24/02/2022

Chapter 3

Clozapine and Psychosocial function in schizophrenia: A systematic review and meta-analysis

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Abstract

Background: Clozapine has unique efficacy for symptoms in treatment-resistant (TRS) schizophrenia; however, symptomatic remission is not necessary nor sufficient for functional improvement. No study has pooled the effect of clozapine on psychosocial function across trials.

Objective: We conducted a systematic review and meta-analysis to compare the effects of clozapine with other antipsychotic drugs on psychosocial function, and described the predictors of functional outcome.

Methods: We searched Medline/PubMed, PsychINFO, EMBASE, CINAHL, Scopus, Web of Science, Cochrane Central Register of controlled trials and clinical trial registries till April 2018, with no language limits. Eligible studies were randomized controlled trials (RCTs) of clozapine versus typical or atypical antipsychotics among adults with TRS. We included studies with flexible or fixed doses of antipsychotics within the therapeutic range to reflect naturalistic care. Effect sizes of studies were pooled using generic inverse variance and random effects models and presented as standard mean differences. Study quality was assessed in accordance with Cochrane collaboration guideline, and subgroup analyses were carried out to identify potential moderators and methodological biases.

Results: Nine studies with 1279 participants and 69.7% males were included. Clozapine showed beneficial effects on psychosocial function, but both short-term trials [n = 3; comparing 99 people on clozapine with 97 controls (standardized mean difference [SMD]= 0.04; 95% Confidence interval [95% CI] = -0.24, 0.32; p=0.77; I^2=0%)] and long-term trials [n = 5; comparing 415 people on clozapine with 427 controls (SMD=0.05; 95% CI= -0.16, 0.27; p=0.64; I^2=50%)] showed no superiority of clozapine to other antipsychotics in this regard. Only one study explored the predictors of psychosocial function. Baseline severity of illness, illicit drug use, extrapyramidal side effects, gender and cognition explained the variability in functional outcome.

Conclusions: Clozapine does not appear superior to other antipsychotics for improvement of psychosocial function. Standardization of psychosocial function measurement is needed to improve the quality of evidence. Further exploration of the predictors of good psychosocial outcomes with clozapine treatment may improve personalisation of care.

Introduction

The improvement of psychosocial function in schizophrenia remains a challenge despite recognition that patients' subjective well-being, quality of life (QoL) and day-to-day capability should be a fundamental objective of recovery-focussed care.[1, 2] Functional impairment is a core feature of schizophrenia and patients with poor treatment response tend to experience significant disability in this regard.[3-5] Although underutilized, clozapine is thought to have unique efficacy for treatment of symptoms and is regarded as the gold-standard antipsychotic for treatment-resistant schizophrenia (TRS), [6, 7] defined as failed response to adequate trial of two or more different antipsychotic drugs. [8-10] While complete symptomatic remission is possible with clozapine, functional recovery can vary across patients and through the course of illness [3, 11-13]

When first introduced about six decades ago, clozapine was approved for the treatment of all patients with schizophrenia. In fact, it was considered a major breakthrough for motor side effects and response in the one-third of patients resistant to typical antipsychotics.[14-17] It was however withdrawn from the market due to a cluster of deaths associated with agranulocytosis reported in Finland in the mid-1970s. Due to its effectiveness, clozapine was re-introduced in the 1990s with routine white cell count monitoring to safeguard against severe neutropenia.[18, 19] Clozapine is associated with a range of other serious side effects including seizures, myocarditis, cardiomyopathy, severe constipation and metabolic syndrome and is reserved for schizophrenia resistant to at least two other antipsychotics.[2, 10, 20] Hesitation in clozapine use can result in a long duration of ineffective treatment, chronicity, worsening of psychosocial function and poorer prognosis in patients. [21, 22]

The mechanism of clozapine efficacy is unknown. The additive effect of antagonism for a range of neuroreceptors including low affinity for D2 receptors, high affinity for 5HT2A, muscarinic and histaminergic receptors,[16,23] and clozapine's modulatory action on glutamatergic neurotransmission may be central to its effectiveness.[24] Evidence suggests a complex interplay of genetic predisposition, structural and neurodevelopmental abnormalities and neurotransmitter deficits are explanatory of the variability in clozapine response.[16, 25]

There is agreement that clozapine effectively reduces "positive" symptoms compared to other antipsychotics in TRS,[10,26-29] although as much as 40-70% of TRS patients may be clozapine resistant.[7,26, 30-33] Patients treated with clozapine can experience improvement in cognition and

functional outcomes.[10,29, 4,35] However, there has been no comprehensive analysis of clozapine effects on psychosocial function across clinical trials. [8,27,28, 34,35] Additionally, there has been no systematic review of the predictors of changes in psychosocial function in clozapine treatment trials. There has been limited consensus on the definition of psychosocial function, and the lack of clear standards to index 'healthy' levels of accomplishments in functional domains for the process of recovery are common challenges for comprehensive comparative analyses.[36, 37]

Although psychosocial function can be measured without incorporating patients' subjective well-being, it is now generally considered best practice to include QoL in its definition.[38-41] Thus, we defined psychosocial function in this study as a multidimensional concept that looks at individuals' function in the context of the combined influence that psychological factors and the surrounding social environment have on their physical and mental wellness, their ability to function, and maintain wellbeing.[39, 42] The essential components can include multiple domains of basic-daily function, socio-occupational function, interpersonal relationship, adaptive function, life satisfaction and QoL.[39,40,42] Such multi-dimensional construct of psychosocial function that include composite measures of patient's personal experience have recently gained support as more reliable, valid, comprehensive and holistic indicators.[43]

The assessment of psychosocial function with rating scales is widespread in clinical settings and trials. These scales can be interviewer-administered to allow a degree of objectivity or self-reported to incorporate the subjective experiences of patients. Such ratings are often supplemented with data from 'hard' proxy indicators of psychosocial function including hospital use, community tenure and productive or supported employment activities. Although, these proxy outcomes are considered reliable to ascertain 'real-world' effectiveness of antipsychotics,[44,45] their generalizability can be limited, methodological biases are possible and they fail to capture the personalised experience of mental illness. For example, hospitalization can differ significantly across healthcare systems, and acceptability of hospital-use data is generally poor among end-users due to their fear of service-providers bias.[44]

The value of an optimum construct for evaluating psychosocial function is evident. It can allow a comprehensive capturing of the multifaceted aspects of functioning to inform diagnosis and plan recovery-oriented care. We therefore conducted this systematic review and meta-analysis using multi-dimensional measures of psychosocial function to compare the effects of clozapine

on functional outcome with control antipsychotics in TRS. We also systematically reviewed factors predictive of improvement in functional outcome across the included trials. Lastly, we appraised the quality of assessments of psychosocial function applied across the included trials.

Methods

Search methods for study identification

This study was conducted in accordance with the Cochrane collaboration guideline and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement recommendations.[46-48.] This was to ensure comprehensive and transparent reporting in the background, search strategy, methods, results and discussion. We searched electronic databases such as Medline/PubMed, PsychINFO, EMBASE, CINAHL, Scopus, Web of Science, Cochrane Central Register of controlled trials and clinical trial registries (http://clinicaltrials.gov/) from inception until April 2018, with no language limits. In the case of PubMed, the terms used as string in combination to search in titles, abstract and as MeSH terms included: (clozapin* OR clozaril OR zaponex OR denzapin* OR clopine) AND (Schizophrenia OR Schizophren* OR Schizo*) AND (Quality of Life OR Life Quality OR Health-Related Quality of Life OR HRQOL OR QoL OR Function* OR "Psychosocial Function*"). An additional search was done with the names and standard abbreviations of scales used to measure psychosocial function and QoL. The scales included; "global assessment of function", "Heinrichs-Carpenter QoL scale", "Short Form-36 Health Survey", "Personal and Social Performance scale", "Strauss-Carpenter Levels of Functioning" and "Social and Occupational Functioning Assessment". The reference lists of retrieved articles and reviews were also searched to identify additional relevant articles. Experts in the field and authors of studies were contacted for additional or missing data.

Eligibility criteria

We included all relevant randomized controlled trials (RCTs) recruiting adult patients 18 years or older with TRS[10] treated with clozapine compared with typical or atypical antipsychotics, that provided information on measures of psychosocial function and QoL. The main outcome was change in psychosocial function. Where possible we also collected data on factors that predicted

change in psychosocial function. The age-group for the included studies reflects the pattern in clozapine trials among adults, and agrees with existing literature on the epidemiology of schizophrenia.[49] The use of clozapine in children and adolescents is less encouraged because of several challenges including pharmacokinetics, its potential effects on brain development and sensitivity to adverse side-effects.[50, 51] These are important issues in paediatric clozapine trials that may interplay with psychosocial function and warrants expansive discussion. The range of psychosocial function measures in these adult trials are validated for adult population, and limits head-to-head comparison with paediatric trials. Overall, we suggest analysis of adolescent studies is outside the scope of this current review.

Study selection and screening

We included rater-blinded open label RCTs to improve study power. Studies with flexible or fixed doses of antipsychotics within the recommended therapeutic range for clinical efficacy were shortlisted to reflect naturalistic care.[52] Non-randomised controlled studies, and single arm prospective experimental trials were excluded.[48] Predictors of functional outcome were only reported in one study, described as a systematic review.[3]

All identified papers were screened at title and abstract level by Andrew T. Olagunju [ATO] and Scott R. Clark [SRC] independently. Full texts of the 114 selected papers were reviewed by ATO and by SRC for eligibility based on the highlighted study criteria.

Outcome parameter

The main outcome was longitudinal change in psychosocial function associated with clozapine treatment in comparison to all types of control antipsychotics. We also collected data on factors that predicted change in psychosocial function. Studies were grouped into short term (less than 3 months) and long-term (3 months or more) trials.[6, 27] Where multiple outcome time points were reported in the same study, the data for the last outcome time point in each period (short or long term) were used. We also performed analysis for all time points, with the data for the last outcome time point in each study.[6, 47, 48]

Data extraction

Data extraction was done by ATO and verified by SRC using a piloted form based on the PRISMA guidelines, and included the PICOS data items (population, intervention, comparison, outcomes, and setting). Data extraction forms collected the following data: first author, funding source, study design; study country or sites, participants characteristics (age range, total number, gender, diagnosis and treatment setting), trial duration, antipsychotics (clozapine versus comparator drugs), dosage, trial arms, measures of psychosocial function, clinical scales, findings on psychosocial function (baseline, endpoint and mean change), and identified predictors with statistical significance. During data collection, we resolved discrepancies through discussion and consultation of the senior author Bernhard T. Baune (BTB) where necessary.

Study quality and risk of bias

We assessed risk of bias in the included studies using the criteria stipulated in the Cochrane Collaboration guidelines.[48] Study quality was assessed with respect to random sequence generation, allocation concealment, blinding of personnel, blinding of outcome assessment, incomplete data reporting, selective reporting and other sources of bias including industry sponsorship.[6, 48] The presence of possible publication bias was visually assessed with funnel plots and egger test was conducted.[38, 53]

Statistical analyses

We conducted a systematic review of findings on psychosocial function in all included studies, and on predictors of psychosocial function in one report. All outcomes were analysed as continuous measures in meta-analyses. We used Review Manager Version 5.3 for Windows [48] to perform meta-analyses and compared clozapine with all comparator antipsychotics on change in psychosocial function using standardized mean difference (SMD) as the primary effect size. Funnel plots with egger test were performed using STATA. [54] Analysis was conducted considering all time points, with data for the last outcome time point (short OR long-term trials) in each study used to calculate change from baseline. In cases of missing data standard deviations for mean change in score from baseline, statistical calculation was done based on Cochrane Collaboration methodology.[32, 48]

To address the heterogeneity in the measures of psychosocial function, we used the generic inverse variance model and random effects to estimate the pooled SMD of the included studies and p-value <0.05 (two-tailed) was considered statistically significant. Effect size of SMD of 0.2 was considered small, 0.4 medium and 0.8 large.[48] If change score was not available, the endpoint value was subtracted from baseline. Where possible intention-to-treat analysis was used.[55,56] Study heterogeneity was investigated using the sensitivity test and the chi-square test of homogeneity (p-value <0.05) together with the I^2-statistic. We considered 50% heterogeneity or higher non-negligible and looked for explanations in the included studies.[48, 57]

In addition to primary outcome analyses, subgroup analyses were carried out to identify potential moderators, and methodological biases. We considered industry sponsorship, and duration of trial.[58] To check the effects of trial duration, we categorized the included studies into short term for trials not beyond three months and those greater than three months were grouped as long term.[27]

Results

Article selection and flow diagram

A total of 1520 papers were identified from electronic databases after duplicates were removed, and 1406 were excluded as ineligible at the title and abstract screening. Of the 114 full texts reviewed, nine were shortlisted while 105 papers were excluded due to irrelevant design and measures (n=90), duplicate report or data (n=20), and irrelevant treatment (n=24). Some of the studies were excluded based on multiple reasons. Nine shortlisted papers were included in a qualitative review. Three of the papers identified from the search lacked useable data. Thus, six papers that reported three short-term and five long-term studies were shortlisted for the meta-analysis. Only one paper reported predictors of psychosocial function [3]. Figure 1 presents a PRISMA- flow diagram of paper selection.[46]

[See Figure 1-PRISMA Flow chart]

Study characteristics

The study characteristics are shown in Table 1 and supplemental table S1. All nine papers were published from 1996 to 2009, and included 1279 participants with 69.7% males. Trial duration ranged from ten to 104 weeks, categorised into short-term (n=3) [12, 13, 62] and long-term (n=5)

trials **[12,13,60,61,63]** based on cut-off of 12 weeks.[6, 27] Two papers[12,13] reported both short-term and long-term studies. Three naturalistic studies compared clozapine with typical or atypical antipsychotics.[3, 12, 59] Two studies each compared clozapine to haloperidol[11,60] and olanzapine.[12, 61] A single study compared clozapine to risperidone[62] and ziprasidone.[63] With exception of one single centre trial[11] performed in the United States (US), other trials were multi-centre, including four trials in US[3,12,59,60] and one each in Germany, [61] Finland,[62] Italy,[63] and United Kingdom.[13] Diagnosis of schizophrenia spectrum disorders was based on Diagnostic and Statistical Manual of Mental Disorders (DSM) (third edition-text revised and fourth edition)[64] criteria in all studies. Recruitment took place from the community in two studies,[11,12] while other trials recruited from both hospital and community patients. In addition to semi-structured DSM diagnostic scales, other clinical scales used to assess symptom severity were the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Symptom Scale (PANSS), Clinical Global Impression of Severity (CGI-S), Calgary Depression Scale (CDS), and Schedule for Affective Disorders and Schizophrenia Lifetime (SADS-L). Extra-pyramidal side effects were assessed using the Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS) and Barnes Akathisia Scale (BARS). Cognitive function (Cogtest) was investigated in two studies.[3, 12]
In total, eight scales were used to measure psychosocial function. Most of the studies assessed function with a single scale (n=4).[12, 59, 60, 63] and two scales (n=4), [3, 11, 61, 62] while one study used three scales.[13] Heinrichs-Carpenter QoL scale (QLS)[65] was used in five studies, Global Assessment of Function (GAF)[64] in four, Short Form Scale in two studies (SFS)[66] and one study each used Strauss-Carpenter Levels of Functioning Scale (LOFS),[67] Munich Life Dimension List (MLDL), Quality of Life Interview (QoLI)[68] and European Quality of Life Scale (EuroQoL).[69]
[See Table 1 here]

Study Quality and risk of bias

Study quality was fair (see Figure 2). Six studies reported adequate allocation concealment,[3, 11, 12, 60-62] while one study was single blinded[13] (interviewers were blinded) and two others were open labelled.[59, 61] All included studies were randomised, however only four provided detailed information including the use of unbiased coins,[46] permuted blocks,[13] random number table,[12] and computer-generated randomization.[62] No study reported whether blinding was successful.

Five studies [3, 12, 13, 60, 61] considered functioning measures as primary outcome. Three studies [60, 61, 63] were industry sponsored [Additional details included in supplementary S1 and S2].

Psychosocial function in short-term and long-term trials

All studies reported improvement in psychosocial function in patients on clozapine and control antipsychotics. Three short-term studies reported usable data for change in psychosocial function for 99 people given clozapine and 97 controls on varieties of typical and atypical antipsychotics. While the pooled effect favoured clozapine numerically (Standardized Mean Difference [SMD] = 0.04; 95% Confidence interval [95% CI] = -0.24, 0.32; p=0.77; n=196; I^2=0%), difference in function between treatment groups was not significant (See Figure 3). This finding was sustained in five long-term trials comparing 415 people on clozapine with 427 controls (SMD=0.05; 95% CI= -0.16, 0.27; p=0.64; n=842; I^2=50%). The combined effects across short-term and long-term studies using longest time endpoints when a single study reported both short-term and long term trials showed no superiority (SMD= 0.04; 95% CI=-0.15, 0.24; p=0.10; n=862=; I^2=38%) [Details included in supplementary S3].

Sensitivity-subgroup analyses

Industry funding did not have trial effects (SMD= -0.01; 95% CI=-0.16, 0.14; p=0.89; n=666; I=0%). Egger test showed no publication bias considering all studies (intercept, -0.031; 95% CI= -0.556, 0.494; p=0.783), and when short-term (intercept, -0.047; 95% CI= -.083, 3.062; p=0.837) and long-term trials (intercept, 0.560; 95% CI=-3.081, 4.203; p=0.691) were considered [Details included in supplementary S4].

Predictors of psychosocial function

One study reported on predictors of function at 12-month follow up in a sample of 455 patients with chronic schizophrenia enrolled in a multisite, multi-arm comparison of other medications with clozapine.[3] Table 2 shows that at baseline poorer quality of life, higher severity of illness, illicit substance use, urban residence, poor cognition and extra-pyramidal side effects predicted worse psychosocial outcome at 12 months with small effect size. Female gender was protective against poor functional outcome. While baseline quality of life was the strongest predictor at 13.2 %, combined these factors accounted for 28% of the variance in psychosocial function.

Discussion

This is the first study to pool the effects of clozapine for psychosocial function across trials, combining three short-term and five long-term studies. A total of 1279 participants and 69.7% males were included. All trials looked at patients with treatment-resistant schizophrenia, a sub-group that often experiences severe psychosocial impairment and disability.[7] Overall, clozapine showed beneficial effects on psychosocial function, but was not superior to other antipsychotics.

Clozapine's lack of superiority in the treatment of functional deficits can be in part explained by its limited impact on long term negative symptom burden.[6] Negative symptoms and psychosocial dysfunction are well correlated in schizophrenia, and experts have proposed a contiguous neurobiological basis for these two phenomena.[70] Given poor response to treatment, it is possible that patients within clozapine trials are a group with more severe neurodevelopmental pathology and diminished cortical reserve, which limits their margin for recovery with current interventions.[71] Alternatively, delay to clozapine use and associated chronic exposure to antipsychotics has been linked with decrease in brain volume, limited improvement and worse long-term prognosis.[16,71]

Recovery is influenced by several factors that include symptom stability,[70,72] and the skills for psychosocial functioning are partly "learning-training based." Thus, clozapine therapy alone may not be sufficient for adaptive adjustment and functional recovery.[73] Taking together, recovery in the context of clozapine pharmacotherapy can become more apparent with incorporation of multi-modal psychosocial therapies that allow learning-training of psychosocial skills.[72,73]

In the one trial that assessed baseline factors, a range of variables including male gender, baseline psychosocial function, severity of illness, illicit substance use, extra-pyramidal side effects and poor cognition predicted poor functional outcome in chronic schizophrenia.[3,74] The majority of these factors have an established linkage with poor prognosis.[70,73] The influence of illness severity and cognition on recovery cannot be over-emphasized because psychosocial engagement, role performance and inter-relational skills do flourish with clinical remission-stability, while faulty cognitive appraisal of the illness experience can hinder insight, medication adherence and the positive emotion needed for recovery.[75,76] It is not surprising that both illicit drug use and extra-pyramidal side effects partly explained the variability in psychosocial recovery. In addition to their discomfort, extra-pyramidal symptoms can serve as barriers to

instrumental daily activities,[3] and may hinder productive activities due to fear of embarrassment and stigma.[3] Similarly, illicit substance use has strong correlation with medication non-adherence, extra-pyramidal symptoms and poor functional outcome.[77] That said, it is interesting that the aggregate effects of the predictors explained greater variability in psychosocial function than individual factors and justifies the recent proposal of a multi-dimensional model for prognostic and trajectory prediction to allow targeted intervention.[78]

In general, findings in this study underscore the challenging nature of psychosocial impairments in schizophrenia, particularly in those with poor treatment response, and the potential limitation of clozapine despite its unique efficacy. Clozapine therapy alone may have a limited impact on real-world psychosocial functioning for some patients, thereby paving the way for trials of novel multi-modal treatment approaches.[73]

Research into novel treatments for functional recovery in schizophrenia is ongoing, and several approaches including multimodal pharmacotherapy and psychosocial therapies such as cognitive behavioural therapy, cognitive remediation, psychosocial rehabilitation, illness self-management training, and family support have been suggested as alternatives for clozapine partial or non-responders.[30] Reduction of negative symptoms can be achieved by augmentation of clozapine with agents such as aripiprazole, fluoxetine and memantine[79] but the impact of these treatments on function is yet to be systematically explored. The use of clinical predictors and biomarkers to personalise the selection of interventions in TRS has potential to improve outcomes in the future.[80-82]

The evidence for the efficacy of psychosocial treatment in schizophrenia has been summarised in a series of clinical trials and meta-analyses that have occurred over last two decades.[83-87] For instance, a comprehensive work comparing a combination of psychosocial and drug treatment with pharmacotherapy alone found that combined treatment was superior to medication alone with an effect size of 0.39.[84] Overall, the current evidence base for the effects of psychosocial interventions includes thousands of studies on hundreds of interventions. However, implementation issues exist at the levels of providers, provider training programs, service delivery systems, and payers.[88]

Generally, psychosocial treatment is recommended as adjunct treatment in schizophrenia for recovery in clinical treatment guidelines.[1,2,31] However, the subsequent steps entailed in bringing

a psychosocial intervention into routine clinical care are less well defined. Guidelines recommend a comprehensive implementation that will serve the full range of people with schizophrenia, providing access to the full range of recovery-oriented evidence-based services, providing "patient-centred care."[1,2,20,31] Ultimately, the availability of psychosocial interventions is highly influenced by the policies of payers. It is therefore tenable to conclude that an optimum model for psychosocial intervention should fundamentally be "patient specific" and context-specified.

Despite this weight of evidence, the majority of antipsychotic treatment trials are modelled to test the efficacy of pharmacotherapy and less focused on a "pharmaco-psychosocial model,"[86] although a small number of trials have investigated clozapine augmentation with CBT.[89,90] More trials on the effects of "pharmaco-psychosocial" interventions are needed. ''Pharmaco-psychosocial'' therapy will be best informed by an improved knowledge of clozapine effects on functional outcome, and its predictors. We recommend comprehensive assessments of psychosocial function with multidimensional measures that are less overtly cofounded by symptoms and reliably incorporate patients lived-experiences. Both short- and long-term aspects of functioning are important to capture its dynamic nature, and inform the emerging dimensional model of psychopathology and individual-focused care in psychiatry.

Findings in this study should be interpreted in light of several limitations. Previous meta-analyses of clozapine symptomatic efficacy included many more clozapine trials; however, most of these trials either did not measure psychosocial function, or did not report these findings.[6,91] Heterogeneity was apparent in psychosocial outcomes across studies. A range of psychosocial measures was used either alone or in combination, but the quality of reporting was not consistent across the trials. Due to the multiple other antipsychotics used in trial arms, we were not able to compare clozapine head-to-head with other antipsychotics.[3,13,59] We attempted to address the associated heterogeneity using random effects models and by conducting sensitivity and subgroup analyses. Encouragingly, psychosocial function was a primary outcome in more than half of the included trials. Unlike previous meta-analyses,[6,92] industry funding was not a concern because most trials were non-industry funded and a sensitivity analysis did not alter the results. Finally, it is important to note that the results in any trial of clozapine may be systematically biased due to required monitoring and unique adverse drug reactions.[6, 53]

Overall there is a need to standardize the measurement and reporting of psychosocial function in trials.[8, 28] It is surprising that no recent trial has revisited psychosocial function in patients on clozapine, despite greater emphasis on recovery-oriented care.[2] Of further concern is that only one of the studies[3]analysed the predictors of psychosocial functioning.

Conclusion: To conclude, although clozapine was beneficial for psychosocial function in meta-analysis, its impact was equivalent to other antipsychotics. Clozapine's greater potential to reduce positive symptoms may improve learning of psychosocial skills towards recovery such that combined "pharmaco-psychosocial" therapy may be synergistic toward better outcomes. The quality of evidence and standardization of measurement of psychosocial function need improvement.

Conflict of interest

All the authors (ATO, SRC and BTB) declare that they have no conflict of interests concerning this paper.

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Figure 1: Flow diagram of study selection

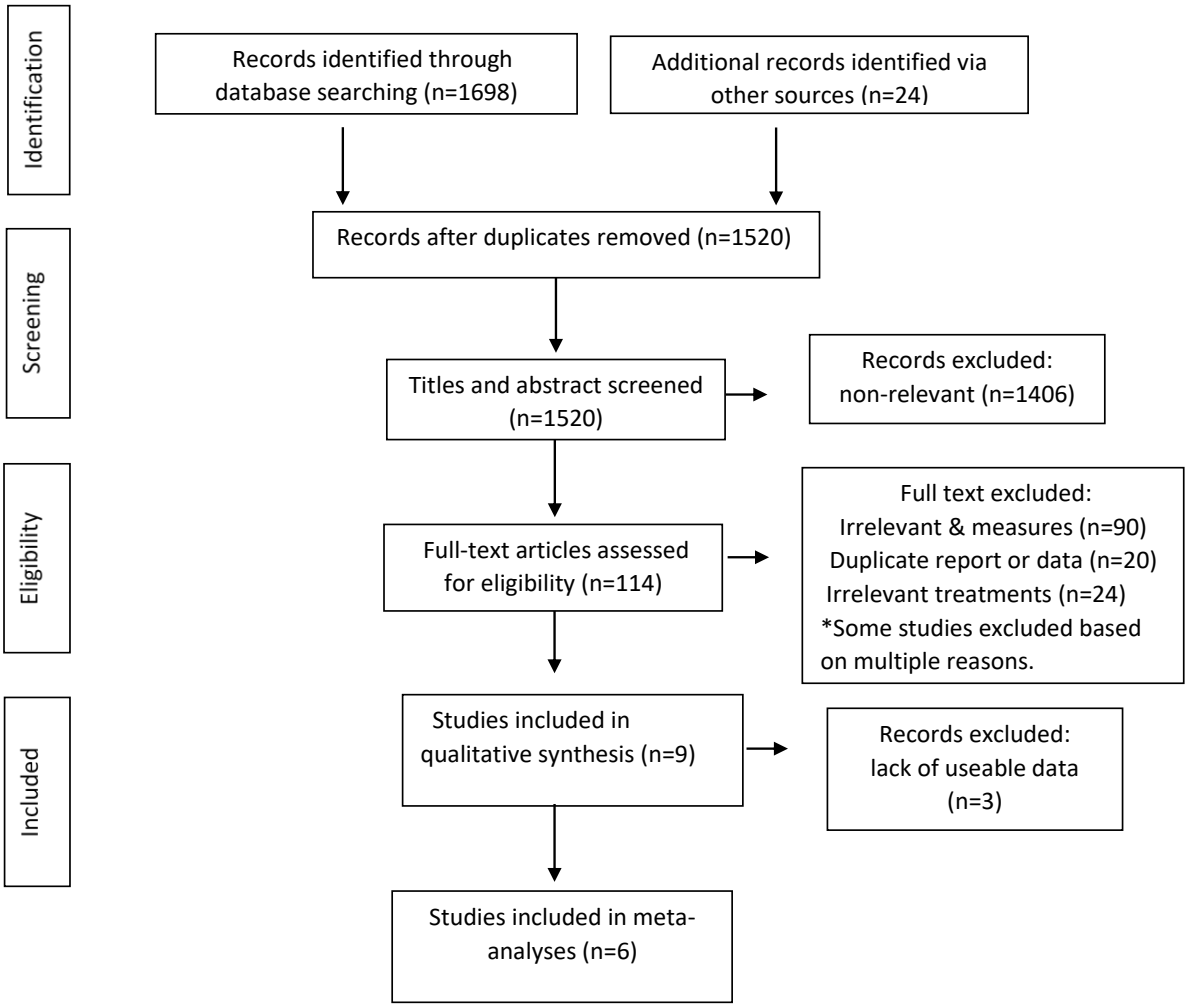


Figure 2: Summary of risk of bias for included studies

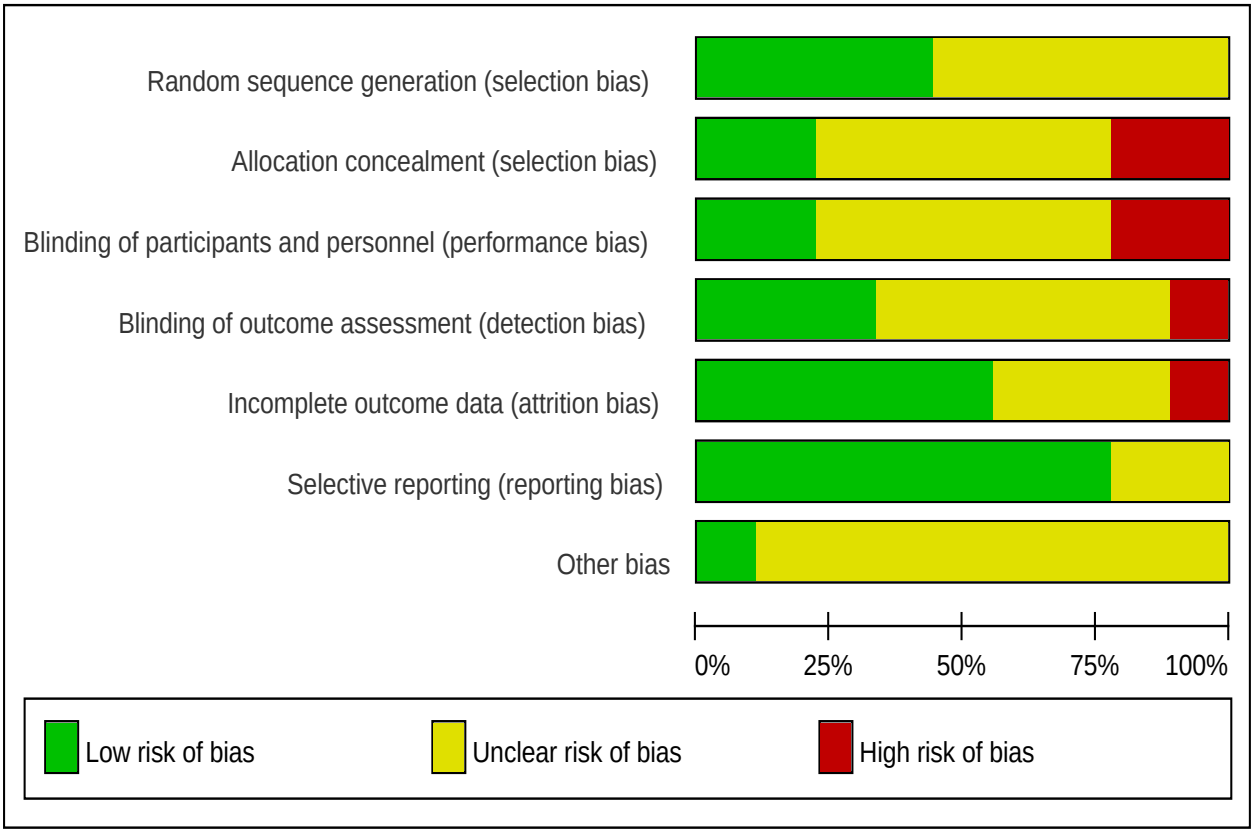


Figure 3: Short-term and long-term trials of clozapine versus controls

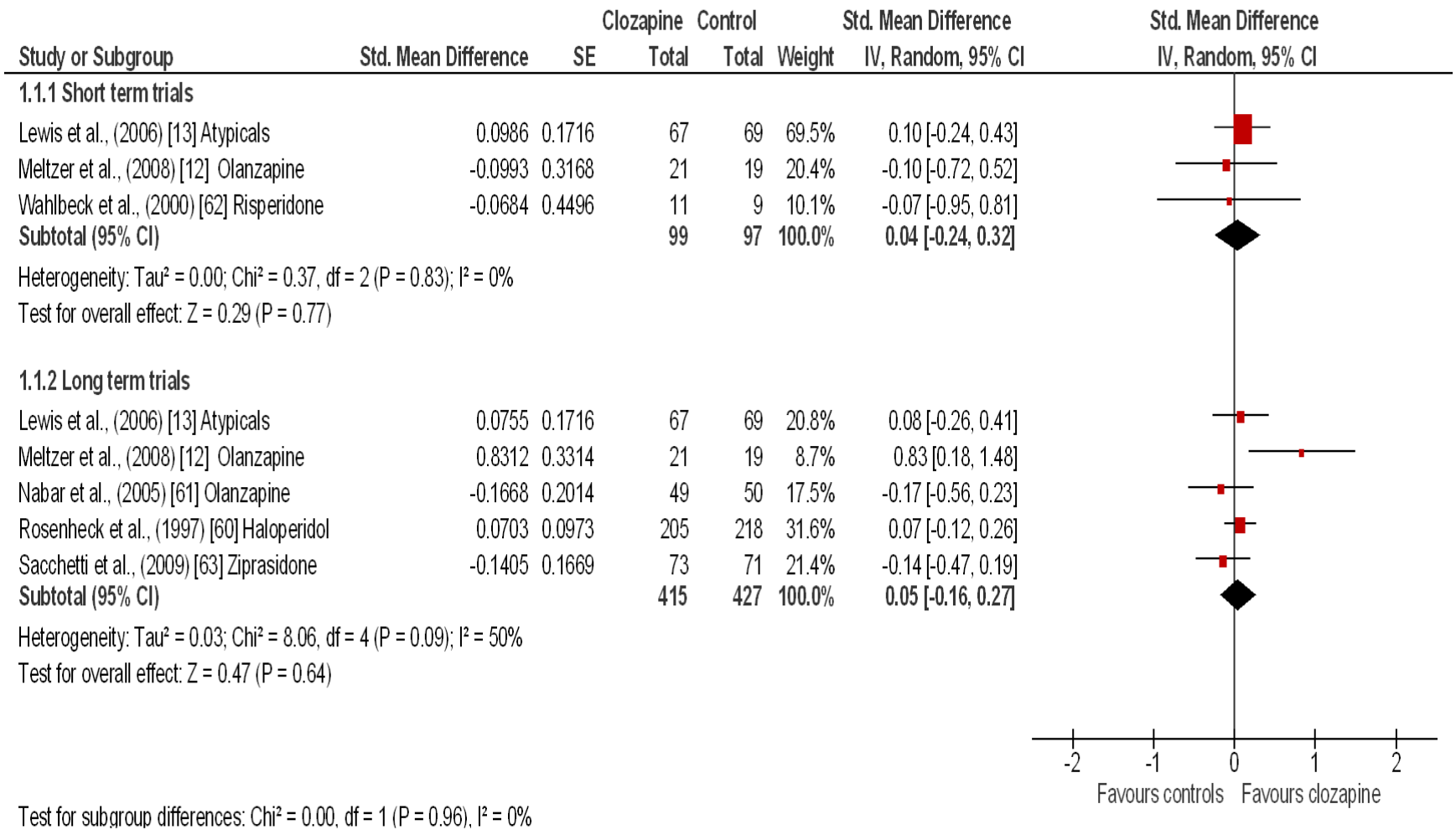


Table 1: Characteristics of included studies

Study	Design	Sample Gender (%)	Comparator Drugs	Functional measures	Clinical scales	Findings on functional measures
Buchanan et al., (1998) [23]	RCT double-blind Ratio=1:1 Clozapine Vs Haloperidol	N= 75 M=70·0%	Haloperidol	QLS; LOFS	DSM-III-R; BPRS; SANS; SAS	**QLS/LOFS*:*** Greater increase in total functional score over time in clozapine compared to haloperidol but difference not significant.
Essock et al., (1996) [59]	RCT open label, Ratio 1:1.5 Clozapine Vs Open list	N=227 M=60.7%	Typicals or Atypicals (usual care)*	QoLI	DSM-III-R; BPRS; CGI; AIMS	**QoLI:** There was no significant difference in quality of life scores between clozapine compared to oral drugs (4.7 for both groups, P>0.05), although both groups improved over the trial time.
Lewis et al., (2006) [13]	RCT single-blind Ratio=1:1 Clozapine Vs Atypicals	N=136 M= 68.4%	Amisulpride, Olanzapine, Quetiapine, Risperidone	QLS, EQ-5D, GAF	DSM-IV; CDS; PANSS; AIMS, BARS, SAS; DAI; PSQ; ANNSERS	**QLS:** Clinically significant change (increase) in total score from baseline to endpoint in larger proportion of those on clozapine (31%) compared to atypicals (25%). No significant difference in QoL improvement between clozapine versus atypicals based on change in mean (±SD) score on QLS.
Meltzer et al, (2008) [12]	RCT double-blind Ratio:1:1 Clozapine Vs Olanzapine	N=40 M=67.5%	Olanzapine	GAF	DSM-IV; SAS; BARS; AIMS; SANS; PANSS; CGI; CogTest	**GAF:** Clozapine treatment resulted in greater improvement in function than treatment with olanzapine (p=0.01)

Study	Design	Sample Gender (%)	Comparator drugs	Functional measures	Clinical scales	Findings on functional measures
Naber et al., (2005) [61]	RCT double-blind Ratio: 1:1 Clozapine Vs Olanzapine	N=114 M= (61%)	Olanzapine	SWN, MLDL	DSM-IV; SAS; BPRS; PANSS; CGI-S	**SWN**: Significant difference in longitudinal change (improvement) in clozapine 8.2 (±15.8) and olanzapine 11.3 (± 20.7) group, but no superiority was shown between the two drugs. **MLDL:** Improvement in quality of life in olanzapine 1.3(± 2.0) and clozapine 1.3(±1.6) and no superiority was shown.
Rosenheck, et al., (1997) [60]	RCT double-blind Ratio1:1 Clozapine Vs Haloperidol	N= 423 M=97.6%	Haloperidol	QLS	DSM-III-R, BPRS; CGI-S; SANS; PANSS; AIMS; SAS; BARS	**QLS**: Significant improvement in functioning in clozapine and haloperidol at treatment endpoint. The proportion of those with improvement in functioning in clozapine (53%) was significantly different compared to haloperidol 37% (p=0·02).
Sacchetti et al., (2009) [63]	RCT double-blind Ratio 1:1 Clozapine Vs Ziprasidone	N= 144 M=69.1%	Ziprasidone	GAF	DSM-IV; SAS; PANSS; CGI-I; CGI-S; DAI-10; AIMS; BARS	**GAF:** Results showed progressive and significant improvement in functioning over time from baseline in both treatment groups. No evidence of significant differences between ziprasidone and clozapine arms emerged at endpoint
Swartz et al., (2007) [3]	RCT double-blind Ratio 1:1 Clozapine Vs Atypical drugs	N=99 M=81%	Olanzapine, Quetiapine, Risperidone	QLS; SF-12	DSM-IV; CDS; PANSS; CGI-S; AIMS; BARS; SAS; CogTest	**QLS:** Significant change in score (increase) over time in clozapine and atypical drugs indicating improved functioning. There was significant difference between clozapine and the atypical group in quality of Life Scale.
Wahlbeck et al., (2000) [62]	RCT open-label Ratio 1:1 Clozapine Vs Risperidone	N=21 M=52.6%	Risperidone	GAF; SFS	DSM-IV; CGI-S PANSS; DAI; PGI	**GAF/SFS**: Total scores were non-significantly superior for clozapine over risperidone at study end.

AIMS=Abnormal Involuntary Movement Scale; ANNSERS= Antipsychotic Non-Neurological Side-Effects Rating Scale Record; BARS= Barnes Akathisia Scale; BAS= Burden Assessment Scale; BPRS= Brief Psychiatric Rating Scale; CDS=Calgary Depression Scale; COA=Common objects and activities; Cogtest= Cognitive battery test; C-SSRS=Columbia-Suicide Severity Rating Scale; CGI-S-SCA=Clinical Global Impression of Severity for Schizoaffective Disorder; DAI=Drug Attitude Inventory; DIEPSS= Drug-Induced Extrapyramidal Symptoms Scale; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders-fourth edition; DSQ=Deliberate Self-harm Questionnaire; ESRS=Extrapyramidal Symptom Rating Scale; GAF-=Global Assessment of Function; M=male; MLDL= Munich Life Dimension List; MSQ= Medication Satisfaction Questionnaire; LOFS=Strauss-Carpenter Levels of Functioning Scale; N=frequency; nr= not reported; PANSS=Positive and Negative Symptoms Scale; %= Percentage; PGI= Patient Global Impression Scale; QLS= Heinrichs-Carpenter QoL scale; QoLI=Quality of Life Interview; RCT-randomised controlled trials; SADS-L=Schedule for Affective Disorders and Schizophrenia Lifetime; SANS=Scale for Assessment of Negative Symptoms; SAS=Simpson-Angus Scale; SFS= Social Functioning Scale; SF-12=12-Item Short Form Health Survey; SQLS-R4= Schizophrenia Quality-of Life Scale Revision 4; SWN-S=Subjective Well-being Under Neuroleptic Treatment-short version *Usual care with typical and atypical drugs including haloperidol, chlorpromazine, fluphenazine,, thiothixenes, thioridazine, loxapine, perphenazine, mesoridazine, molindone, trifluoperazine, chlorprothixene, and risperidone

Table 2: Predictors of change in functioning in Clozapine

Study	Predictors of change in function	Statistics (Regression coefficient & Effect size)
Swartz et al., (2007) [3]	**Predictors of change in psychosocial function** Symptoms severity, illicit substance use, extra-pyramidal side-effects and poor neurocognition were significantly associated with poor psychosocial function. While women were more likely to have better psychosocial function.	**Partial r^2 (df=1)** Baseline Quality of Life Scale total score r^2 = 0.136; P<0.01 Change in CGI severity rating r^2=0.034; P<0.01 Illicit substance abuse r^2= 0.017; P <0.01 Baseline neurocognitive score r^2=0.015; P <0.01 Gender r^2=0.015 P<0.01 Extrapyramidal symptom change r^2= 0.007; P=0.005 Combination of factors explained 28% variability in psychosocial function in a regression model (R^2=0.28)

CGI=Clinical Global Impression; df= degree of freedom; p=level of significance; r^2 and R^2 = Coefficient of determination

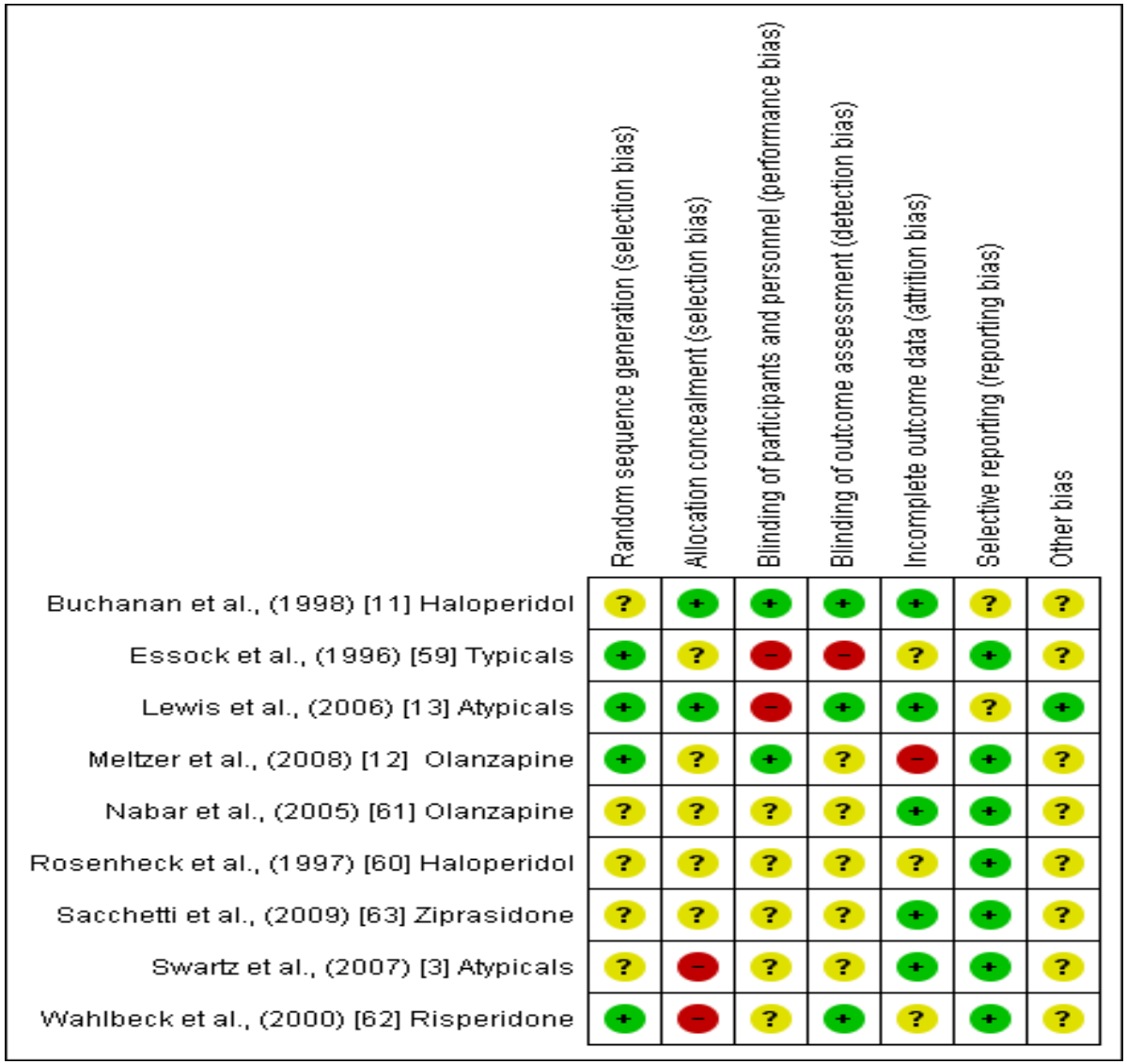
Supplemental S1: Additional information on included studies

Study	Study location	Dosage	Participants details	Duration	Functioning was primary study outcome/Analyses	Industry sponsor/ Trial number
Buchanan et al., (1998) [11]	Single-center: United States	CL=200-600mg/d HA= 10–30 mg/d	Mean age= 36.0 (±8.0) years Diagnosis: Schizophrenia or Schizoaffective disorder; outpatient	10 weeks	No ITT	No nr
Essock et al., (1996) [59]	Multi-center- United State	CL=496mg/d TY=1,386mg/d*	Mean age= 41(±16.3) years Diagnosis: Schizophrenia or Schizoaffective disorder; inpatient	104weeks	No ITT	No nr
Lewis et al., (2006) [13]	Multi-center: United Kingdom	CL= 330mg/d AT=flexible	Mean age=37.6(±12.2) years Diagnosis=Schizophrenia or schizoaffective disorder; inpatient or outpatient	52 weeks	Yes ITT	No nr
Meltzer et al., (2008) [12]	Multi-center: United States	CL=300-900 mg/ OL=25-45mg/d	Mean age=46·4(±10·3) years; Diagnosis: schizophrenia or schizoaffective disorder; outpatient	26 weeks	Yes ITT	No NCT00179231
Naber et al., (2005) [61]	Multi-center; Germany centers	CL=100–400mg/d OL=5–25 mg/d	Mean age=34.0(±10.6) years Diagnosis: Schizophrenia; inpatient or outpatient	26 weeks	Yes Per-protocol	Yes nr

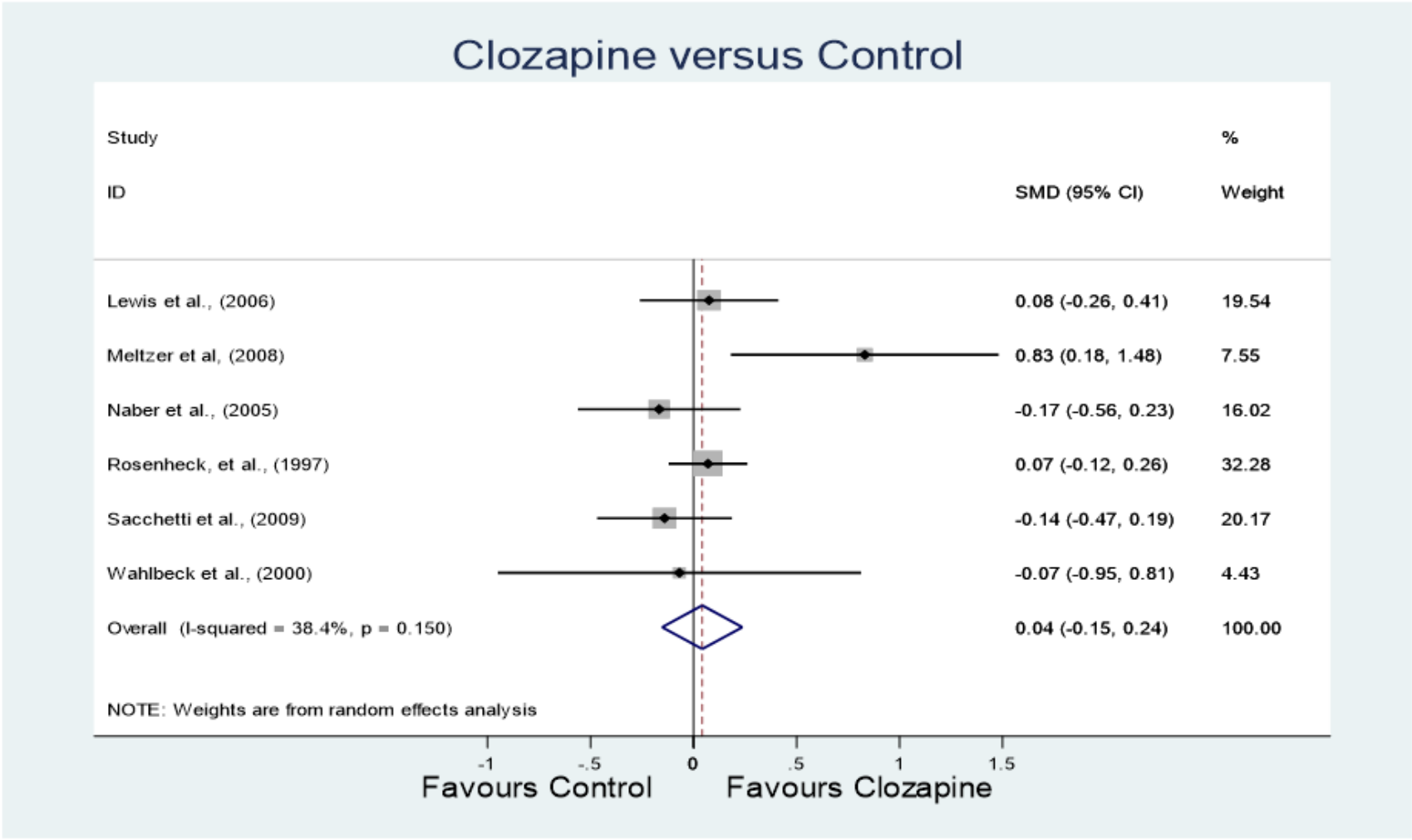
Study	Study locations	Dosage	Participants details	Duration	Function was primary study objective/Analyses	Industry sponsor/ Trial number
Rosenheck et al., (1997) [60]	Multi-center: United States	CL=100 to 900 mg/d HA=5 to 30 mg/d	Mean age=43.6(±10.9) years Diagnosis: Schizophrenia; inpatient or outpatient	52 weeks	Yes ITT	Yes nr
Sacchetti et al., (2009) [63]	Multi-center: Italy	CL=250–600 mg/d ZI= 80–160 mg/d	Mean age=42·1(±) years; Diagnosis: Schizophrenia; inpatient or outpatient	18 weeks	No ITT	Yes nr
Swartz et al., (2007) [3]	Multi-center: United States	CL=200–600 mg/d AT=flexible	Mean age= 39.7(±10.4) years Diagnosis: Schizophrenia; outpatient	52 weeks	Yes ITT	No NCT00014001
Wahlbeck et al., (2000) [62]	Multi-center: Finland	CL= Flexible ≤600 mg/d RI= Flexible ≤6 mg/d	Mean age: 36.3(±13.9) years Diagnosis: schizophrenia; inpatient or outpatient	10 weeks	No ITT	No nr

CL=Clozapine, HA=Haloperidol; ITT=Intention-to-treat; nr=Not reported; mg/d= Milligram per day; RI=Risperidone; TY=Typical antipsychotics; AT=Atypical antipsychotics; *dose in chlorpromazine equivalent; ZI=Ziprasidone

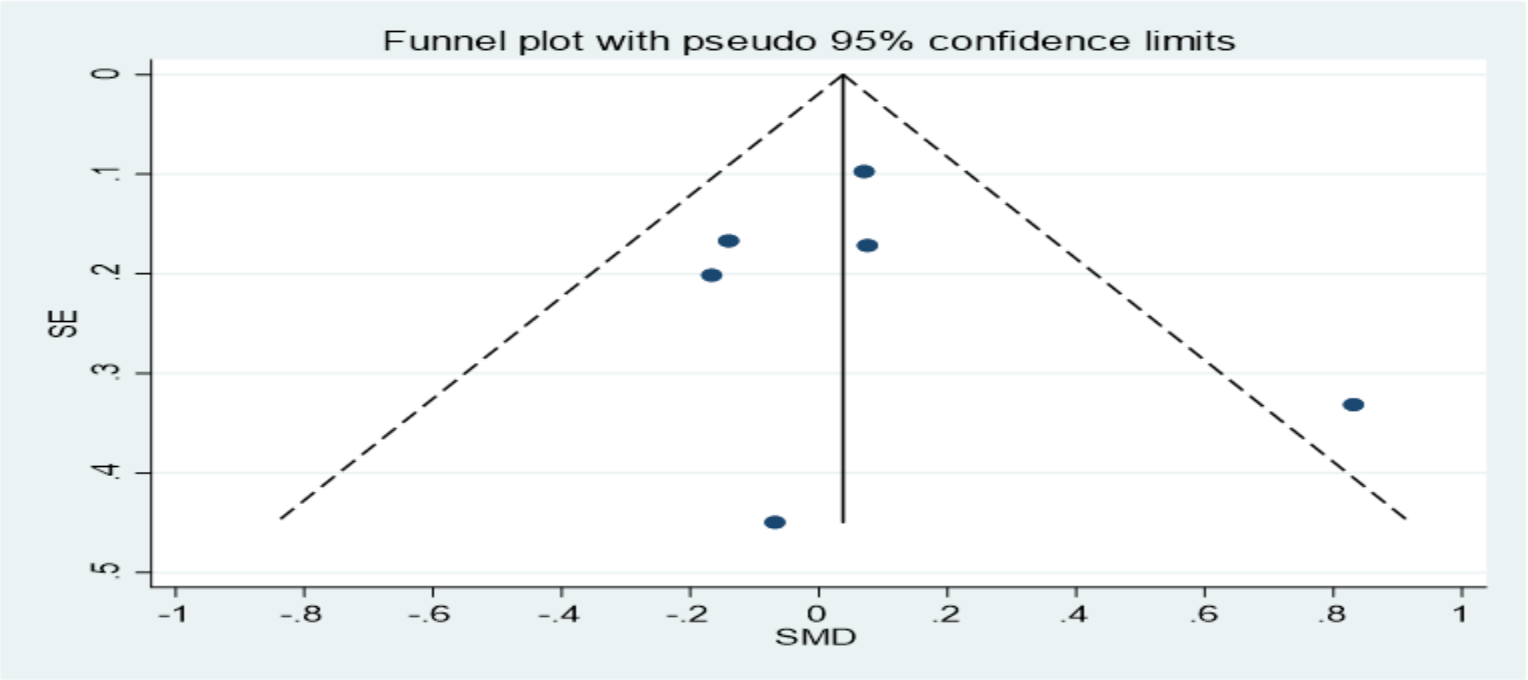
Supplementary S2: Risk of Bias



Supplementary S3: Forest plot for all studies



Supplementary S4: Funnel plot for all studies and Egger test



Egger test for all studies

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.0468969	.2195677	-0.21	0.841	-.6565145	.5627208
bias	.5605681	1.311881	0.43	0.691	-3.081798	4.202935

Statement of Authorship

Title of Paper	Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS): Rationale, Design, and Characteristics
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Contribution to the Paper	Study implementation, drafting and revision of the manuscript.		
Overall percentage (%)	40%		
Certification:	This paper reports on the methodology of the project that provided data for empirical studies. The project was conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am a co-author of this paper.		
Signature		Date	24/02/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	24/02/2022

Chapter 4

Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS): Rationale, Design and Characteristics

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Abstract

Prediction of treatment response and illness trajectory in psychotic disorders including schizophrenia, bipolar affective disorder, schizoaffective disorder, and psychotic depression is difficult due to heterogeneity in presentation and outcome. Consequently, patients may receive prolonged ineffective treatments leading to functional decline, illness chronicity and iatrogenic physical illness. One approach to addressing these problems is to stratify patients based on historical, clinical and biological signatures. Such an approach has the potential to improve categorisation resulting in better understanding of underlying mechanisms and earlier evidence-based treatment with reduced side effect burden. To investigate these multimodal signatures, we developed the Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS) employing a prospective study design and a healthy control group comparison. The main aim of this study is to investigate cognitive, and biological "genomics" markers of psychotic illnesses that can be integrated with clinical data to improve prediction of risk and define functional trajectories. We also aim to identify biological "genomic' signatures underpinning variation in treatment response and adverse medical outcomes. The study commenced in June 2016, including patients with primary diagnosis of psychotic disorders including schizophrenia, bipolar affective disorder, schizoaffective disorder, and psychotic depression according to DSM-5 criteria. The assessment covers a wide range of participant history (life stressors, trauma, and family history), cognitive dimensions (social perception, memory and learning, attention, executive function, and general cognition), measures to assess psychosocial function and quality of life, psychotic symptom severity, clinical course of illness and parameters for adverse medical outcome. Blood is collected for comprehensive genomic discovery analyses of biological (genomic, transcriptomic, proteomic, and cell-biologic) markers. The CoFAPSS is a novel approach that integrates clinical, cognitive and biological "genomic" markers to clarify clinico-pathological basis of risk, functional trajectories, disease stratification, treatment response and adverse medical outcome. The CoFAPSS team welcomes collaborations with both national and international investigators.

Introduction

Psychiatric illnesses presenting with psychotic symptoms, including schizophrenia, bipolar affective disorder, schizoaffective disorder, and psychotic depression are highly prevalent, affecting up to 5% of the population, and are leading contributors to disability-adjusted-life-years, and years-lost-to-disability globally.[1,2] For example, in Australia the 12-month prevalence of psychotic illness managed within public mental health services was recently estimated at 4.5/1000 people. The majority of these cases meet diagnostic criteria for schizophrenia or schizoaffective disorder.[3,4] Up to one half of these patients have reported a suicide attempt in their lifetime, over 60% report only partial recovery or continuous chronic illness, 32% have a severe dysfunction in the quality of self-care, and 85% rely on a government pension as their main source of income.[3] There are high rates of comorbid chronic medical conditions and in a large Australian sample over 50% met criteria for metabolic syndrome, 75% were overweight or obese, nearly half had raised cholesterol or triglycerides, and one third had raised fasting glucose.[5] Life expectancy in those with schizophrenia is decreased in excess of 16 years largely due to cardiovascular diseases.[6,7]

From longitudinal epidemiologic studies, it is clear that illness trajectory and progression in psychosis, varies greatly between and within individuals. For example, only about 20% of young people diagnosed as being at Clinical High Risk (CHR) for developing a psychotic disorder actually develop a full-blown mental illness,[8] while 20% of those experiencing a psychosis will only have a single episode.[9] At the other end of the spectrum, current treatments for schizophrenia are ineffective in up to 25% of cases, classified as treatment resistant (TRS), and only 30-60% of these patients will respond to the unique, second-line antipsychotic clozapine.[10] While clinical factors conferring increased vulnerability to adverse outcomes in psychotic disorders, such as a prolonged duration of untreated psychosis,[9] or non-adherence to prescribed treatments,[11] have been well documented, the biology underlying these findings is not well defined. Further, trans-diagnostic categorization of psychotic disorders can be difficult because they often exhibit epidemiological comorbidity and share symptoms suggesting etiologic overlap through shared heritability.[12] This is substantiated by genome-wide association studies (GWASs) showing high genetic correlations among psychotic disorders and overlapping of common risk variants across traditional diagnostic boundaries.[12-14] Mapping genetic underpinnings of common

psychotic disorders using cross-diagnostic design may therefore help in informing the search for the biological pathways underlying their pathophysiology, improve diagnosis and treatment.[12]

Currently, diagnosis and treatment recommendations for mental disorders are solely based on clinical assessments and broad clinical guidelines,[15,16] and it is impossible to predict illness course and treatment response for individual patient.[17] As a result, many patients receive treatments over prolonged periods of time which are either ineffective, or carry an unfavourable risk to benefit ratio, leading to illness chronicity, functional decline, poor adherence, or iatrogenic physical illness. Diagnostic categories in psychiatry are heterogenous in terms of presenting symptoms, underlying biology and longitudinal outcomes. Stratification models for major mental illnesses can help to improve the efficacy of outcome prediction and intervention.[18] Stratification is increasingly used in general medicine to define prognosis and allow personalised treatment. The process requires a clinico-pathological description using genetic and/or endophenotypic measures, and stratification into risk or response groups through the integration of patient's clinical data with other information including cognitive, neurophysiology and biological "genomics."[19] Stratification may improve knowledge of underlying disease mechanisms via the development of 'bio-signatures' that can characterise, validate or redefine clinical diagnosis.[8,20,21] In turn, stratification may lead to early-targeted treatment with better initial response, favourable risk-benefit ratio, and modification of individual's risk of disease progression through state-appropriate treatments. For example, in Oncology, molecular methods have led to better diagnosis and individualised treatment for cancer patients. Response to the anti-cancer drug - trastuzumab, a monoclonal antibody that blocks cell proliferation signals, is associated with over expression of the HER2 protein.[22] Similarly, prognosis and the selection of chemotherapy for chronic lymphocytic leukaemia is dependent upon the presence of clinical risk factors, cell surface antigens and specific mutations such as the deletion of 11q or 17p and mutations of TP53.[23]

In order to truly progress preventive and personalised clinical approaches in psychosis, we need to understand the underlying psychological and neurobiological mechanisms and biomarkers associated with specific illness and functional trajectories. Similarly, we need to understand factors that promote functional regeneration and recovery following first episode psychosis.

Recent years have seen progress in the identification of neurobiologically distinct biotypes developed using biomarkers across genetics, proteomics, neuroimaging, cognition, and electrophysiology leading to alternative classifications of psychotic illness,[14, 24] improved prediction of transition to first-episode psychosis,[25] response to lithium therapy in bipolar disorders, [26,27] and response and relapse in schizophrenia.[28] However, the majority of these investigations have been carried out in small samples without replication and there is a need for larger cohorts of psychosis patients with adequate clinical and biological phenotyping. Such cohorts, in addition to yielding improved information about individual risk profiles for illness progression, would also allow for systematic assessment of the factors promoting individual patient's potential for full functional recovery and adverse outcome. To generate a deeply phenotyped psychosis cohort for the determination of multimodal signatures we developed the Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS) employing a prospective study design and a healthy control group comparison. The main aim of this study is to investigate cognitive, and biological "genomics" markers of psychotic illnesses that can be integrated with clinical data to improve prediction of risk and define functional trajectories. We also aim to identify biological "genomic" signatures underpinning variation in treatment response and adverse medical outcomes.

Methods

Research aims and hypotheses

The overall aim is to develop clinical, cognitive and biological 'genomic" markers of the risk of progression, functional trajectories and outcomes in psychotic disorders that can inform stratification. The study hypotheses and specific aims are:

Hypothesis 1: Participants with psychosis, compared to matched healthy controls are characterised by specific genomic, transcriptomic, proteomic, and cell-biological signatures, which differ across illness trajectories and between risks for illness progression. The aims are: (a) to sample DNA, RNA, and protein expression in participants with psychosis and healthy matched controls, and (b) to compare global expression profiles focusing on heterogeneous illness trajectory.

Hypothesis 2: There are specific genomic, transcriptomic, proteomic, and cell-biologic signatures correlating with poorer neuropsychological function in the cognitive domains of social perception, memory and learning, attention, executive function, and general cognition, and these markers reflect the increased risk for disease progression in psychotic people with impaired cognition. The aims are: (a) to assess neuropsychological performance in the cognitive domains of social perception, memory and learning, attention, executive function, and general cognition in participants with psychotic disorders and in healthy matched controls, and (b) to correlate neurocognitive profiles with genomic, transcriptomic, proteomic, and cell-biologic signatures and the risk for disease progression.

Hypothesis 3: There are specific genomic, transcriptomic, proteomic, and cell-biologic signatures of favourable and unfavourable functional outcomes in people with psychosis. These markers may be similar or different to biomarkers correlating with cognitive impairment (see H2), and are specific to the various trajectories of psychotic disorders. The aims are: (a) to assess the functional outcome profiles of psychotic disorders, (b) to assess the relationship between functional outcome and biomarker signatures in psychosis, (c) to assess the relationship between cognitive function and functional outcome, and to compare their respective biomarker signatures, and (d) to assess the differences between subjective and objective rating of psychosocial functioning in people with psychotic disorders, and to correlate these differences to actual functional outcomes.

Hypothesis 4: There are specific genomic, transcriptomic, proteomic, and cell-biologic signatures of adverse medical outcomes in people with psychosis that are specific to psychotic disorders. The aims are: (a) to investigate metabolic, cardiovascular, haematological, gastrointestinal neurological outcomes in people with psychotic disorders, and (b) to investigate associations of these outcomes with genomic, transcriptomic, proteomic, and cell-biologic signatures

Study Design and Recruitment

The CoFAPS-Study employs methodology and instruments adapted in part from the Cognitive Function and Mood Study [CoFAM-Study].[29] The outlined CoFAPS-Study commenced in June

2016 with data collection at baseline, follow up assessment at 6-months and then annually for three years. The study design is prospective in nature and involves naturalistic recruitment of patients aged 18 to 65 years from inpatient and outpatient psychiatric services through research clinics of the Department of Psychiatry University of Adelaide, Central, Eastern, Western, Northern Adelaide and Country Health Networks, South Australia. Healthy controls and people with a history of psychotic illness are also recruited from the general community via public advertisement. The study is exploratory in nature and forms the basis for biobanking of deeply phenotyped genomic and proteomic samples from patients with psychosis and healthy controls.

Inclusion and Exclusion Criteria

Participants with a current or previous diagnosis of psychotic disorders (e.g. schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorders, and psychotic depression) according to the Diagnostic and Statistical Manual of mental disorders- fifth edition-DSM-5[30] are included in the study. We excluded potential participants unable to understand English, or to give informed consent, or tolerate assessment procedures. Those with impaired cognitive and functioning abilities associated with severe physical illness, comorbid developmental or neurological disorders, or learning disability are also excluded from the study. In addition, acutely distressed participants who display clear acute impairments of mental state requiring urgent medical or psychiatric attention are excluded. Healthy controls are expected not suffer from any disorder as defined by DSM-5.

Ethics

The study was approved by Human Research Ethics at the Royal Adelaide Hospital (approval number: R20140709 HREC/13/RAH/281). Participants are provided all the study details in writing and in person before informed consent is obtained. Special care is taken in consent of those with impaired capacity or other vulnerability by involving parents, next of kin or legal guardian according to the principles of the Declaration of Helsinki.

Clinical, Self-report and Cognitive Assessments

Diagnostic Screening and Interview

All participants with clinical diagnosis of psychotic disorders (including schizophrenia, schizoaffective disorder, bipolar affective disorder, and psychotic depression) made by their psychiatrists are screened for lifetime prevalence of mental illness including psychosis based on DSM-5 criteria.[30] Specific scales are used to measure symptoms of psychosis, depression, anxiety, suicidality, psychosocial functioning, and health service use.

Demographics, Psychiatric and Medical History

Basic demographics including age, gender, ethnicity, income, living circumstances, marital status are collected. A psychiatric history checklist is administered to capture key items including: age of illness onset, number of life-time episodes, number of hospitalizations, class of psychotropic medications used and family history of mental illness. A physical illness checklist is administered to record any diagnoses of physical illnesses (including neurological disease, heart disease, diabetes, cancer) in participants, their parents, siblings, children, grandparents, uncle, aunt, spouse and close relatives and cause of death in any close relatives.

Psychotic and Mood symptom severity, and other clinical characteristics

The severity of psychotic symptoms is assessed using the Positive and Negative Syndrome Scale (PANSS).[31] The PANSS is a 30-item instrument designed to provide symptom severity across three subscales, namely positive (7-item), negative (7-item) and general psychopathology (16-item) scales. It is standardized, valid and sensitive to provide a balanced assessment of psychotic symptoms. To assess severity of depression and anxiety symptoms, the Structured Interview Guide of the Hamilton Anxiety and Depression Scale (SIGH-AD)[32] will also be administered. The SIGH–AD is a 31-item structured interview that combines the Hamilton Depression Scale (HAM-D, 17 items) and the Hamilton Anxiety Scale (HAM-A, 14 items). Values over 15 represent clinically significant levels of anxiety or depression. In addition, overall symptom severity was rated using the Clinical Global Impression Severity Scale (CGI-S).[33] The CGI-S is frequently used in clinical research because of its face validity and practicability.

Suicidal ideation and behaviour will be assessed using the Colombia Suicide Severity Rating Scale (C-SSRS) structured interview. The C-SSRS measures 4 constructs of suicidality: severity, intensity, behaviour and lethality. The measure shows good divergent and predictive validity, high sensitivity, specificity, and is sensitive to change over time.[34]

Extrapyramidal side effects are formally assessed using the Abnormal Involuntary Movement Scale (AIMS)[35] and the Barnes Akathisia Scale.[36]

Functioning

Participants are administered a range of functional assessments including the Functioning Assessment Short Test (FAST), the Specific Level of Functioning (SLOF) scale and the Global assessment of Function Scale (GAF) and an employment related function questionnaire. The FAST scale consists of 24 items developed for the clinical evaluation of the main difficulties in daily functioning for psychiatric patients.[37, 38] It is brief, easy to apply, and is available in several languages. The items are rated 0 (no impairment), 1 (mild impairment), 2 (moderate impairment), or 3 (severe impairment). Total FAST score ranges from 0 to 72. Higher scores indicate greater disability and scores above indicate the presence of significant disability. The time frame for evaluation is the previous 14 days.[37, 38]

The SLOF scale[39] includes participant ratings of their ability to perform 43 specific tasks encompassing 6 domains: (a) physical functioning (e.g., vision, hearing, and walking), (b) personal care skills (e.g., eating, personal hygiene, and dressing), (c) interpersonal relationships (e.g., forming and maintaining friendships, initiating contact with others), (d) social acceptability (e.g., verbally or physically abusing others, performing repetitive behaviours), (e) activities (e.g., shopping, self- medication, handling personal finances using a telephone), and (f) work skills (e.g., has employable skills, works with minimal supervision). Ratings are made on a 5-point Likert scale indicating the level of assistance the participant needs to perform the task, with higher score indicating better functioning. The SLOF has excellent reliability and validity [39] and is commonly used to assess functioning in patients with schizophrenia.[40-42]

The GAF combines an evaluation of symptoms as well as relational, social and occupational functioning on a single axis. The scale runs from 1 to 100 and is divided into 10 equal parts providing defining characteristics, both symptoms and functioning, for each 10-point interval. A low rating reflects worse symptoms and a poorer level of functioning, whereas a high rating reflects less symptoms and a better level of functioning.[43]

A self-made employment questionnaire is administered to the participants. This questionnaire was developed to assess the impact of cognitive problems on employment status and work productivity in individuals suffering from mood disorders.[29] The questionnaire is an interviewer-administered instrument. The studied time frame refers to the current employment status of the participant in the first section and their work productivity over the last seven days in the second section. It is quick and easy to administer (on average it takes approximately five minutes) and provides a comprehensive assessment of the impact psychosis-related cognitive dysfunction has on occupational functioning.

Treatment response to psychotropic medications

The Lifetime Psychotropic Treatment Response scale (LPTR) was modified from the Lithium Lifetime Treatment Response scale (LLTR).[44] The LPTR scale covers treatment response to various types of psychotropic medication and hence replaces the LLTR. Criterion A is used to estimate response to a specific treatment whilst Criterion B is used to establish whether there is a causal relationship between clinical improvement and the treatment. The ALTR scale is quick and easy to administer (on average it takes about five minutes) and gives an overall picture of the effectiveness of psychotropic medications.

Collateral for Objective Functional Assessment and Confirmation of History

Consent is sought from each participant to contact a nominated member of their clinical treatment team who knows them well (e.g. their care coordinator or treating doctor) to assess insight, provide objective assessment of everyday functioning to confirm treatment and psychiatric history. Confirmation of history and insight is particularly important for participants with chronic psychosis whose self-report may be incomplete or unreliable.[44] If the participant

does not wish for a clinician to be contacted for this purpose, they can nominate a family member or friend, or can indicate that nobody should be contacted.

Self-Report of additional Clinical Characteristics

Participants complete a self-report battery using standardised scales designed to assess perception of stress, coping strategies, health beliefs, general capacity to function, health service utilisation, and quality of life. All components are derived from well validated and widely used measures that are available in the public domain.

The Family Inventory of Life Events (FILE) provides an index of 71 family stressors occurring during or prior to the last 12 months.[45] The Perceived Stress Scale (PSS) contains 14 items that assess how often a participant felt under stress, rated on a 5 point Likert scale over the preceding month.[46-49] The Short Form Health Survey (SF-36) is a set of 36 quality of life measures that can be scored in specific functional domains.[50-54] The Childhood Trauma Questionnaire (CTQ) is a set of 28 items that explore positive and negative experiences during childhood including neglect and abuse.[55] The Resilience Scale is a 26 item measure of coping ability and positive perspective, each rated on a 7 point Likert scale Scale.[56] The Health Beliefs Questionnaire is a 20-item scale assessing an individual's beliefs about their personal health, relationships and life course, each rated on a -5 to +5 Likert scale. The health service utilization questionnaire is a locally developed measure of the participant's interaction with health care systems across medical and allied health.[29]

Cognitive Assessments

Participants are administered a series of paper and computer-based game-like activities designed to assess memory and learning, attention and working memory, social cognition and executive function.[9, 57, 58] All tests have been psychometrically validated and are used extensively in cognitive function research. The Psychology Experiment Building Language (PEBL) is free, open-sourced software that allows design sharing, and modification of approximately 70 behavioural tests.[59] We chose this battery because it is robust, available on a range of platforms, and offers a range of cognitive tests that are appropriate for our study objectives. The CoFAPS-Study uses the Tower of London and the Stroop Colour Word Test (SCWT) from the PEBL. The Tower of London Test.[60, 61] is widely used for the assessment of executive functioning,

specifically to detect deficits in planning that may occur in a variety of medical and neuropsychiatric conditions. The test requires the participant to shift a series of discs one at time across 3 pegs to match a suggested pattern. The SCWT measures processing speed, attention, cognitive flexibility and working memory.[62-64] The test utilizes the "Stroop Effect", which is the cognitive interference that occurs when the processing of a specific stimulus feature (e.g. word meaning) impedes the simultaneous processing of a second stimulus attribute (word colour). Participants are requested to respond to the colour of the word and not its meaning which is also a colour. The administration of this test takes 7-10 minutes.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a brief paper-based assessment of neurocognitive status. The RBANS is validated for people aged 12-89 years, as a screen for cognitive decline or abnormal functioning [65] and has also been validated in studies of psychotic illness, depression and dementia.[66] The battery gives scaled index scores for five cognitive domains including immediate memory, visuo-spatial/constructional, language, attention, and delayed memory. The instrument has been shown to have reliability, test-retest stability, construct validity, inter-rater reliability, and content validity.[57, 58]

The THINC tool battery is a brief screening instrument designed to detect cognitive deficits by employing a variety of well-established cognitive tests in a gamified platform.[67] The tool contains tests of digit symbol substitution test,[68] the choice reaction time test (69), the trail making test B,[70] the n-back working memory paradigm[71] and a self-report 5-item questionnaire on perception of cognitive function – the perceived deficit questionnaire (PDQ-5).[72] It has been validated for use in major depression.[73] The digit symbol substitution test is a measure of attention, perceptual speed, motor speed, visual scanning, and memory.[68] The test requires the examinee to identify a unique geometric shape with its corresponding number provided in a key containing numbers one to six. The task of the participant is to match the number with the corresponding symbol when a series of number is shown on the screen. The Choice Reaction Time test measures both psychomotor speed and choice reaction time.[69] Participants are asked to respond by pressing arrow keys pointing to the right or left side of the keyboard corresponding to the direction an arrow on the screen is pointing. The N-Back test measures executive control of information updating in working memory.[71] In this test, participants are presented with series of

symbols moving at a constant rate. The task is to map a target symbol to the one they have seen recently (one position back) that is hidden and press the correctly corresponding letter key. The Trail-Making Test B measures visual attention, visual speed, search speed, scanning, mental flexibility, processing speed, and executive function.[70] Participants are expected to connect a set of 18 dots as fast as possible while still maintaining accuracy. The dots include both numbers and letters in ascending order, and participant draws lines to connect the dots in an ascending pattern, with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The PDQ-5 is a 5 item self-report questionnaire asking participants to rate problems with memory, attention or concentration over the previous 7 days, on a 5-point Likert scale.[72]

Social cognition is assessed using components of the Wechsler Adult Intelligence Scale Advanced Clinical Solutions Package (WAIS-IV-ACS), a well validated and widely used battery.[74] The WAIS-ACS provides an integrated test of interpretation of facial affect, prosody, body language, and mental state interpretation. Assessors follow a paper-based protocol in which the participants are shown a series of photographs of people and interpersonal interactions, displaying different emotions and behavioural scenarios. Participants are asked to interpret these emotions based on the photographs alone and in the context of recorded speech designed to simulate more nuanced emotional expression such as sarcasm. We use the three subtests, facial affect naming, prosody-face-matching, and prosody-pair-matching to test different aspects of social cognition.[57, 58]

Physiological Measures

A wide range of physiologic measures are collected including body temperature in degrees Celsius, weight in Kilograms, height in Meters, blood pressure in Millimetres of Mercury, heart rate per minute, and blood sugar level in Milli-moles per litre. A peripheral blood sample is taken at the time of assessment by a person qualified for venepuncture. Samples are processed to provide storable DNA, RNA, serum, and blood cell specimen in line with standard operating procedures. The storage of biomaterials is split between refrigerators, all of which are monitored by a central alert system continuously 24 h/day 7 days/week.

Participant DNA and RNA will be extracted from whole blood samples. Blood proteins will be derived from whole blood, serum, and plasma samples. Genetic variation amongst participants will be assessed by DNA microarrays. These data will contribute to international consortium initiatives pursuing genome-wide association studies (GWAS) in the field of psychosis research;[75] additionally, genetic data will be used to determine the role of polygenic scores (PGS) for psychiatric and somatic phenotypes in the trajectory differentiation of psychotic disorders.[26,76] Differences in gene expression between better and poorer illness trajectories will be undertaken using RNA sequencing.[77] We will employ 'classic' differential expression analysis as well as systems biology approaches including weighted gene co-expression network analysis (WGCNA)[78] and analysis of expression quantitative trait loci (eQTL),[79] which we have previously successfully used in complex psychiatric traits.[80-82] For proteomic analyses, we will use liquid chromatography-tandem mass spectrometry (LC-MS/MS) technology to perform: 1) differential expression analysis in shotgun discovery experiments, 2) semi-targeted analyses using data independent acquisition (DIA) approaches,[83] and 3) targeted testing for promising markers using multiple reaction monitoring (MRM).[84]

Quality Assurance and Data Management

The main purpose of all quality assurance processes is to derive high-quality data. The CoFAPS-Study standard operation manual contains operating procedures for recruitment, clinical interviews, physical examination, blood collection and storage, and handling of bio-specimen, Human Biobank and Genetic Research Database. Members of CoFAPS-Study team have training before commencement of study and follow-up quality checks are carried out. Performance is closely supervised, monitored and routinely reviewed to ensure adherence. Data collection and management were implemented concurrently based on standardized procedures, and partly automated procedures for data processing and credibility checking. Data backup routines are scheduled on a daily basis.

Biometric concept and statistical analyses

The primary endpoints of CoFAPSS are the detailed characterisation of trajectories of symptoms, cognition, psychosocial and general function, and associated genomic, protein, lipid and metabolomic markers of psychotic illnesses derived from peripheral blood. Secondary outcomes

include changes in these variables over time. Depending on the type of outcome scale, (continuous vs categorical), and time point of assessment (baseline or follow-up), the statistical methods comprise of multivariable linear regression or logistic regression analyses or mixed-models and latent class or growth mixture modelling to identify predictor and outcome trajectories,[85] - accounting for time-varying predictors and repeated outcome assessment. As discussed above, genomic marker analyses require specific software for genetic analyses, gene expression analyses, network analyses, proteomic analyses, and other specialised analysis software packages.

Multimodal data will also be integrated into personalised prediction models using a range of machine learning techniques including naive Bayes,' [86, 87] penalised regression, support vector machines, random forest and artificial neural networks.[88] To avoid data leakage and model overfitting, all models will be implemented within in a pipeline architecture using either Scikit-learn[89] or the Caret package in R[90] with k-fold cross validation including all data pre-processing, feature selection and classification processes. Model performance will be described in terms of variance explained (R^2) in regression, or for classification discriminative ability (sensitivity and specificity), positive and negative predicted value, area under the receiver operating curve (ROC-AUC), F1, and goodness-of-fit statistics for calibration.[91]

Study implementation and dissemination

To date, data has been collected from 74 patients with established psychosis (75% schizophrenia, 25% schizoaffective disorder) recruited from inpatient and outpatient psychiatric services through research clinics of the Department of Psychiatry University of Adelaide, Central, Eastern, Western, Northern Adelaide and Country Health Networks, South Australia. Participants are mostly male (70%) Caucasians (86.3%), with average age 39.9yrs (range 19-61), reflecting the local public outpatient clinic population. Data collection will continue as required to build robust multimodal models, with a focus on broadening recruitment to include controls, balance gender and include earlier age groups with first presentations of psychotic symptoms. We have presented baseline clinical, cognitive and functional data at National and International conferences and plan publications on baseline biological markers in international peer reviewed journal.

Discussion

Psychiatric illnesses with psychotic features comprising of schizophrenia, bipolar affective disorder, schizoaffective disorder, and psychotic depression are heterogeneous disorders associated with chronic or recurrent disabling symptoms.[1, 2] To address the limited diagnostic reliability, improve prediction of treatment response, reduce risk-benefits ratio, and personalise recovery-oriented care, a stratification of psychotic disorders is proposed (18-20). Such a stratification model requires multi-dimensional linkage of clinical, neurophysiological and neurobiological factors to define illness trajectory and plan treatment. The CoFAPS-Study aims to improve the understanding of neurobiological and cognitive underpinnings of psychotic illnesses to advance classification, predict risk and personalise treatment to promote recovery and prevent adverse outcome. Study enrolment of cases and controls into CoFAPSS commenced in 2016 and will continue until December 2020.

Firstly, the CoFAPS-Study is designed to identify cognitive, functional and biological "genomic" markers of psychotic illness trajectories in comparison to healthy controls. The main goal is to improve the characterization of psychosis and prediction of symptomatic and functional outcomes by incorporating neurobiological and psychosocial correlates. The design is similar to CoFAMS[29] for cross disorder comparison, and the data set is well characterised for consortium work and suitable for systems biology approach.

Secondly, we hope to improve understanding of the decline in psychosocial function and highly variable recovery in psychotic illness by exploring the validity of stratifying patients across different illness trajectories. Stratification of psychosis into functional trajectories will help to characterise those at early risk of long-term poor outcomes.

Third, genomic, transcriptomic, proteomic, cell-biologic signatures and neuropsychological correlates of treatment response and adverse medical outcome are specifically lacking in the field. A possible reason may be due to heterogeneous nature of psychosis resulting from current syndromic classification. The integration of illness and functional trajectories with predictive biological markers will assist in the early personalisation of care to optimise outcomes in psychotic illness.

In conclusion, the CoFAPS-Study is a novel approach utilizing clinical, cognitive and biological "genomic" markers to improve prediction of risk, psychosocial function and treatment response in psychotic disorders. The CoFAPSS team welcomes collaborations with both national and international investigators.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Chapter 5

Functional status in individuals with schizophrenia: A comparative analysis with major depressive disorder and healthy controls

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Abstract

Background: While people with schizophrenia in general are recognized to have more prominent deficits in comparison to mood disorders, there is overlap in cognitive and functional impairment. Few studies have systematically explored these differences, specifically considering variation with illness severity. An improved understanding of the comparative range and variation across functional domains may help to improve targeting of rehabilitation programs. We compared patients with schizophrenia to those with lifetime major depressive disorder (MDD) and healthy controls (HC) on multiple aspects of functional status and quality of life (QoL), considering contribution of age gender, education and illness severity on variability.

*Methods***:** We assessed functional status in patients with schizophrenia (n=67), MDD (n=153), and HC (n=157) with Function Assessment Short Test (FAST) and QoL with the 36-item Short Form health survey (SF-36). Linear regression analyses in separate models were conducted to compare patients with schizophrenia to MDD and HC on multiple aspects of functional status and QoL.

Results: The mean (SD) ages of participants with schizophrenia, MDD and HC were 38.5 (SD=1.1), 30.6(.85) and 27.8(.06) years respectively, and patients with MDD (81.1%) and HC (86.6%) were predominantly females compared with schizophrenia (34.3%). In comparison to patients with MDD and HC, patients with schizophrenia reported significantly lower scores (indicative of greater impairment) on SF-36 mental health and physical composite QoL domains ($p<0.05$). Similarly, patients with schizophrenia had a greater level of disability in all aspects of functional status, including global functioning, autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure compared to patients with MDD and HC. Illness severity was significantly related to all the measured aspects of functional status and QoL. Older age was significantly related to higher impairments in global functioning, cognitive function and physical health composite QoL but not related to autonomy, occupational functioning financial issues, interpersonal relationships and leisure. While having more years of education was positively related to better mental and physical health composite QoL, it was not related to all the aspects of functional status. Finally, males reported greater disability in financial issues and inter-personal relationships but no significant difference between males and

females with respect to global functioning, autonomy, occupational functioning, cognitive functioning, leisure and the mental-physical health composite QoL.

Conclusion: Greater impairment in multiple aspects of functional status and QoL was apparent in patients with schizophrenia compared with MDD and HC. Given the significant relationship between illness severity and all aspects of functional status and QoL, adequate treatment of symptoms is primary. While general and cognitive function and perceived physical health deteriorates with age, other aspects of QoL and function are preserved. More extensive education was protective for QoL but not function. Males were more vulnerable to relationship and financial issues.

Introduction

It is widely accepted that schizophrenia is a disabling mental disorder,[1] however a proportion of patients do have favorable functional outcome. While the precise proportion of patients with recovery remains unclear, studies have shown that recovery rates are smaller (less than 15%), when based on both clinical remission and functional recovery lasting for at least two years,[2] and much higher when less stringent criterion of functioning is used.[3,4]

Improvement in the ability to participate in daily functional activities including the performance of social, personal, vocational, and familial roles is a common treatment goal for patients and their families,[5,6] however functional recovery remains a major challenge from a therapeutic perspective. Several psychosocial treatments (including social skills training, cognitive behavioral therapy, cognitive remediation, and social cognition training) are currently in use as adjunct strategies with pharmacotherapy to improve patients' function.[7]

With the gains in support for recovery-based care, there is consensus agreement (96.2% of consensus) among experts that functional assessment is essential in both clinical practice and research settings.[8] The evaluation of functional status in schizophrenia is critical to understanding patients' difficulties across multiple areas of functioning, and their recovery process. The outcome of such patient-level functional evaluation is valuable for meaningful discussion with patients and effective engagement with psychosocial treatments. Further, functional measurements are now recommended as valuable co-primary outcome in clinical trial studies to evaluate the real-world effectiveness of interventions, especially those targeting cognitive and psychosocial function in schizophrenia in patient-centred care model.[9-11]

Several functional measures (e.g., global assessment of function [GAF], Social and Occupational Functioning Assessment Scale [SOFAS], Personal and Social Performance scale [PSP], and Social Adjustment Scale [SAS] etc.) can index patients' global functional status and are currently in use in clinical settings and research studies on psychosocial function.[10,12] However, multidimensional measures of functional status are recommended to provide a comprehensive perspective of patient's basic-daily function, adaptive function, interpersonal relationships, socio-occupational function, life satisfaction, and subjective wellbeing.[13-16] In addition, multi-domain assessment can improve insight into patient's personal functional life and difficulties on

one hand, while on the other hand, it can reflect patient's personal resources and functional strengths in dealing with the psychosocial impacts of schizophrenia.[13,17]

Two recent meta-analytic studies[14,16] pooled the effects of long-acting antipsychotics and clozapine on psychosocial function in patients with schizophrenia using a composite construct, involving multiple dimensions of functional status mentioned earlier.[9,13,14,16] Specifically, the studies showed the positive effects of antipsychotic medications on psychosocial function and summarized multiple clinico-demographic factors (including illness severity, sex, substance use, psychopathology, insight, and duration of treatment) as identifiable predictors of functional outcome. These review studies underscored the benefits of assessing psychosocial function while highlighting the complex and multifaceted nature of functional impairments in patients with schizophrenia.[13,14,16,17] Given the clinical importance and the variability in the expression of psychosocial deficits in people with schizophrenia, there is need for a deeper knowledge of the assessment of multiple aspects of functional impairment in naturalistic populations to better understand the personal and social contexts in which schizophrenia and its recovery occur.

Rehabilitation or psychosocial interventions (e.g., cognitive remediation, social skills training, psychoeducation, social cognition training, and cognitive retraining, etc.) for patients with schizophrenia are well developed and critical to bolster recovery.[18-20] Similar to schizophrenia, patients with lifetime history of depressive illness are known to have functional deficits.[21,] For example, specific cognitive deficits in processing speed, learning, memory, attention, concentration, and executive function have been replicated in several studies among people with major depressive disorder (MDD).[21]However, there is limited research comparing multiple aspects of functional deficits and quality of life (QoL) in schizophrenia with MDD to establish if the well-developed rehabilitation interventions[7,8,19] for patients with schizophrenia can be applied or adapted for patients with MDD. Moreover, there is limited information on the pattern and predictors of specific aspects of functional impairments in patients with schizophrenia to individualize care for improved function. Hence, we pursued this study to compare patients with schizophrenia to patients with MDD and healthy controls (HC) on multiple aspects of functional status and QoL. Specifically, the study objective is to investigate the similarities and differences in functional deficits among individuals with schizophrenia compared with major depression and healthy controls, considering variation due to age, gender, education and illness severity.

Methods

In this study, we compared data collected on patients with schizophrenia enrolled in the Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS) with patients diagnosed with MDD and HC derived from the Cognitive Function and Mood Study (CoFAMS). The details of these two naturalistic prospective studies are contained in two published protocol papers.[22,23] Both CoFAMS and COFAPPS were aimed at investigating the cognitive, functional, clinical, and genomic correlates of mood disorders and psychotic disorders respectively in comparison to healthy controls. We consider only baseline cross-sectional data including symptom measures, function, quality of life and demographics.

The recruitment of study participants in these two studies was naturalistic, including adult patients, aged 18 years and above who were diagnosed with schizophrenia or mood disorder based on the Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5) criteria.[24-27] Recruitment covered both the inpatient and outpatient psychiatric services of the Department of Psychiatry, University of Adelaide and Health Networks in South Australia. Healthy controls and people with a history of psychotic illness were also recruited from the general community via public advertisement. Those with impaired cognitive and functioning abilities associated with severe physical illness, comorbid developmental or neurological disorders, or learning disability were excluded. Study approval was obtained from the Human Research Ethics board at the Royal Adelaide Hospital (RAH Protocol No: 140709 for CoFAPSS, and RAH Protocol No: 111230 for CoFaMS). We obtained written informed consent from all participants before enrolment, and special care was taken to adhere to standard guideline in accordance with the Declaration of Helsinki.[28,29]

To address the objectives of the present study, we identified data on patients (aged 18-65 years) diagnosed with schizophrenia or schizoaffective disorder, lifetime MDD without psychotic symptoms and unmatched HC without a history of psychiatric or neurological disorders. For patients with schizophrenia, the diagnosis was made based on clinician assessment and they were screened for psychotic symptoms based on DSM-5[27] criteria. For MDD, we included patients with a lifetime history of MDD based on the Mini-International Neuropsychiatric Interview (MINI),[26] excluding any patients with a history of psychosis or mania/hypomania. Healthy controls screened negative for any DMS-5 diagnosis based on clinical interview using the MINI.

The measures used for the present study outcomes (cognition, symptoms profile captured as illness severity, functional status and QoL) are described below.

Measures for assessing functional status and subjective wellbeing (QoL)

Functional status was assessed with Function Assessment Short Test (FAST) and QoL with the Short Form Health Survey (SF-36). The FAST consists of 24 items developed for clinical evaluation of difficulties in daily functioning for psychiatric patients in the previous two weeks.[30,31] In addition to the total score, the FAST assesses six specific aspects of function including: autonomy, occupational functioning, cognitive functioning, financial issues, leisure and interpersonal relationships. It is brief, easy to apply, and available in several languages. The items are rated using a 4-point scale, 0 (no impairment), 1 (mild impairment), 2 (moderate impairment), and 3 (severe impairment). The total score used as an index of global functioning ranges from zero to 72, and the higher the score the more serious the difficulty indicating greater disability or higher impairment in global functioning. It has the advantages of being a simple instrument, easy to apply, and requires a very short time to be administered.[30]

On the other hand, the SF-36 is a generic measure designed to examine person's perceived health status. It contains a set of 36 quality of life items that can be scored in specific wellbeing subscales including: physical functioning (PF), role limitation due to physical problems (RP), role limitation due to emotional problems (RE), social functioning (SF), mental health (MH), bodily pain (BP), energy and vitality (VT), and general perception of health (GH). The SF-36 can also yield Mental and Physical Health Composite scores.[31-37] Scoring was based on Likert's method for summated rating scales as previously described.[38] Both FAST and SF-36 have been shown to have good internal consistency, reliability, and validity across groups differing in clinical diagnosis, psychosocial and demographic characteristics.[39,40]

Measures for assessing clinical symptoms and illness severity

We assessed symptom severity in participants with schizophrenia using the positive and negative symptoms scale [PANSS][41] and Hamilton depression rating scale [HAMD][42]in patients with MDD and HC. To allow uniformity in the operationalization of symptom severity across all study participants, we devised mapping PANSS and HAMD scores to illness severity using the clinical global impression [CGI][43] as proposed by Leucht et al.,[44,45] Specifically, illness severity

in patients with schizophrenia was categorized based on PANSS scores into normal, mildly ill, and moderately ill.[44] On the other hand, patients with MDD were categorized based on HAMD score into normal, mildly ill, and moderately ill.[45] See Table 1 for additional details.

Statistical analyses

Data analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. Data was examined for normality and homogeneity of variance. Descriptive statistics including frequency and percentage for categorical variables, and mean and standard deviation for continuous variables are presented. For example, we reported means and standard deviations (SD) for age, years of education, symptoms scales, and functional measures for each group (schizophrenia, MDD, and HC) and frequency with percentage for sex. Comparative analysis of patients with schizophrenia versus MDD and HC on functional status was performed with the generalized linear model. In the model, the dependent variables (in separate models) were SF-36 and FAST subscales, the predictor was diagnostic categories, and the models were adjusted for multiple clinico-demographic factors, including age, sex, years of education, and illness severity (patients with schizophrenia, MDD, and HC were categorized into normal, mild, and moderate illness severity as described above in the methods).[44,45] We reported the 95% confidence intervals [95% CI] for the models and the mean differences [MD] to highlight the relative differences among groups or indices of the relationship of identifiable clinico-demographic factors with functional status. Assumptions of linear regression were tested for each model. and a p-value<0.05 was used to determine significance in all statistical tests.

Results

Study participants

We collected data from patients diagnosed with schizophrenia (n=67), lifetime MDD (n=153), and HC (n= 157). A detailed description of the characteristics of the study participants is presented in Table 2. Patients with schizophrenia were older, with a mean age (±SD) of 38.5(±1.1) compared to patients with MDD (30.1±0.9) and HC (27.8±0.1) years. Approximately one-third of patients with schizophrenia (34.3%) were females compared to patients with MDD (81.1%) and HC (86.6%) with a predominance of females. Patients with schizophrenia reported fewer years of education (11.7±0.1) compared to patients with MDD (13.2±0.2), and HC

(14.0±0.3) years. The mean score (±SD) of patients with schizophrenia on PANSS was 53.8(±1.8), while for patients with MDD and HC mean scores on HAMD were 10.2(±0.6) and 3.2(±0.2) respectively. There were statistically significant differences among participants with schizophrenia, MDD and HC concerning age, sex, years of education and illness severity ($p<0.05$). See Table 2

Comparison of functional status in schizophrenia with MDD and HC based on FAST

Findings from general linear model analyses to investigate the relatedness of multiple aspects of disability (measured with FAST subscales) with diagnostic categories, adjusting for illness severity, age, sex and years of education are presented in Table 3. We also included Figures 1-7, depicting the comparisons of patients with schizophrenia, MDD and HC on mean FAST scores versus illness severity. In addition, a summary of the results from each FAST subscale is provided below.

FAST total score: There was a statistically significant association between global functional impairment (FAST total score) and diagnosis, adjusting for illness severity, sex, age and years of education (global p-value<0.001). Healthy controls had a mean FAST total score 12.9 units less than participants with schizophrenia (MD=-12.9; 95% CI=-15.9, -10.0; comparison p-value<0.001) and participants with MDD had a mean FAST total score 11.2 units less than participants with schizophrenia (MD=-11.2, 95% CI= -13.9, -8.4; comparison p-value<0.001). Further, the severity of illness was significantly associated with FAST total score, adjusting for diagnostic categories, sex, age and years of education (global p-value<0.001). Participants who were normal on the illness severity measure reported a mean FAST total score 6 units less than participants with mild illness (MD=-6.0; 95% CI=-7.0, -4.0; comparison p-value<0.001) and 14.6 units less than participants with moderate illness (MD=-14.6; 95% CI=-18.2, -11.1; comparison p-value<0.001). On the other hand, participants with mild illness reported a mean FAST total score 8.7 units less than those with moderate illness (MD=-8.7; 95% CI=-12.2, -5.1; comparison p-value<0.001).

Although there was no association between FAST total score and sex (global p-value=0.154) and years of education (global p-value=0.352), older age was positively associated with increasing FAST total score (MD=0.085; global p-value 0.047). See Figure 1

FAST Autonomy: A significant association was observed between impairment in autonomy (FAST autonomy) and diagnosis (global p-value<0.001), such that participants with MDD (MD=-1.9; 95% CI= -2.49, -1.24, and HC (MD=-1.7; 95% CI= -2.3, -0.997; comparison p-value) reported mean FAST autonomy scores 1.9 and 1.7 units less than participants with schizophrenia respectively. With respect to the severity of illness, there was a statistically significant relationship with FAST autonomy (global p-value<0.001). In particular, normal participants reported mean FAST autonomy scores that are 1.37 and 2.95 units less than participants with mild (MD=-1.37; 95% CI -1.81, -0.93; comparison p-value <0.001) and moderate (MD=-1.58; 95% CI =-2.39, -0.76; comparison p-value <0.001) illness respectively. Age, sex and years of education were not statistically associated with FAST autonomy. See Figure 2

FAST Occupational Functioning: The association between impairment in occupational functioning (FAST occupational functioning) and the diagnosis was statistically significant (global p-value <0.001). Participants with MDD (MD=-4.269; 95% CI= -5.235, -3.303; comparison p-value <0.001) and HC (MD=-4.803; 95% CI= -5.84, -3.77; comparison p-value <0.001) had mean FAST occupational functioning scores 4.27 and 4.80 units less than participants with schizophrenia. In the same vein, illness severity maintained a significant association with FAST occupational functional (global p-value=0.001). Normal participants had mean FAST occupational functioning score 0.79 and 2.23 units less than participants with mild (MD=-0.79; 95% CI= -1.47, -0.11; comparison p-value=0.023) and moderate (MD=-2.23; 95% CI=3.484, -0.977; comparison p-value <0.001) severe illness respectively. Participants with mild illness reported mean FAST occupational functioning score 1.44 units less than those with moderate illness (MD=-1.44; 95% CI=-2.693; -0.187; comparison p-value=0.024). Age, sex and years of education were not significantly associated with FAST occupational functioning. See Figure 3.

FAST Cognitive Function: The diagnosis was significantly associated (global p-value <0.001) with impairment in cognitive function (FAST cognitive function). Participants with MDD (MD=-1.34; 95% CI =-2.235, -0.448; comparison p-value=0.003) and HC (MD=-2.63; 95% CI= -3.588, -1.674; p-value<0.001) had mean FAST cognitive function scores 1.34 and 2.63 units less than participants with Schizophrenia. The severity of illness also had a significant association with FAST cognitive function (global p-value<0.001). Normal participants had mean

FAST cognitive function scores 1.53 and 2.24 units less than participants with mild (MD=-1.53; 95% CI=-2.16, -0.89; comparison p-value <0.001) and moderate (MD=-2.24, 95% CI=-3.41, -1.07; comparison p-value<0.001) illnesses respectively. Compared to participants who were moderately ill, the mean FAST cognitive function score was 0.712 unit less in participants with mild illness (MD=-0.712; 95% CI=-1.879, 0.456; comparison p-value=0.023). While older age was positively associated with higher impairment in FAST cognitive function (MD=0.031; global p-value=0.028), both sex and years of education were not statistically significant. (See Figure 4)

FAST Financial Issues: There is a significant association (global p-value<0.001) between diagnosis and impairment in financial issues (FAST financial issues). The mean FAST financial issues scores for participants with MDD (MD= -0.773; 95% CI=-1.088, -0.458; comparison p-value<0.001) and HC (MD=-0.56; 95% CI=-0.898, -0.223; comparison p-value<0.001) were 0.77 and 0.56 unit less than participants with schizophrenia respectively. Similarly, the severity of illness was associated with FAST financial issues (global p-value<0.001). Normal participants had mean FAST scores 0.38 and 0.76 units less than participants with mild (MD=-0.38; 95% CI=-0.61, -0.159; comparison p-value=0.001) and moderate (MD=-0.76; 95% CI=-1.19, -0.363; comparison p-value=0.0062) illness respectively. Age and years of education were not associated with FAST financial scores; however, males showed a significantly higher impairment in financial issues compared to females (MD=0.321, global p-value=0.013). See Figure 5

FAST Inter-personal Relationships: Impairment in interpersonal relationships (FAST interpersonal relationships score) was associated with diagnosis (global p-value<0.001), participants with MDD (MD=-2.329; 95% CI=-3.68, -1.75; comparison p-value <0.001) and HC (MD= -2.72; 95% CI=-3.68, -1.75; comparison p-value<0.0010) reported mean FAST interpersonal relationships scores 2.33 and 2.72 units less than those of participants with schizophrenia. The severity of illness was also associated with FAST interpersonal relationships (global p-value<0.001). Normal participants had mean FAST interpersonal relationships score 0.99 and 4.88 units less than those in patients with mild (MD=-0.99; 95% CI=-1.63, -0.35; comparison p-value=0.002) and moderate (MD=-4.882; 95% CI=-6.052, -3.712; comparison p-value<0.001) illness. While males were more likely to report higher impairments (MD=0.983,

global p-value=0.008) in the aspect of interpersonal relationships, age and years of education were not statistically associated. (See Figure 6)

FAST Leisure: There was a statistically significant association (global p-value<0.001) between diagnosis and impairment in leisure (FAST leisure). Both participants with MDD (MD= -2.329; 95% CI=-3.232, -1.426; comparison p-value <0.001; and HC (MD=-2.717; 95% CI= -3.683, -1.751; comparison p-value 0.001) had mean FAST leisure scores 2.33 and 2.72 units less than participants with schizophrenia. The severity of illness showed a statistically significant relationship with FAST leisure (global p-value <0.001). In particular, normal participants showed mean FAST leisure 0.92 and 1.53 units less than those with mild illness (MD=-0.915; 95% CI=-1.227, -0.602; comparison p-value <0.001) and those with moderate illness (MD=-1.526; 95% CI=-2.103, -0.949; comparison p-value <0.001). In the same vein, participants with mild illness reported 0.61 units less in mean FAST leisure scores compared to participants with moderate illness (MD=-0.611; 95% CI=-1.188, -0.035; comparison p-value=0.38). While males reported less impairment compared to females with respect to FAST leisure (MD=-0.525, global p-value=0.004), age and years of education were not significantly associated. [Figure 7]

Comparing quality of life in schizophrenia with MDD and HC based on SF-36

Table 4 presents the results of the investigation of any associations between multiple aspects of functional impairments (measured with SF-36 subscales) and identifiable clinico-demographic factors, including diagnostic categories, illness severity, age, sex and years of education. We also included figures 8 and 9 to compare patients with schizophrenia, MDD and HC on SF-36 composite subscales against illness severity. A summary of the results is provided below. Figures 8 and 9

SF-36 Mental Health composite: The participants' diagnosis was significantly associated with impairment in the aspect of functional status measured by the SF-36 mental health composite (global p-value= 0.002). Healthy controls (MD=3.265; 95% CI=0.0009, 8.722; comparison p-value=0.005) reported a mean SF-36 mental health composite score 3.365 units more than (indicating better subjective wellbeing) patients with schizophrenia and patients with MDD (MD=-4.275; 95% CI=-8.044, -0.505; comparison p-value=0.026) had mean SF-36 mental health composite score 4.275 less than those with schizophrenia. Severity of illness was associated with impairment in the SF-36 mental health composite (global p-value <0.001). Normal participants

had a mean score on SF-36 mental health 9.78 and 14.53 units more than patients with mild (MD=9.78; 95% CI= 6.49, 13.07; comparison p-value <0.001) and moderate (MD=15.524; 95% CI=9.19, 19.85; comparison p-value<0.001) illness. While the mean SF-36 mental health score for participants with mild illness was 4.745 units more than participants with moderate illness, the difference was not statistically significant (MD=4.745; 95% CI=-0.533, 10.023; comparison p-value=0.078). Age, sex and years of education were not statistically associated with impairment in the SF-36 mental health composite. See Figure 8

SF-36 Physical Health: There was a statistically significant association between participants' diagnostic group and impairment in SF-36 physical health composite (global p-value=0.001). Specifically, healthy controls (MD=4.988; 95% CI=0.758, 9.219; comparison p-value =0.021) and participants with MDD (MD= 6.789; 95% CI=3.129, 10.450; comparison p-value<0.001) reported mean SF-36 physical health scores 4.98 and 6.79 units more than participants with schizophrenia, indicating better physical health QOL. In the same vein, illness severity showed a significant relationship with SF36 physical health composite (global p-value=0.021). Normal participants had mean SF-36 physical health composite scores that were 3.12 and 6.66 units more than participants with mild (MD=3.116; 95% CI=-0.072, 6.303; comparison p-value=005) and moderate (MD=6.661; 95% CI=1.485, 11.837; comparison p-value=0.012) illness, suggesting worse physical health QOL with greater mental illness symptom burden. Age (MD=-0.120; 95% CI=-0.231, -0.010; comparison p-value=0.033), sex (MD= 4.680; 95% CI=1.812, 7.548; comparison p-value=0.001) and years of education (MD=0.814; 95% CI=-1.473, -0.155; comparison p-value=0.0016) were significantly associated with impairment in SF-36 physical health composite. [See Table 4], such that younger age, being male, and having more years of education were associated with better physical health QoL. See Figure 9

Discussion

To our knowledge, this case-control study is the first to carry out a comprehensive mapping of specific aspects of functional difficulties (based on SF-36 and FAST subscales) in patients with schizophrenia compared with MDD and HC, considering age, sex, education, and illness severity. We found a higher impairment in functional status, QoL, and their domains in patients with schizophrenia compared with MDD and HC. While illness severity was positively

associated with impairments across all the measured aspects of psychosocial function, specific domains showed variable associations with age, sex, and years of education. Older age was related to higher impairment in global functioning, cognitive function and physical health composite QoL but not related to autonomy, occupational functioning, financial issues, interpersonal relationships, and leisure. While having more years of education was positively related to better mental and physical health composite QoL, it was not related to all the aspects of functional status. Finally, males reported greater disability in financial issues and inter-personal relationships but no significant difference between males and females with respect to global functioning, autonomy, occupational functioning, cognitive functioning, leisure and the mental-physical health composite QoL.

Our finding of significant impairment in global functioning in patients with schizophrenia is consistent with existing literature on the disabling nature of schizophrenia[1,30,40] and patients with schizophrenia had a significantly higher impairment in global function compared with MDD. Previous studies have reported functional status of patients with schizophrenia using global functional measures, and observed marked levels of disability compared with the general population or healthy controls, with medium to large effect sizes.[40,46]

In general, global functional scores have been used for a simplistic comparison between groups and represent a high-level measure of functional outcome,[40,46] findings on specific aspects of functional status provide a more comprehensive and granular perspective on patient's functional difficulties, especially because the domains of function are not always affected equally.[14,16,46-48] In the present study, patients with schizophrenia had higher impairments in all aspects of functional status measured with FAST and SF-36 compared to MDD and HC. However, the magnitude of differences across the domains of psychosocial function between patients with schizophrenia and the comparative groups varied. Similar findings of unequal patterns of impairment across specific aspects of psychosocial function have been reported in other studies comparing schizophrenia with healthy controls and MDD.[46,47] For example, worse impairments in global function, financial issues, quality of life and multiple aspects of psychosocial function were reported in patients with schizophrenia compared with MDD.[48-50] However discrepant and mixed findings showing better and no difference in psychosocial function in schizophrenia relative to MDD have also been observed.[51,52] Yasuyama et al, in their study, reported no

difference between patients with schizophrenia and MDD in the total social functioning scale scores but patients with schizophrenia had significantly poorer interpersonal communication compared with MDD.[52]

In a broader sense, our study findings reiterate the high variability or complexity in the clinical expression of psychosocial function in schizophrenia, and bring to fore the advantages of multi-domain functional assessments in terms of comprehensiveness and promotion of individualization of care.[13,14,16] It is evident that global or composite functional status may be of limited use for developing domain specific plans for psychosocial treatment or skill training to improve function. For example, meta-analysis of pragmatic clinical trials suggests that social functioning in patients with MDD and schizophrenia can be substantially improved with multidimensional interventions (e.g., cognitive-behavioral therapy, social skills training, exercise and art therapy, psychoeducation, interpersonal therapy, problem-solving therapy and eclectic or combined interventions).[53-56]

The benefits of illness or symptomatic remission to functional recovery and wellbeing are well established.[2-5,57] Given the significant relationship between illness severity and all aspects of functional status and QoL, adequate treatment of symptoms is primary to ensure optimum benefits of rehabilitation programs. Overall, a multi-factorial contribution from several predictors (e.g., symptom remission, good premorbid adjustment, psychosocial support, treatment adherence, good neurocognition, and brief duration of untreated psychosis among others) are linked with a good functional outcome.[40,57,58] The reliability of demographic factors (such as age, sex, and years of education) as consistent predictors of functional outcome is limited given the degree of variability in their relationship with psychosocial function, however, they are important attributes to be considered to individualize care and achieve personal recovery.[48,59,60]

The study strengths including a naturalistic case-control design and the use of multi-dimensional measures allowed a comprehensive mapping of patients' functional status relative to real-life experiences of normal population. Notwithstanding these strengths, some limitations of the study must be acknowledged. First, there is a need for cautious extrapolation of the study findings to other populations of people with schizophrenia and MDD. The control and MDD samples were not matched on age or gender to the schizophrenia cohort, albeit we included these factors as

covariates to address this limitation. This study was conducted at multiple sites in a single metropolitan area of a high-income country which may not exactly reflect the socio-cultural dimensions of psychosocial function in less-resourced settings, particularly low- and middle-income countries. The available resources for psychosocial rehabilitation, community re-integration, and management of patients with schizophrenia differ between advanced and developing contexts. The data presented in this paper is derived from the cross-sectional baseline assessments of participants recruited into the CoFAPS and CoFAM studies.[22,23,] The longitudinal data in these naturalistic prospective studies upon completion may throw more light into the complex trajectories of functional outcome and the interplay of other biopsychosocial factors in the course of the illness. We used a novel mapping of structured symptoms scales across disorders to the clinical global impression scale. This approach has only been previously validated within individual disorders.[44,45] Such approaches reduce the dimensionality and richness of information regarding symptoms and their associations with function, however we found consistent relationships with increasing severity and impairments in function that support the validity of this approach. These findings support further exploratory use of this method to combine existing schizophrenia and MDD datasets that use the PANSS and HAMD respectively. We did not correct for multiple testing in this exploratory analysis.

Conclusion

Functional impairment is common in patients with schizophrenia and MDD. Compared to MDD and HC controls, higher impairments in multiple aspects of functional status and subjective wellbeing were reported by patients with schizophrenia. Further, lower cross-sectional symptom burden confers lower impairments in global, socio-occupational, interpersonal, physical, and mental functioning. Given that the domains of function were not equally affected, multidimensional functional assessments can generate a comprehensive mapping of psychosocial function for targeting intervention at specific areas of functional difficulties in individual patients. Adequate treatment of symptoms is beneficial for targeted intervention to improve specific aspects of function given that a significant relationship between symptoms (captured as illness severity) and functional status and QoL.

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Table 1: Mapping of symptom measures in schizophrenia and major depressive disorder to illness severity using CGI

Diagnostic Categories	Illness severity [CGI]		
	Normal[#]	Mild	Moderate
Schizophrenia (PANSS score)	<54	54-74	75-94
Major depressive disorder (HAMD score)	0-8	9-16	17-23

#= below illness threshold, CGI- Clinical Global Impression (CGI) rating scales, PANSS- Positive and Negative Symptoms Scale, HAMD-Hamilton Depression Rating Scale. Adapted from Leucht et al[44, 45]

Table 2: Characteristics of participants with schizophrenia, major depressive disorder and healthy controls

Variables	Schizophrenia (n=67)	Major Depression (n=153)	Controls (n=157)	TOS	p-value
Sex n (%)					
Male	44(65.67)	29(18.95)	21(13.38)	$\chi 2$ =73.533	<0.001
Female	23(34.33)	124(81.05)	136(86.62)		
Age in yrs, mean (SD)	38.46(1.14)	30.58(.85)	27.77(.06)	F=31.206	<0.001
Yrs of education, mean (SD)	11.71(.04)	13.18(.22)	14.0(.25)	F=23.460	<0.001
HAMD score, mean (SD)	n/a	10.24(.61)	3.19(.23)	t=-12.584	<0.001
PANSS score, mean (SD)	53.75(1.82)	n/a	n/a	--	--
*Illness severity, n (%)					
Normal	32(11.8)	81(30.0)	157(58.2)	$\chi 2$=92.723	<0.001
Mild	29(25.7)	84(74.3)	-		
Moderate	28(82.35)	6(17.65)	-		
FAST-domains, mean (SD)					
Total score	23.30(1.75)	11.72(1.15)	3.07(.45)	F=99.069	<0.001
Autonomy	3.20(.41)	1.27(.22)	.28(.10)	F=37.037	<0.001
Occupational Functioning	6.78(.62)	2.61(.39)	.66(.16)	F=110.42	<0.001
Cognitive Function	5.24(.45)	3.87(.38)	.98(.16)	F=51.220	<0.001
Financial Issues	1.05(.19)	.29(.09)	0.19(.08)	F=32.396	<0.001
Inter-personal Relationship	5.46(.52)	2.5(.41)	0.51(.17)	F=52.475	<0.001
Leisure	1.58(.23)	1.16(.17)	.44(0.09)	F=4.953	0.008
SF-36 composite, mean (SD)					
Mental health	59.71(2.72)	58.79(2.32)	79.78(1.71)	F=31.713	<0.001
Physical	46.24(1.67)	49.52(1.37)	49.74(1.05)	F=2.806	0.062

%-percent, FAST- function assessment short test, HAMD- hamilton depression rating scale, HC-healthy controls, n-frequency, n/a-not applied, PANSS- positive and negative symptoms scale, TOS-test of significance, *Severity of illness was derived by mapping HAMD/PANSS scores with CGI severity categories adapted from Leucht et al., 2004 & 2012)

Table 3: Comparative analysis of functional status (FAST) in schizophrenia, major depressive disorder and healthy controls with adjustment for confounders

Outcome	Confounder	Comparison	MD (95% CI)	Comparison p-value	Global p-value
FAST Total	Diagnosis	Controls vs Schizophrenia	-12.9 (-15.9, -10.0)	<0.001	<0.001
		MDD vs Schizophrenia	-11.2 (-13.9, -8.4)	<0.001	
		Control vs MDD	-1.8 (-3.7, 0.2)	0.076	
	Illness severity	Normal vs Mild	-6.0 (-7.9, -4.0)	<0.001	<0.001
		Mild vs Moderate	-8.7 (-12.2, -5.1)	<0.001	
		Normal vs Moderate	-14.6 (-18.2, -11.1)	<0.001	
	Sex	Male vs Female	1.6 (-0.6, 3.8)		0.154
	Age		0.085 (0.001, 0.169)		0.047
	Education (years)		-0.18 (-0.57, 0.20)		0.352
FAST Autonomy	Diagnosis	Controls vs Schizophrenia	-1.7(-2.3, -0.997)	<0.001	<0.001
		MDD vs Schizophrenia	-1.9(-2.49, -1.24)	<0.001	
		Control vs MDD	.198(-.025, .065)	0.386	
	Illness severity	Normal vs Mild	-1.37(-1.81, -0.93)	<0.001	<0.001
		Mild vs Moderate	-1.58(-2.39, -0.76)	<0.001	
		Normal vs Moderate	-2.951(-3.77, -2.13)	<0.001	
	Sex	Male vs Female	0.066(-0.44, 0.57)		0.798
	Age		0.11(-0.008, 0.030)		0.251
	Education (years)		-0.057(-0.145, 0.031)		0.206
FAST Occupational Functioning	Diagnosis	Controls vs Schizophrenia	-4.803(-5.84, -3.77)	<0.001	<0.001
		MDD vs Schizophrenia	-4.269(-5.235, -3.303)	<0.001	
		Controls vs MDD	-0.534(-1.224, 0.155)	0.129	
	Illness severity	Normal vs Mild	-0.790(-1.471, -0.110)	0.023	0.001
		Mild vs Moderate	-1.44(-2.693, -0.187)	0.024	
		Normal vs Moderate	-2.230(-3.484, -0.977)	<0.001	
	Sex	Male vs Female	0.651(-0.121, 1.423)	0.099	0.099
	Age		0.28(-0.001, 0.058)		0.062
	Education (Years)		-0.024(-0.159, 0.111)		0.729

Table 3 continued

Outcome	Confounder	Comparison	MD (95% CI)	Comparison p-value	Global p-value
FAST Cognitive Function	Diagnosis	Controls vs Schizophrenia	-2.631(-3.588, -1.674)	<0.001	<0.001
		MDD vs Schizophrenia	-1.341(-2.235, -0.448)	0.003	
		Control vs MDD	-1.289(-1.932, -0.646)	<0.001	
	Symptoms severity	Normal vs Mild	-1.53(-2.162, -0.896)	<0.001	<0.001
		Mild vs Moderate	-0.712(-1.879, 0.456)	0.023	
		Normal vs Moderate	-2.241(-3.41, -1.073)	<0.001	
	Sex	Male vs Female	0.124(-0.595, 0.843)	.735	.0735
	Age		0.031(0.003, 0.058)		0.028
	Education (years)		-0.055(-0.181, 0.070)		0.387
FAST Financial Issues	Diagnosis	Controls vs Schizophrenia	-0.561(-0.898, -0.223)	<0.001	<0.001
		MDD vs Schizophrenia	-0.773(-1.088, -0.458)	<0.001	
		Control vs MDD	0.213(-0142., 0.439)	0.066	
	Illness severity	Normal vs Mild	-0.383(-0.606, -0.159)	0.001	<0.001
		Mild vs Moderate	-0.392(-0.804, 0.020)	0.062	
		Normal vs Moderate	-0.775(-1.187, -0.363)	<0.001	
	Sex	Male vs Female	0.321(0.067, 0.575)		0.013
	Age		0.005(-0.009, 0.01)		0.943
	Education (years)		0.002(-0.042, 0.047)		0.922
FAST Inter-personal Relationship	Diagnosis	Controls vs Schizophrenia	-2.717(-3.683, -1.751)	<0.001	<0.001
		MDD vs Schizophrenia	-2.329(-3.232, -1.426)	<0.001	
		Controls vs MDD	-0.389(-1.032, 0.256)	0.237	
	Illness severity	Normal vs Mild	-0.989(-1.627, -0.350)	0.002	<0.001
		Mild vs Moderate	-3.883(-5.063, -2.723)	<0.001	
		Normal vs Moderate	-4.882(-6.052, -3.712)	<0.001	
	Sex	Male vs Female	0.983(0.259, 1.706)	0.008	0.008
	Age		0.021(-0.007, 0.045)		0.146
	Education (Years)		-0.081(-0.207, 0.048)		0.207

Table 3 continued

Outcome	Confounder	Comparison	MD (95% CI)	Comparison p-value	Global p-value
FAST-Leisure	Diagnosis	Controls vs Schizophrenia	-0.540(-1.013, 0.068)	0.025	0.029
		MDD vs Schizophrenia	-0.592(-1.033, -0.151)	0.009	
		Control vs MDD	0.0515(-0.2657, 0.369)	0.750	
	Illness severity	Normal vs Mild	-0.915(-1.227, -0.602)	<0.001	<0.001
		Mild vs Moderate	-0.611(-1.188, -0.035)	0.038	
		Normal vs Moderate	-1.526(-2.103, -0.949)	<0.001	
	Sex	Male vs Female	-0.525(-0.884, -0.170)	0.004	0.004
	Age		-0.003(-0.016, 0.011)		0.700
	Education (years)		0.012(-0.05, 0.074)		0.703

FAST=Functional assessment short test, MD=mean difference, MDD= major depressive disorder, 95% CI= 95% confidence interval

Table4: Comparative analysis of quality of life (SF-36) in schizophrenia, major depressive disorder and healthy controls with adjustment for confounders

Outcome	Confounder	Comparison	MD (95% CI)	Comparison p-value	Global p-value
SF-36 Mental Health Composite	Diagnosis	Controls vs Schizophrenia	3.365(0.009, 8.722)	0.05	0.002
		MDD vs Schizophrenia	-4.275(-8.044, -0.505)	0.026	
		Control vs MDD	8.640(5.068, 12.2123)	<0.001	
	Illness severity	Normal vs Mild	9.779(6.497, 13.068)	<0.001	<0.001
		Mild vs Moderate	4.745(-0.533, 10.023)	0.078	
		Normal vs Moderate	14.524(9.194, 19.854)	<0.001	
	Sex	Male vs Female	-2.463(-5.416, 0.491)		0.102
	Age		0.092(-0.022, 0.206)		0.112
	Education (years)		0.657(-0.021, 1.336)		0.058
SF-36 Physical Composite	Diagnosis	Controls vs Schizophrenia	4.988(0.758, 9.219)	0.021	0.001
		MDD vs Schizophrenia	6.789(3.129, 10.450)	<0.001	
		Control vs MDD	-1.801(-5.270, 1.668)	0.309	
	Illness severity	Normal vs Mild	3.116(-0.072, 6.303)	0.055	0.021
		Mild vs Moderate	3.546(-1.529, 8.672)	0.175	
		Normal vs Moderate	6.661(1.485, 11.837)	0.012	
	Sex	Male vs Female	4.680(1.812, 7.548)		0.001
	Age		-0.120(-0.231, -0.010)		0.033
	Education (years)		0.814(-1.473, -0.155)		0.016

SF-36= 36-item short health form, MD=mean difference, MDD= major depressive disorder, 95% CI= 95% confidence interval, p-value

Figure 1: Comparison of mean FAST total scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)

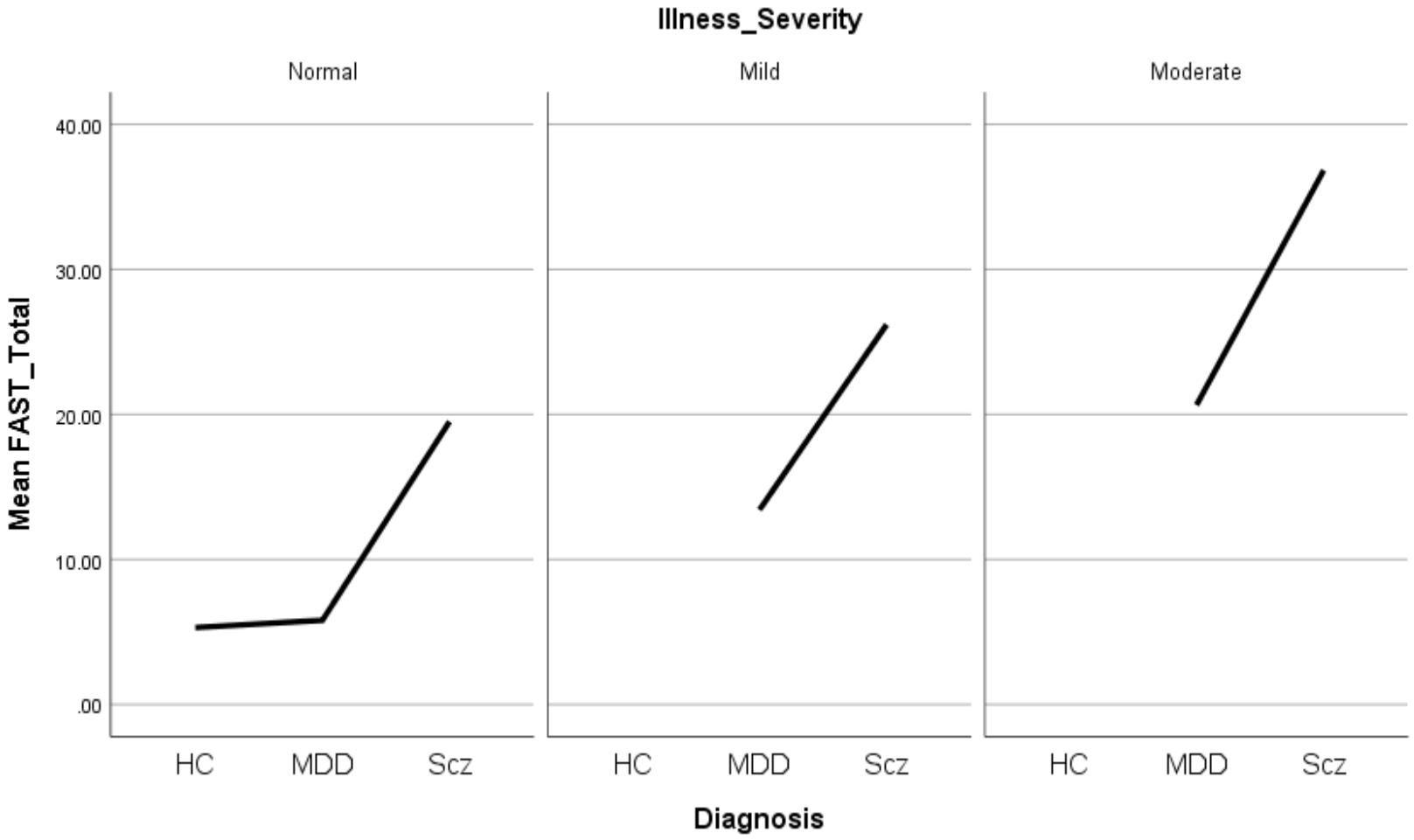


Figure 2: Comparison of mean FAST autonomy scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)

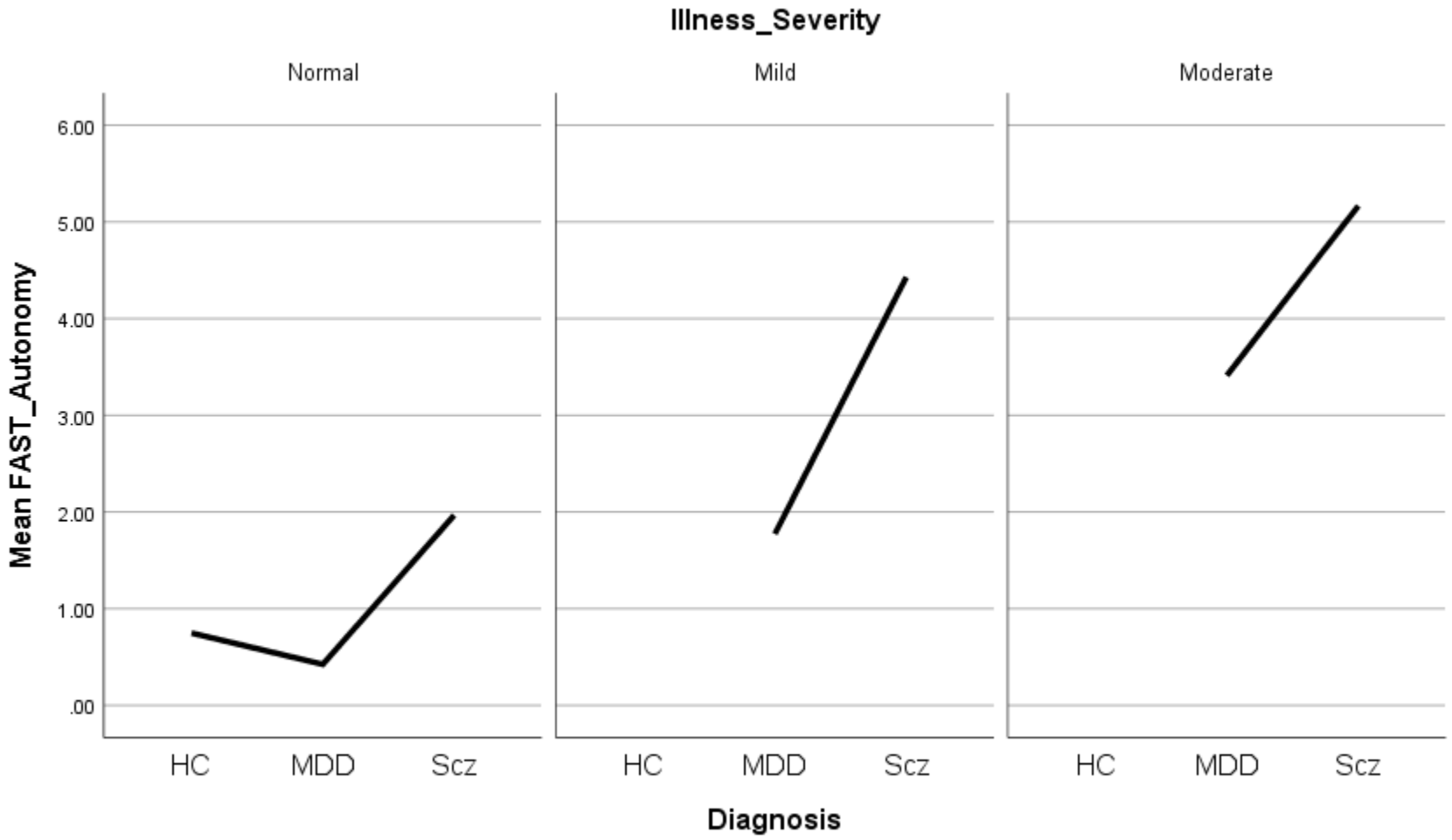


Figure 3: Comparison of mean FAST occupational function scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)

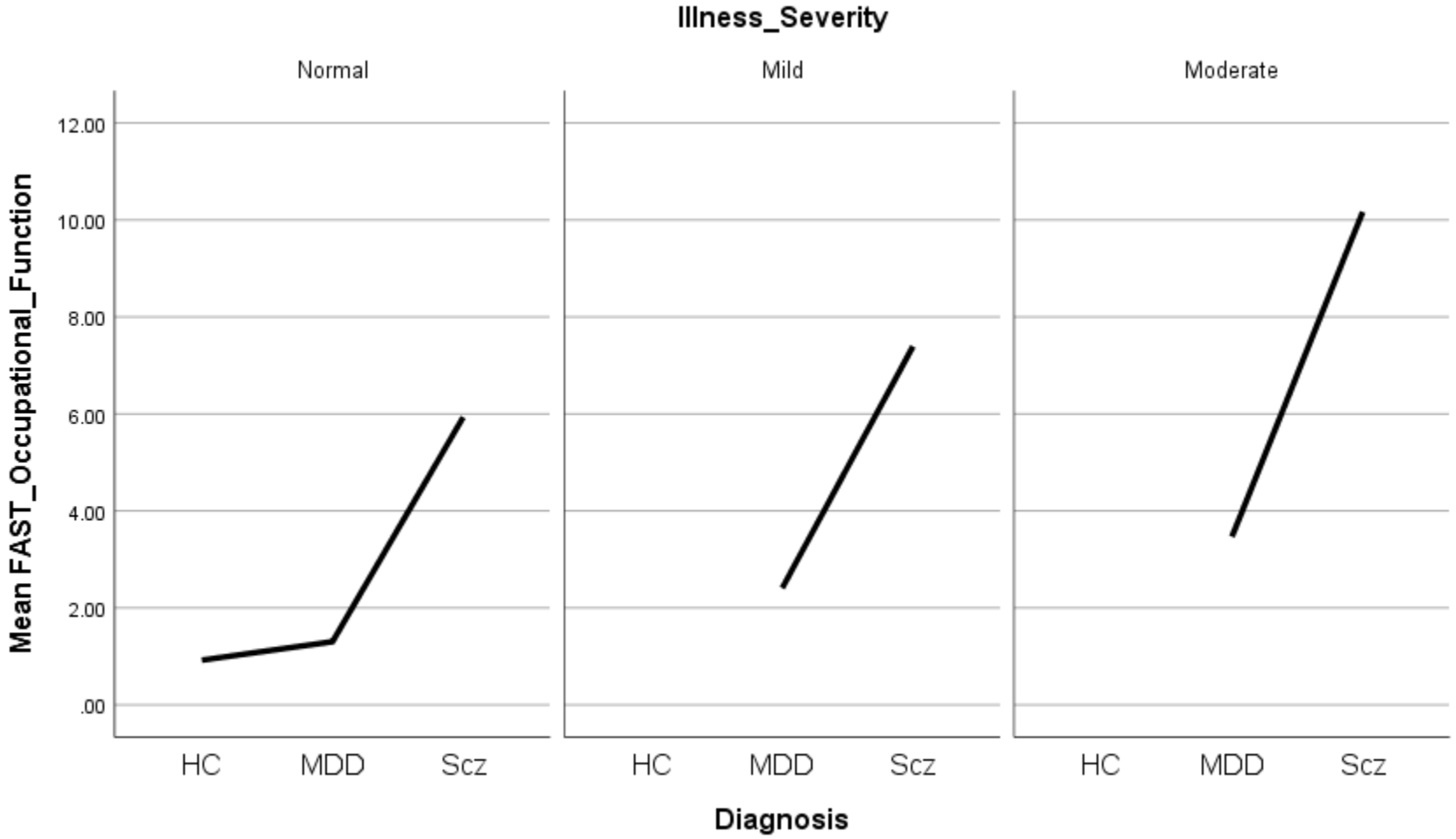


Figure 4: Comparison of mean FAST cognitive function scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)

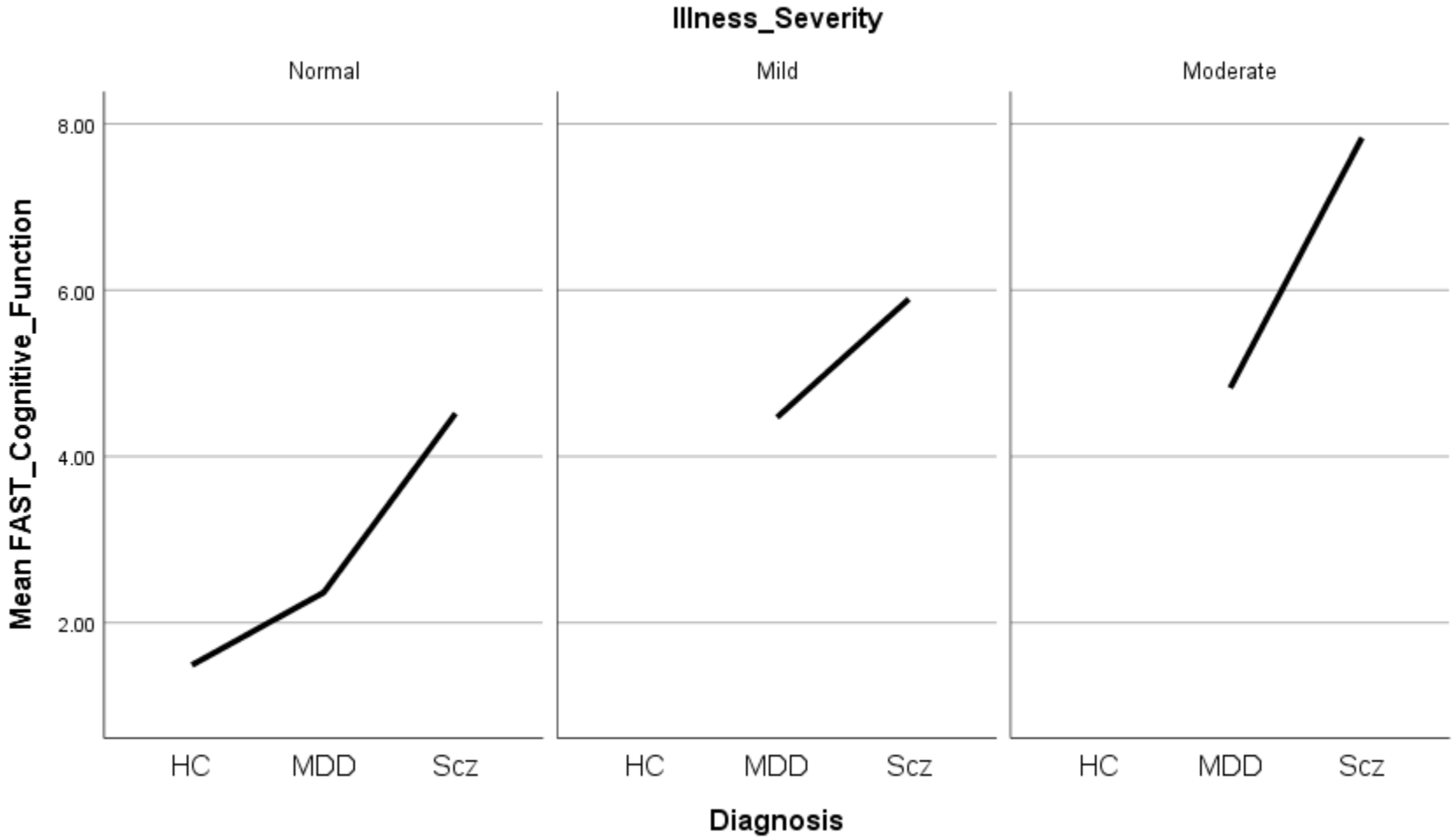


Figure 5: Comparison of mean FAST financial issues scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)

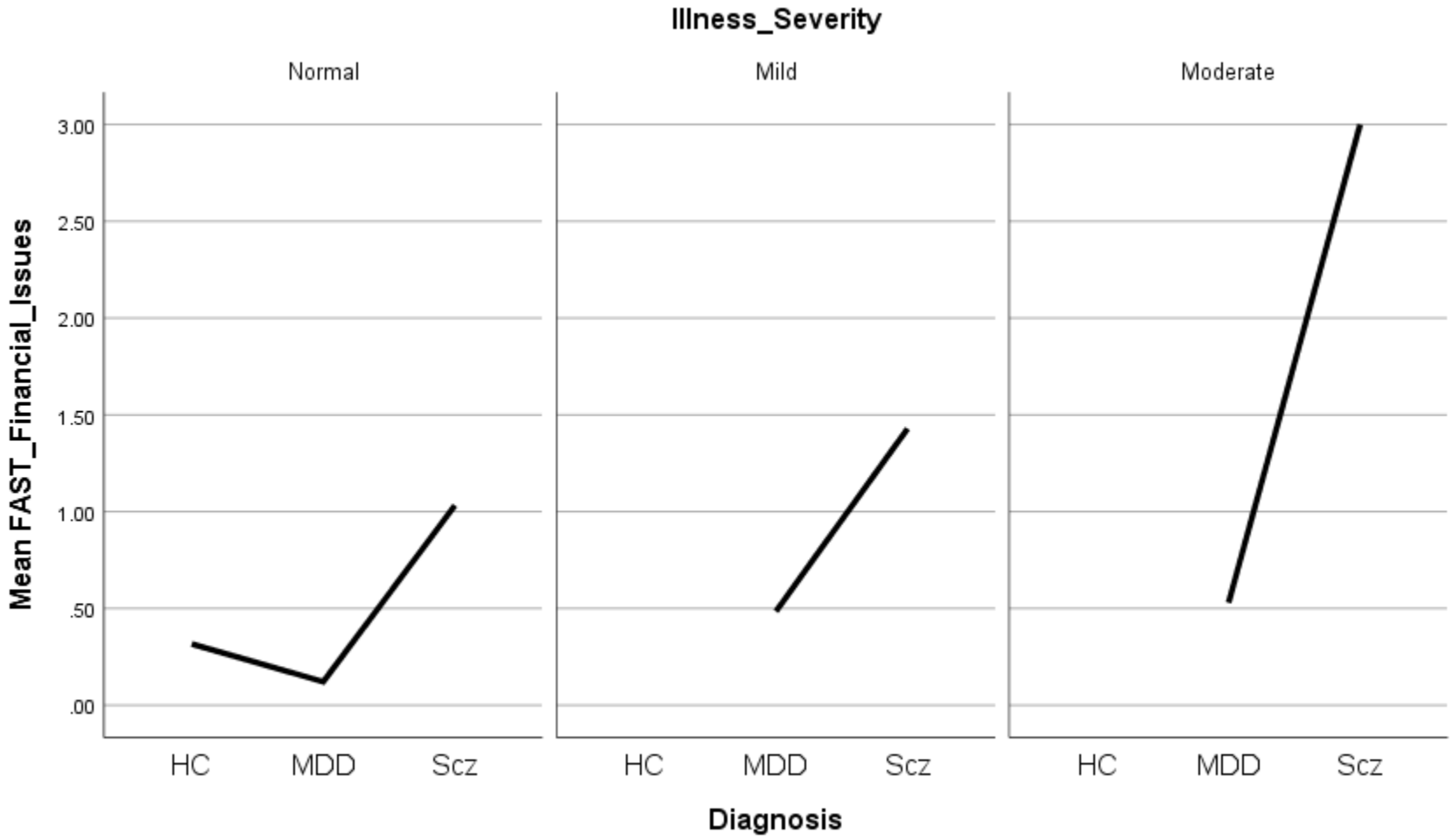


Figure 6: Comparison of mean FAST interpersonal relationship scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)

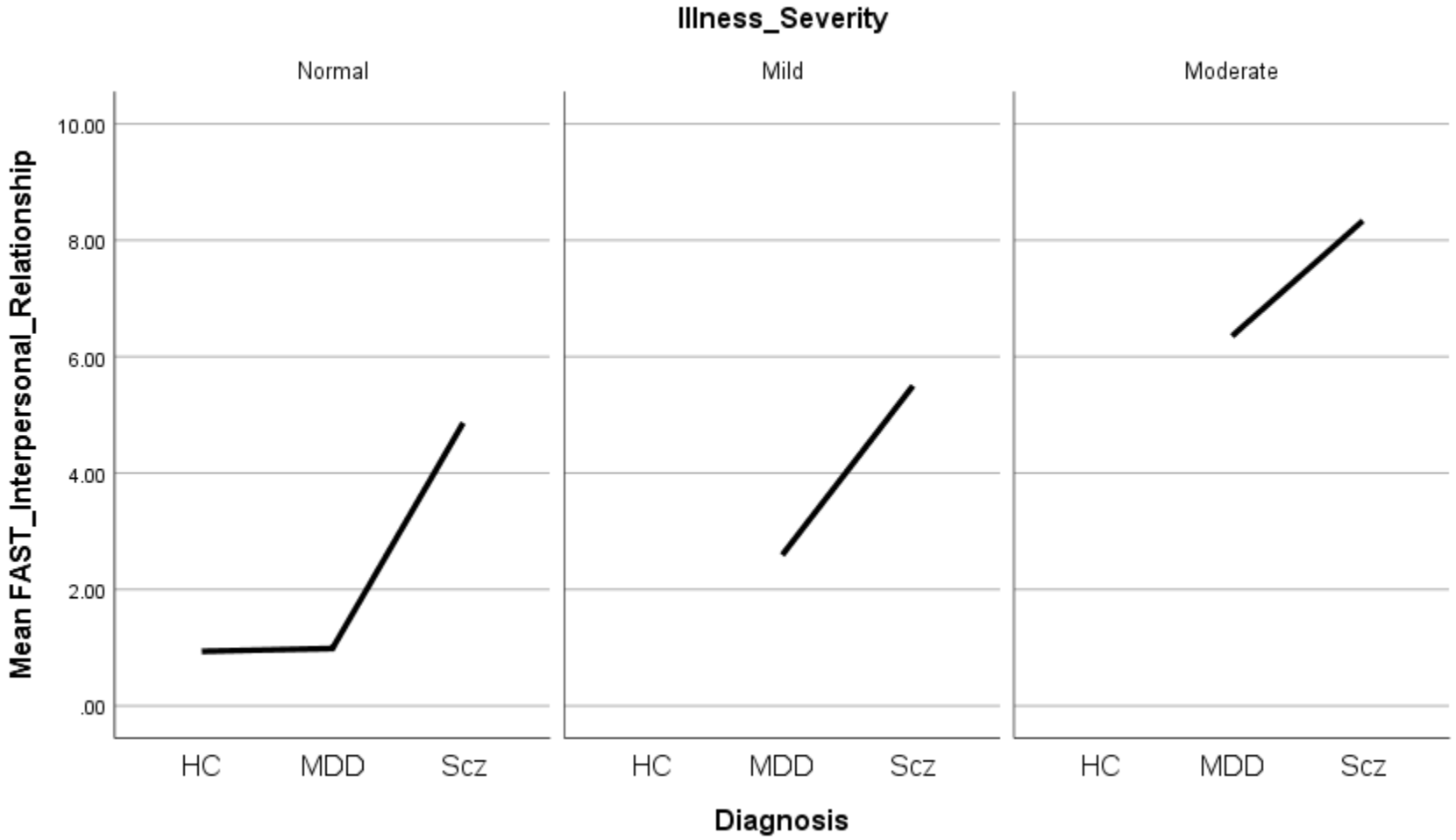


Figure 7: **Comparison of mean FAST leisure scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)**

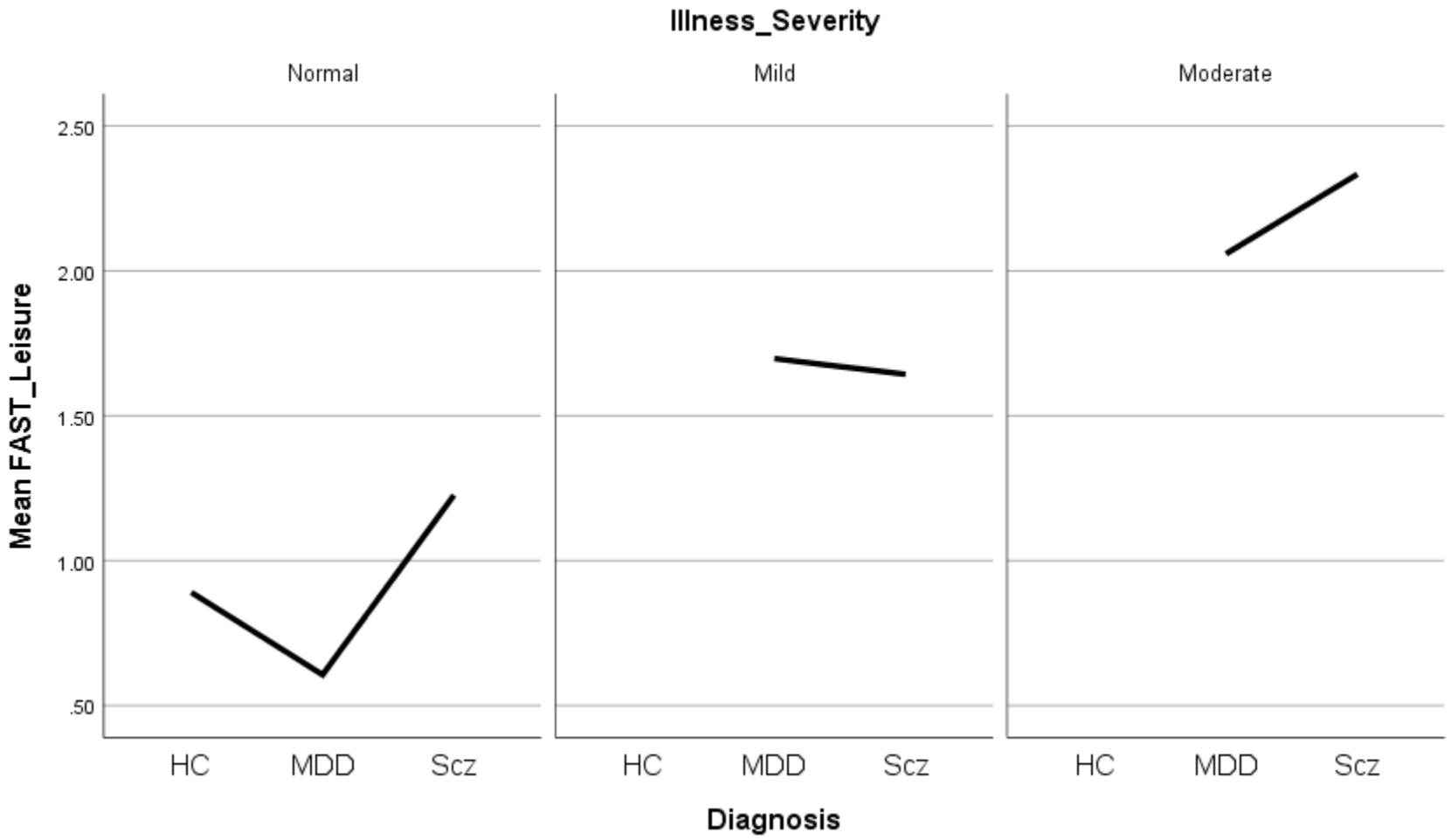


Figure 8: Comparison of mean SF-36 mental health scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)

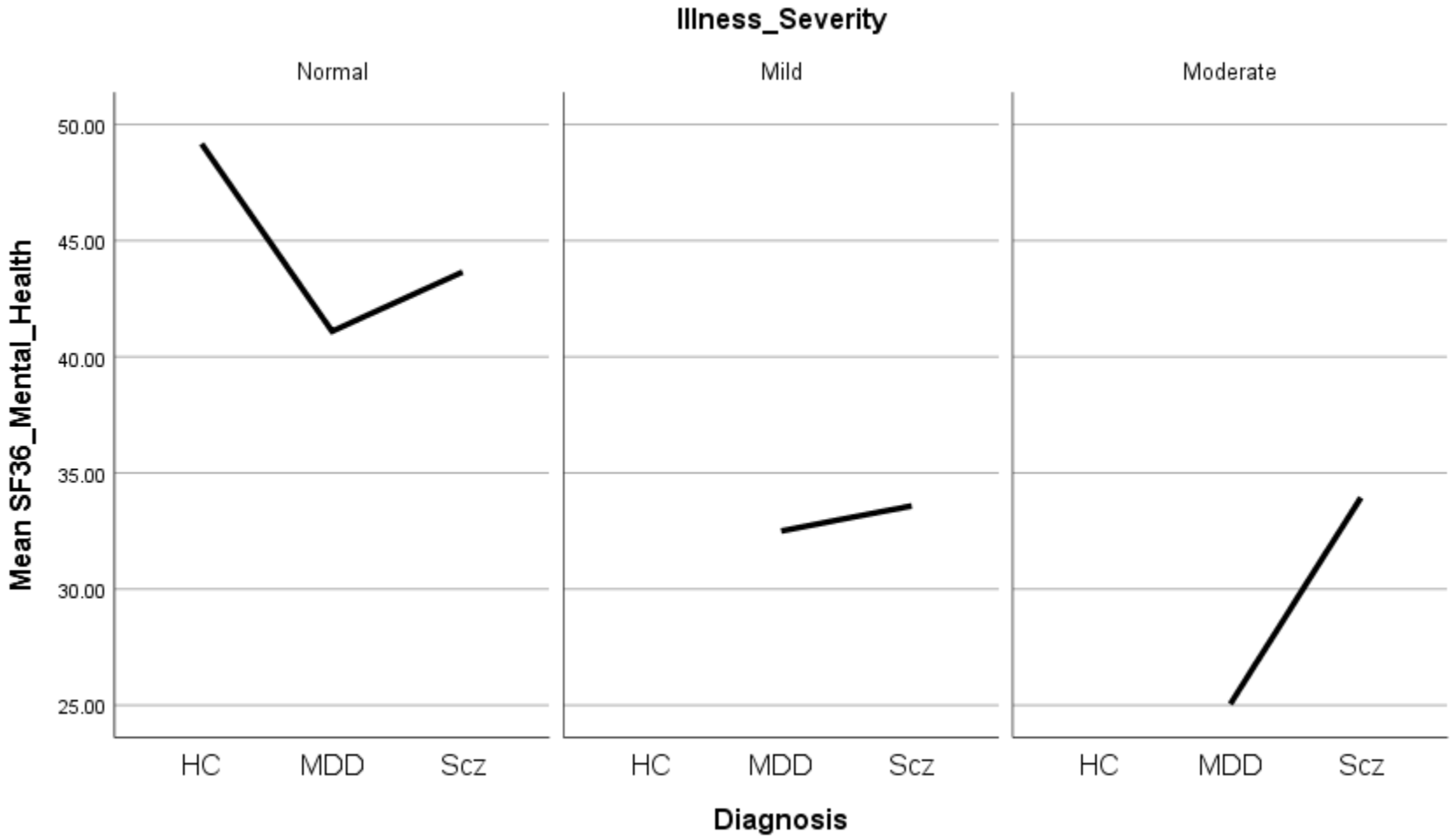
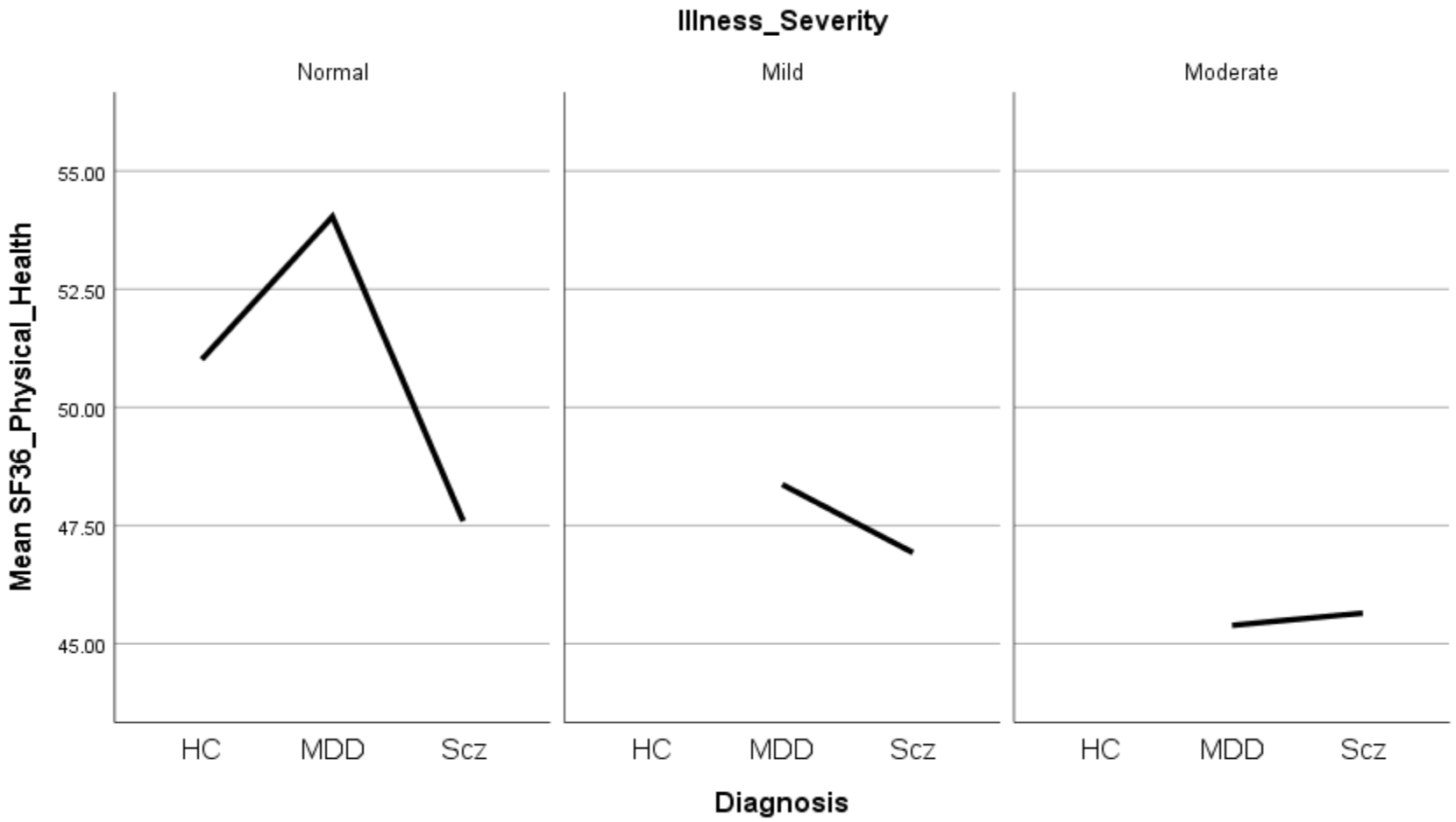


Figure 9: Comparison of mean SF-36 physical health scores by illness severity in participants with schizophrenia (Scz), major depressive disorder (MDD) and healthy controls (HC)



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Chapter 6

Relationship of functional status with illness severity and cognitive function in patients with schizophrenia compared with major depressive disorder and healthy controls

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Abstract

Background: Functional deficit is thought to be influenced by multiple factors in patients with schizophrenia, however, cognitive dysfunctions play a central role in determining the pattern of impairments in function. Similar to patients with schizophrenia, functional and cognitive deficits have been identified in patients with major depressive disorder (MDD). However, little is known about any overlap or differences in the relationship between cognitive deficits and impairment in psychosocial function between these disorders. This study investigates the differences and similarities in impaired function in patients with schizophrenia compared to MDD and healthy controls (HC) considering variation due to cognitive deficits and illness severity. We controlled for cofounding effects of age, gender, and years of education.

Methods: The study participants (n=156) completed assessments with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Functioning Assessment Short Test (FAST), and the 36-Item Short Form Survey Instrument (SF-36). We conducted linear regression analysis in separate models to compare patients with schizophrenia, MDD, and healthy controls on specific aspects of functional status and QoL, considering the effects of multiple domains of cognitive function. This was followed by mediation analysis to provide more insight into the effect of cognitive deficits on the relationship between illness severity and functional status/QoL in all the study participants to test if this mediation effect is transdiagnostic.

Results: The participants included those that met the DSM-5 diagnosis of schizophrenia (n=56), MDD (n=66) and HC (n=34). Patients with schizophrenia were older, had fewer years of education, and were likely to be males compared to MDD and HC. Patients with schizophrenia also showed the most severe form of deficits across all the measured aspects of cognitive function, functional status and QoL followed by patients with MDD, compared to HC ($p<0.05$). A model combining multiple aspects of cognitive function and identifiable clinico-demographic factors (including illness severity, age, gender, and years of education) showed they were collectively related to all the domains of functional status and QoL, with small to medium effect sizes. Individually, illness severity (that captured symptom load) was significantly associated with functional status and QoL. Older age, male sex, and fewer years of education were associated with poorer physical health QoL, and older age was associated with impaired mental health QoL. While attention and immediate memory were positively related to QoL, attention,

spatial cognition, and immediate and delayed memory, indirectly mediated the relationship between illness severity and functional status/QoL.

Conclusion: Individuals with schizophrenia showed the most severe form of deficits across all the measured aspects of cognitive function, functional status and QoL followed by patients with MDD, compared to HC. Attention was positively related to functional status and negatively related to QoL (direct effect). Deficits in multiple aspects of cognition showed an indirect effect on psychosocial function, mediating the effects of illness severity on functional status and QoL. Consequently, interventions targeted at improving cognitive deficits (such as cognitive remediation, neurocognitive enhancement therapy, work therapy, and verbal memory task based on dichotic listening, etc) may have direct benefits on functional outcomes, and indirect positive effects as a mediating factor on the relationship between symptom or illness severity and psychosocial function.

Introduction

Schizophrenia is a chronic mental disorder with a lifetime prevalence of about 4-7 individuals per 1000.[1, 2] The characteristic symptoms of schizophrenia in the diagnostic manuals include thought abnormality, hallucination, and disorganized behaviour, however functional deficit is a major problem, accounting for disability in a significant proportion of patients.[3-5] In a meta-analytic review of 50 studies of patients with schizophrenia, only 13.5% met the criteria for clinical and social recovery, highlighting impaired function as a pervasive problem in individuals with schizophrenia.[5] The real-world ramifications of impairment in psychosocial function are wide-reaching, affecting individual patients with schizophrenia, their families and society.[4-6] For instance, functional impairment interferes with patients' day-to-day life, social relationship, and their ability to maintain gainful employment,[6] contributing appreciably to the economic costs and psychosocial burden of schizophrenia. [6, 7] In recent estimates of the global burden of diseases, schizophrenia is ranked among the top causes of disability worldwide.[8, 9]

The functional deficit in patients with schizophrenia is thought to be influenced by multiple factors (e.g., illness severity, cognitive deficits, substance use, psychological events, medications, adherence, number of episodes and length of untreated illness), however cognitive dysfunctions play a central role in determining the pattern of impairments in function.[7,10-13] Moreover, an individual's ability to recognize, process and respond to information needed for everyday life function and perform social roles is contingent on intact cognitive processes.[14] In patients with schizophrenia, various forms of deficits across several cognitive domains, including speed processing, working memory, verbal learning, visual learning, attention/vigilance, reasoning, social cognition, problem solving and executive function have been observed.[7, 9, 10] These deficits can restrict patients' ability to acquire, retain or relearn skills that are needed for real-world functioning, social relationships and performance of employable tasks.[6,12-15] In a previous study, two standard deviations reduction in global cognitive function was observed in patients with schizophrenia compared to the general population, and this was associated with poorer functional outcomes in schizophrenia.[15] While deficit in global cognitive functions has been established as a strong predictor of functional outcome in schizophrenia with small to medium effect sizes in previous studies,[16] the association between specific aspects of cognitive function with psychosocial functions is variable.[16, 17] Hence a comprehensive analysis to better

understand the interplay between specific aspects of cognitive deficit and functional impairment is important in clinical and research practice to improve evidence guided interventions.[15] Specifically, such comprehensive analysis has clinical benefits for extending current knowledge and practice of contemporary interventions (such as cognitive remediation, training or rehabilitation) and can facilitate the development of novel targets to improve cognitive and functional outcomes in people with schizophrenia.[15, 18-20]

The benefits of cognitive remediation treatments (e.g., individual executive functioning training, cognitive enhancement therapy, integrated psychological therapy, and attention process training etc.) on psychosocial function are well demonstrated in patients with schizophrenia, albeit evidence suggests that these treatments are more effective when they target specific cognitive deficits linked with functional limitations in individual patients.[18-22]

Similar to patients with schizophrenia, cognitive dysfunctions (especially deficits in processing speed, attention, executive function, learning, and memory) have been identified as important determinants of functional impairment in major depression,[23-25] albeit relatively understudied compared to schizophrenia.[26] Again there is limited research comparing the relationship between cognitive deficits and the specific pattern of functional impairments across these psychiatric diagnostic groups (e.g., schizophrenia and major depressive disorder [MDD] in this study) to assess any overlap or differences across the diagnostic categories.[27, 28] Cognitive deficit (e.g., episodic memory, executive function, and processing speed)[29, 30]and impaired function (including communication, financial and social functioning) are established features and treatment targets of both active and remitted MDD to improve overall outcome.[31] For example, there is emerging evidence for the benefits of cognitive training in MDD.[32] Implicitly, a comparison of these diagnostic groups can provide better insight into the benefits of transdiagnostic applications of the well-developed cognitive remedial interventions for patients with schizophrenia[18-20] to patients with MDD or other mental disorders and vice versa. Consequently, we pursued this study to investigate the nature of the relationship between specific aspects of cognitive deficits and functional impairments in patients with schizophrenia compared with MDD and healthy controls (HC). The specific study objectives are:

1. To investigate the relationship between multiple aspects of cognitive deficits and functional status in participants with schizophrenia spectrum disorders compared with

participants with lifetime MDD and HC, considering variability in illness severity, age, sex, and years of education.

2. To investigate if multiple aspects of cognitive deficits have mediation effects on the association between illness severity and functional status/quality of life (QoL) across all study participants.

Methods

Study design and recruitment of participants

This is a cross-sectional study comparing participants with schizophrenia (diagnosed with either schizophrenia or schizoaffective disorder) with participants with life time MDD without psychotic symptoms and HC. The data analysed in this study were obtained from the Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS) and the Cognitive Function and Mood study (CoFAMS). The details of the rationale and characteristics of these two naturalistic prospective studies are provided in two previous publications.[33, 34] Both CoFAMS and CoFAPSS were aimed at investigating the cognitive, functional, clinical, and genomic correlates of mood disorders and psychotic disorders respectively in comparison to healthy controls.[35,36] We considered only baseline cross-sectional data including demographics, cognitive function, symptom measures, functional status, and quality of life in the present analysis.

Study recruitment included both the inpatient and outpatient psychiatric services of the Department of Psychiatry, University of Adelaide and Health Networks in South Australia. Public advertisement in the general community was also done to recruit healthy controls and people with a history of psychotic illness. Exclusion criteria included impaired cognitive and functioning abilities associated with severe physical illness, comorbid developmental or neurological disorders, and learning disability. Approval for the two studies was obtained from the Human Research Ethics Board at the Royal Adelaide Hospital (RAH Protocol No: 140709 for CoFAPSS, and RAH Protocol No: 111230 for CoFaMS).

Participants included in the present study were aged 18-65 years diagnosed with schizophrenia (either schizophrenia or schizoaffective disorder), lifetime MDD without psychotic symptoms and unmatched HC without a history of psychiatric or neurological disorders. For participants with schizophrenia, the diagnosis was based on assessment completed by clinicians and screening for psychotic symptoms based on DSM-5[35] criteria. For MDD, participants with a lifetime history of MDD based on the Mini-International Neuropsychiatric Interview (MINI)[36] were included and we excluded any participants with a history of psychosis or mania/hypomania. Healthy controls screened negative for any DMS-5 diagnosis based on clinical interview using the MINI[36]. The measures used for the present study outcomes (demographics, cognitive function, symptoms profile captured as illness severity, functional status and QoL) are described below. The study participants were selected based on their completion of objective neuropsychological assessments of their cognition using the Repeatable Battery for the Assessment of Neuropsychological Function Status (RBANS),[37] and a clinical interview to evaluate their psychosocial functioning using the Functioning Assessment Short Test (FAST)[38-40] and the 36-Item Short Form Survey Instrument (SF-36).[41-44]

Measure of cognitive function

The RBANS was used as a brief tool to evaluate neuropsychological deficits in study participants. It is a validated tool that assessed performance in multiple aspects of cognition, including immediate memory, language, attention, visuospatial/constructional memory and delayed memory.[37] Several RBANS tests (i.e., digit span, list learning, list recognition, store memory, figure recall, picture naming, figure copy and line orientation tests) were conducted and mapped with norms in the RBANS user manual guide to provide scores on participants' performance in specific domains of cognition.[37, 38]

Measures of functional status and quality of life (QoL)

Functional status was assessed using the FAST,[39] a validated measures for assessing multiple domains of psychosocial function.[39-41] The FAST assesses functional status over the previous two weeks based on 24 items that allow clinical evaluation of difficulties in daily functioning in participants with mental disorders.[40,41] Following an assessment with FAST, scores were generated using a 4-point scale, 0 (no impairment), 1 (mild impairment), 2 (moderate impairment), and 3 (severe impairment) to represent interviewees' global function and

performance in six specific aspects of function including autonomy, occupational functioning, financial issues, cognitive functioning, interpersonal relationships and leisure. FAST has several advantages, including being easy to apply, and available in several languages. The total/global score ranges from zero to 72, with a higher score indicating more serious difficulty or greater disability or higher impairment in functioning.[38-41]

Conversely, the SF-36 was used to measure perceived health status in all study participants.[42,43] It is a 36-item QoL tool scored to represent performance in specific wellbeing subscales including physical functioning (PF), role limitation due to physical problems (RP), role limitation due to emotional problems (RE), social functioning (SF), mental health (MH), bodily pain (BP), energy and vitality (VT), and general perception of health (GH). Further, SF-36 scores can be used to generate mental and physical health QoL composite scores.[44-48] Scores were interpreted using Likert's method for rating scales.[49]

Measures of illness severity

The severity of illness was computed mapping scores on the Positive and Negative Syndrome Scale (PANSS) in participants with schizophrenia[50] and the 31-item structured interview that assessed symptom load using the Hamilton Depression Scale (HAM-D) for participants with MDD[51] based on the method developed by Leucht et al.[52,53] This allowed uniformity in the operationalization of symptom severity as a variable named illness severity across all the study participants. See Table 1 for the mapping of the illness severity (a measure of symptom load) in participants with schizophrenia versus MDD based on PANSS and HAMD.

Statistical analyses

Data analysis was performed using IBM SPSS statistics for windows, Version 27.0[54] and STATA statistical software (for mediation analysis).[55] The data were examined for normality and homogeneity of variance. The characteristics of the study participants were presented using descriptive statistics, including frequency and percentage for categorical variables, and mean with standard deviation for continuous variables. We conducted linear regression analysis with a generalized linear model to investigate the relationship between specific aspects of functional status and QoL with multiple domains of cognition, considering variability in identifiable clinic-demographic factors in participants with schizophrenia versus MDD and HC. In separate models,

we included each specific aspect of functional status measured by FAST (including the global, autonomy, occupational functioning, cognitive function, financial issues, leisure and interpersonal relationships) and QoL measured by SF-36 (mental and physical health composites) as the dependent variable and regressed with multiple aspects of cognitive function (e.g., immediate memory, spatial cognition, semantic memory, attention and delayed memory), adjusting for age, sex, gender and years of education. We reported beta coefficients with a 95% confidence interval for the models. All predictors and pairwise comparative analysis for categorical variables were included in the model. The performance of the overall model was reported, highlighting R-squared (R^2) as the measure of the percent of variance in the dependent variable explained by the predictors in the model. Categorization of effect sizes was based on R^2 (small= 0.10 - 0.30, medium=0.30 - 0.50 and large $\geq$0.50).[56] Assumptions of linear regression were tested for each model and a p-value<0.05 was used to determine the level of significance in all statistical tests. Furthermore, we tested if the dimensions of cognitive function mediate the relationship between functional status/QoL and illness severity.

The mediation analysis (series of regression analyses) was pursued to provide additional insight into our findings of statistically significant association between functional status and QoL outcomes (measured with FAST-total, SF-36 physical composite, and SF-36 mental health composite) and the predictor: illness severity (dichotomized into normal severity versus mild/moderate). Specifically, we included data on the measures of functional status and QoL in separate models as the dependent variables, illness severity as the independent variable in all models, and seven dimensions of cognitive function (indexed RBANS subdomains) as mediators in the models. Each mediator was entered in separate models, resulting in 21 models in total. The mediation analysis included testing the effects or contribution of each domain of cognitive function on the relationship between illness severity and functional status and QoL for all participants (transdiagnostic). We reported the indirect effect as the variance in the relationship between illness severity and functional status and QoL that is mediated by specific dimensions of cognitive function. Direct effect refers to the fraction of the total effects of illness severity on functional status and QoL that is not accounted for by the mediation effects of the domains of cognition (indirect effect). The mediation analysis was completed with the STATA statistical software.[55]

Results

Characteristic of the study participants

We identified data on participants aged 18-65 years who met DSM-5 diagnosis of schizophrenia (n=56), participants with life time MDD (n=66) and unmatched HC (n=34) without a history of psychiatric or neurological disorders. The characteristics of the study participants are presented in Table 2 and highlighted below.

Clinico-demographic: participants with schizophrenia were older, with a mean age of (37.9±11.4) compared to participants with MDD (31.1±14.1) and HC (28.7±15.1) years. The majority of participants with schizophrenia (67.9%) were males compared to participants with MDD (34.8%) and HC (44.1%) with lesser proportion who were males. Participants with schizophrenia reported fewer years of education (11.7±2.8) compared to MDD (13.0±1.9), and HC (13.4±1.6) years. The mean score of participants with schizophrenia on PANSS was (54.5±13.6) while the mean scores of participants with MDD and HC on HAMD were (9.8±5.8) and (2.9±2.0) respectively. The differences in age, sex, years of education, and illness severity of participants with schizophrenia compared with MDD and HC were statistically significant ($p<0.05$)

Cognitive function: There were statistically significant differences among participants with schizophrenia, MDD and HC across all the domains of cognitive function ($p<0.05$). Specifically, participants with schizophrenia compared to MDD, and HC reported lower mean scores in all domains of cognitive function, including immediate memory (73.8±19.2, 101.1±16.2, and 101.5±16.3,), spatial cognition (82.0±15.3, 87.0±15.9 and 93.9±16.0,), semantic memory (86.3±13.4, 100.5±15.4, and 94.6±17.2), attention (78.8±17.9, 103.2±16.3, and 102.6±16.5), and delayed memory (77.4±17.4, 92.2±11.2 and 95.5±8.5) respectively.

Functional status and QoL: Functional status measured by FAST total score was the most impaired in participants with schizophrenia (24.36$\pm$13.43) followed by MDD and HC (3.44$\pm$3.04). All subdomains of FAST, including autonomy, occupational functioning, cognitive function, financial issues, inter-personal relationship, and leisure followed this pattern. Mental health related QoL was lowest on average for those with MDD, with schizophrenia being intermediate and controls reported the highest score (49.41±9.44) among the three groups. In

contrast, physical health QoL was reportedly highest in MDD, followed by controls and was lowest in those with schizophrenia (46.49±12.39). All differences in functional status and QoL among the diagnostic groups were statistically significant at $p<0.05$.

[See Table 2].

Linear regression of functional status (FAST) with cognitive domains and clinico-demographic factors in participants with schizophrenia, MDD and HC

Table 3 presents the results of linear regression analyses that explore the relationship of functional status (measured with FAST-total score and subscales) with cognitive function and identifiable clinico-demographic status. Findings in each domain of FAST are expressed by standardized beta coefficients and 95% confidence interval.

FAST-total score: The first model investigating the predictors of global functioning (indexed by FAST total) showed a statistically significant association between FAST-total score and diagnosis, adjusting for the other covariates in the model (global p-value<0.001). Healthy controls had on average 11.90 units less on the FAST-total score than participants with schizophrenia (β= -11.90, comparison p-value<0.001). Further, participants with MDD show on average 8.52 units less on the FAST-total score than participants with schizophrenia (β = -8.52, comparison p-value<0.001). The difference between MDD and HC was not significant. Similarly, there was a statistically significant association between FAST-total score and illness severity, adjusting for the other covariates in the model (global p-value<0.001). Participants who were normal with respect (definition based on symptom level is provided in table 1) to illness severity show on average, 15.45 units less on FAST-total score compared to participants with moderately severe illness (β = -15.45, comparison p- value<0.001). Participants with mildly severe illness showed on average 8.29 units less on FAST-total score compared to participants with moderate illness severity (β = -8.29, comparison p-value<0.001). In contrast, age (β =0.11, p=0.063), education (β=0.49, p=0.177), immediate memory (β =-0.06, p=0.297), spatial cognition (β= 0.03, p=0.632), semantic memory (β =-0.001, p=0.981), attention (β= -0.009, p=0.848), and delayed memory (β= -0.02, p=0.773) did not significantly predict global functional status. The overall model was statistically significant for the collective effect of age, sex, years of education, illness severity, diagnosis, and multiple aspects of cognitive function on

global functioning, collectively explaining 51% of the variance in FAST-total [F = 9.89, p< 0.001, R^2= 0.51].

FAST-autonomy Score: In the regression model investigating the predictors of FAST-autonomy [dependent variable], there was a statistically significant association with diagnosis, adjusting for the other covariates in the model (global p-value=0.009). Healthy controls (β= -1.49, comparison p-value=0.008) and participants with MDD (β= -1.44, comparison p-value=0.004) show on average 1.49 and 1.44 units less on FAST-autonomy score than participants with schizophrenia respectively. Similarly, there was a statistically significant association between FAST-autonomy and illness severity, adjusting for other covariates in the model (global p-value<0.001). Participants who are normal with respect to illness severity have on average 1.65 units less on FAST-autonomy score than participants with moderate illness severity (β =-1.65, comparison p-value<0.001), and participants with mildly severe illness on the average show 1.27 units less on FAST-autonomy score compared to participants with moderate illness severity (β =-1.27, comparison p-value=0.003). The overall model was statistically significant, with 38% variance in FAST autonomy explained by the collective effects of age, sex, years of education, illness severity, diagnosis, and multiple aspects of cognitive function [F = 6.32, p< 0.001, R^2 = 0.38].

FAST-occupational functioning score: There was a statistically significant association between FAST-occupational functioning and diagnosis, adjusting for the other covariates in the model (global p-value<0.001). Sub-group analysis showed that HC (β=-4.04, comparison p-value<0.001) and participants with MDD (β=-3.26, comparison p-value=<0.001) on the average show 4.04 and 3.26 units less on FAST-occupational functioning score than participants with schizophrenia respectively Similarly, there is a statistically significant association between FAST-occupational functioning and illness severity, adjusting for the other covariates in the model (global p-value=0.008). Participants with normal illness severity have on average 1.26 units less on FAST occupational functioning score compared to participants with mild illness severity (β =-1.26, comparison p- value=0.048). Participants who were classified as normal with respect to illness severity showed on average 2.88 units less on FAST occupational functioning score than participants who were moderately ill severity (β =-2.88, comparison p-value=0.003). There was no statistically significant difference between participants with mild and moderate illness severity (comparative p-value=0.095). Notwithstanding, there was a significant collective

relationship of age, sex, years of education, illness severity, diagnosis, and multiple aspects of cognitive function with occupational functioning. In total, all predictors in the model collectively accounted for 40% variance in FAST-occupational functioning [F=6.69, p= 0.009, R^2 =0.40]

FAST-cognitive function score: When FAST cognitive function was included in the linear regression model as the dependent variable, there was a statistically significant association between FAST-cognitive function and diagnosis, adjusting for the other covariates in the model (global p=0.019). Healthy controls show on average 1.54 and 1.63 units less on FAST cognitive function score compared to participants with schizophrenia (β=-1.54, comparison p-value=0.039) and MDD (β= -1.63, p=0.007) respectively. Further, no statistically significant difference between participants with MDD and schizophrenia with respect to FAST cognitive function (β= 0.009, comparison p-value=0.890). Similarly, there was a statistically significant association between FAST cognitive function and illness severity, adjusting for the other covariates in the model (global p-value<0.001). Participants categorized as normal with respect to severity of illness show on average 1.82 units less on FAST cognitive function score than participants with mild illness severity (β =-1.26, comparison p- value=0.048). Participants who were classified as having normal illness severity show on average 2.12 units less on FAST cognitive function than those participants with moderate illness severity (β =-2.109, comparison p-value=0.007). There was no statistically significant difference between participants with mild and moderate illness severity (comparative p-value=0.708). Similarly, sex (β =-0.27, p=0.541), age (β =0.03, p=0.081), education (β=-0.08, p=0.431), immediate memory (β =-0.02, p=0.188), spatial cognition (β<0.001, p=0.99), semantic memory (β =0.01, p=0.459), attention (β=-0.006, p=0.652), and delayed memory (β=-0.03, p=0.124) did not significantly predict cognitive function statistically. The overall model accounted for 31% variance in FAST-cognitive function [F =4.79, p< 0.001, R^2 =0.31].

FAST financial issues score: There was a statistically significant association between FAST-financial issues score and diagnosis, adjusting for the other covariates in the model (global p=0.05). Participants with MDD show on average 0.67 units less on FAST financial issue score than those with schizophrenia (β=-0.67, comparison p-value=0.016). Conversely, there was no statistically significant difference between healthy controls and participants with MDD (β =0.11, p=0.658) and participants with schizophrenia (β =-0.56 p=0.077). FAST-financial issue domain

was statistically significantly related with illness severity, adjusting for the other covariates in the model (global p-value=0.007). Participants with normal illness severity showed on the average 0.51 and 0.94 units less on FAST financial issues compared to participants with mild illness severity (β =-0.51, p-value=0.019) and moderate illness severity (β =-0.94, p-value=0.005) respectively. Similarly, there was a significant relationship between sex and FAST financial issues (β =-0.27, p=0.016). The overall model showed that age, sex, years of education, illness severity, diagnosis, and multiple aspects of cognitive function had a statistically significant collective relationship with FAST-financial issues [F=2.84, p=0.004, R^2=0.17], and the model explained 17% variance in FAST-financial issue (small effect size).

FAST interpersonal relationship score: There was a statistically significant association between FAST interpersonal relationship and diagnosis, adjusting for the other covariates in the model (global p-value=0.02). Healthy controls showed on the average 3.03 units less on FAST interpersonal relationship score compared to participants with both schizophrenia and MDD (β= -3.03, comparison p-value<0.001). Further, participants with MDD showed on the average 2.18 units less on FAST interpersonal relationship score compared to participants with schizophrenia (β = -2.18, comparison p-value=0.004). Similarly, there was a statistically significant association between FAST interpersonal relationship and illness severity, adjusting for the other covariates in the model (global p-value<0.001). Participants with normal illness severity showed on the average 1.49 and 5.29 units less on FAST interpersonal relationship score compared to participants with mild illness (β=-1.49, p-value=0.012) and moderate illness severity (β = -5.29, comparison p-value<0.001) respectively. Participants with mild illness severity showed on the average 3.804 units less on FAST interpersonal relationship score compared to participants with moderate illness severity (β = -3.804, comparison p-value<0.001). Sex was significantly associated with FAST interpersonal relationship, with male showing on average 1.29 units higher on FAST interpersonal relationship compared with females (β =1.299, p=0.01). However, all predictors collectively predicted 42% variance in FAST interpersonal relationship score [F =5.37, p=0.003, R^2 =0.42].

FAST-leisure score: There was a statistically significant association between FAST leisure score and diagnosis, adjusting for other covariates in the model (global p=0.02). Healthy controls on the average showed 1.11 units less on FAST leisure score compared to participants with

schizophrenia (β=-1.11, p=0.001). Participants with MDD on the average showed 0.92 units less on FAST leisure score than participants with schizophrenia (β=-0.915, comparison p-value=0.002). Conversely, there was no statistically significant difference between healthy controls and participants with MDD (β =-0.196, p=0.472) with respect to FAST leisure. FAST leisure was significantly related to illness severity, adjusting for the other covariates in the model (global p-value=0.002). Participants with normal illness severity on the average showed 0.453 units less on FAST leisure score than participants with mild illness severity (β =-0.453, comparison p- value=0.049). Participants who were classified as having normal illness severity on the average showed 1.22 units less on FAST leisure compared to participants with moderate illness severity (β =-1.22, comparison p-value=0.001). Conversely, sex (β =-1.47, p=0.461), age (β =0.002, p=0.840), education (β=0.24, p=0.614), immediate memory (β=0.003, p=0.666), spatial cognition (β=-0.005, p=0.505), semantic memory (β =0.004, p=0.546), attention (β=0.003, p=0.572), and delayed memory (β=0.007, p=0.465) did not significantly predict FAST leisure statistically. The overall model was statistically significant, explaining 16% of the variance in FAST leisure [F =2.59, p< 0.001, R^2 =0.16].

Linear regression analyses for the relationship between Quality of Life (SF-36) and cognitive domains and clinico-demographic factors in participants with schizophrenia, MDD and HC

Table 4 presents the results from the analysis conducted with SF-36 (QoL) as the dependent variable. The results of the findings in the two composite domains are presented below.

SF-36 mental health composite score: Results from the linear regression analysis showed a statistically significant association between SF-36 mental health composite score and diagnosis, adjusting for other covariates in the model (global p=0.001). Healthy controls on the average showed 7.03 and 9.83 units higher on SF-36 mental health composite score than participants with schizophrenia (β=7.031, p=0.025) and MDD (β=9.825, comparison p-value<0.001) respectively. Conversely, there was no statistically significant difference between participants with MDD and those with schizophrenia (β =-2.794, p=0.317) with respect to SF-36 mental composite. Participants' SF-36 composite score was also significantly related to illness severity, adjusting for the other covariates in the model (global p-value<0.001). Participants with normal illness severity on the average showed 10.75 and 15.56 units higher on SF-36 mental health composite

scores than participants with mild (β =10.75, comparison p-value<0.001) and moderate illness severity (β =15.556, p<0.001) respectively. No statistically significant differences when participants with mild illness were compared with those with moderate illness severity on SF-36 composite (β =4.809, P=0.162). Similarly, sex (β =-1.521, p=0.427), education (β=0.325, p=0.500), immediate memory (β=0.068, p=0.309), spatial cognition (β=0.031, p=0.638), semantic memory (β =-0.037, p=0.561), attention (β=0.003, p=0.572), and delayed memory (β=-0.036, p=0.677) did not significantly predict SF-36 mental composite score. However, both age (β=0.166, p=0.023) and attention (β=-0.125, p=0.032) were significantly predictive of SF-36 mental health composite score. The overall model explained 42% variance in mental health QoL [F =5.19, p< 0.001, R^2 =0.42].

SF-36 physical health composite score: In linear regression analysis, there was a statistically significant association between SF-36 physical health composite score and diagnosis, adjusting for the other covariates in the model (global p=0.009). Participants with MDD on the average showed 6.81 units higher on SF-36 physical health composite score compared to participants with schizophrenia (β=6.809, p=0.003). Similarly, age (β=-0.124, p=0.04), years of education (β=-0.960, p=0.016), sex (β=3.602, p=0.023) and attention (β=0.114, p=0.017) were predictive of the SF-36 physical health composite score. Conversely, illness severity (global p-value= 0.696), immediate memory (β=0.014, p=0.794), spatial cognition (β=0.002, p=0.974), semantic memory (β =-0.022, p=0.675), and delayed memory (β=-.011, p=0.879) did not significantly predict SF-36 composite score. The overall model explained 12% variance in physical health QoL (F=2.12, p=0.006, R^2=0.12).

Investigating the mediation effects of cognitive function on the relationship between illness severity and functional status/QoL in all participants

Table 5 presents results from the analysis conducted to investigate the relationship between illness severity (symptom level) and functional status (measured with FAST-total)/QoL (indexed by SF-36), as mediated by domains of cognitive function measured by RBANS. We reported indirect effect as the variance in the relationship between illness severity and functional status/QoL that is mediated by specific dimensions of cognitive function. Both total and direct effects of illness severity on functional status and QoL were also reported.

In series of regression models (mediation analysis) that included FAST-total score as the dependent variable, the results indicated a statistically significant positive direct effects of illness severity on functional status (indexed by FAST-total score) in all participants, and a statistically significant positive indirect effects of illness severity on functional status as mediated by all the measured RBANS domains, including global (β=2.07, $p<0.05$), immediate memory (β=1.99, $p<0.05$), spatial cognition (β=1.13, $p<0.05$), attention (β=1.64, $p<0.05$) and delayed memory (β=1.29, $p<0.05$), except semantic memory (β=-0.07, $p>0.05$).

The results of the mediation analysis with SF-36 mental health composite score as dependent variable showed a statistically significant negative direct effect of illness severity on SF-36 composite QoL and a small positive indirect effect on SF-36 mental health score, mediated by attention (β=0.84, $p<0.05$). Other subscales of RBANS (immediate memory, spatial cognition, semantic memory and delayed memory) did not show statistically significant mediating effects on the relationship between illness severity and SF-36 mental health QoL ($p>0.05$).

Similarly, the results of analysis with SF-36 physical composite as the dependent variable showed a statistically significant negative direct effect and a small positive indirect effect of illness severity on SF-36 physical health QoL as mediated by global cognitive function (β=-0.93, $p<0.05$), immediate memory (β=-0.71, $p<0.05$) and attention (β=-0.99, $p<0.05$). Other aspects of cognitive function measured by RBANS, including spatial cognition, semantic memory and delayed memory did not show statistically significant mediating effects on the relationship between illness severity on SF-36 physical health QoL ($P>0.05$). See Table 4.

Discussion

Cognitive deficit plays a major role as determinant of impairment in psychosocial function in individuals with schizophrenia and MDD. In this paper, we investigated the relationship between multiple aspects of cognitive deficit and functional status and QoL in participants with schizophrenia compared with MDD and HC, considering variability in age, sex, years of education and illness severity. To unpack the complex interplay of domains of cognitive function on the relationship between illness severity and functional status/QoL, we investigated the effects of illness severity on functional status and QoL, as mediated by multiple aspects of

cognitive deficits across the disorders. Optimally, we hope to provide more insight into the effects of specific domains of cognitive function on the similarities or differences in the nature and severity in psychosocial function deficits in schizophrenia compared with MDD and HC.

Participants in this sample with schizophrenia were older, had fewer years of education, and were more likely to be males compared to MDD and HC. Participants with schizophrenia also showed the most severe form of deficits across most aspects of functional status and QoL followed by participants with MDD, compared to HC. For example, FAST-total score in participants with schizophrenia on the average was about twice and seven times higher (indicative of greater impairment) compared to MDD and HC respectively. While mental health QoL was poorest in participants with schizophrenia followed by MDD compared to HC, physical health QoL was poorest in schizophrenia followed by HC compared to MDD. Participants with schizophrenia showed the most severe deficits across all domains of cognitive function followed by MDD compared with HC. This pattern of worse functional impairments in schizophrenia has been reported previously,[57] however, conflicting results, suggesting no difference between participants with schizophrenia and MDD on certain aspects of cognition[57, 58] and psychosocial function[59] have also been reported.

We found specific patterns of functional deficits across the diagnostic groups after controlling for other covariates in a regression model. Total FAST, autonomy, occupational and interpersonal function was worse in schizophrenia in comparison to MDD and HC, while schizophrenia and MDD were similarly more impaired than HC on financial and leisure domains of FAST.

We also found specific patterns of the impact of illness severity on FAST domains. For total FAST, autonomy, interpersonal relationships, and leisure domains there was a stepwise increase in functional impairment with increased severity of illness. For occupational, cognitive and financial function there was a similar significant impact of mild or moderate illness in MDD and schizophrenia over participants with no substantial cross-sectional symptoms.

We did not find a main effect of any cognitive domain predicting function as measured by the FAST score, independent of age, gender, education, diagnosis and illness severity as covariates. We conducted additional analyses to explore if cognition mediates the relationship between illness severity and functional status or QoL. We found a small but significant positive mediating

effect of all the measured domains of cognitive function other than semantic memory on the relationship between symptoms and FAST total score. Together these results suggest that higher symptom burden impairs function, and cognition may play smaller role as a mediator. The relationship between illness severity and cognition on recovery is complex and cannot be over-emphasized because psychosocial engagement, role performance and inter-relational skills do improve with clinical remission-stability, while faulty cognitive appraisal of the illness experience can hinder insight, medication adherence and the positive emotion needed for recovery.[60,61] With worse cognitive deficit participants interpretation of their illness may be affected, and may report better day to day function. Consequently, physicians' ratings of patients' functional status or QoL based on patient report alone may be inaccurate. Consistent with this concern, we found that attention has both a direct negative and an indirect positive relationship with mental health QoL, suggesting that those with better attention report worse mental health, and higher symptom burden potentially acts to alter cognition and appraisal of mental QoL such that it improves.[62] In contrast, attention was both directly positively and indirectly negatively associated with physical health, suggesting that those with higher symptom burden reported better physical health. However, with greater symptom load this effect was attenuated in line with more prominent deficits in attention and immediate memory.

Multiple aspects of cognitive function and identifiable clinico-demographic factors collectively predicted all the domains of functional status and QoL, with small to medium effect sizes. For example, 51%, 42% and 12% variance in global functioning, mental health composite QoL and physical health composite QoL respectively were explained by all the predictors (age, sex, years of education and subdomains of cognitive function) in the model collectively. Overall, these findings highlight the need to consider a multi-variate explanatory factors for functional status and QoL.[63,64]

There are several implications of our study findings. First, our study results suggest that functional assessments that include self-appraisal need to be considered in the context of symptom and cognitive burden.[65-67] The impact of cognitive deficits on function was indirect in this sample as it mediated the relationship between symptom burden and functional status. This suggests that the benefits of optimal symptomatic treatment on function across disorders may in part be explained by improved cognitive function. The relationship between cognition and

quality of life is more complex,[66,67] but also potentially mediated by insight into mental and physical comorbidities. Based on these results, it seems that attention is protective for mental health quality of life, although as attention and immediate memory worsens, physical health compromise becomes more of a concern. In this case, potentially cognitive deficit is associated with greater impairment in physical health QoL. This finding is not surprising because good cognitive function has been associated with good health decisions, treatment seeking behaviour and better QoL.[68-70]

These findings should not discourage the growing traction for innovative interventions (such as cognitive remediation, metacognitive behaviour therapy, cognitive behavioural therapy, cognitive enhancement therapy, and skills training) designed to improve specific cognitive deficits (including attention and immediate memory) in participants with schizophrenia or MDD.[23,71] Treating symptoms is paramount to capacity to improve cognitive function. Optimally, interventions aimed at improving cognitive deficits (involving specific aspects such as attention, memory, and spatial cognition) can improve psychosocial function directly or confer positive effects as a mediator on the impacts of other predictors (such as symptom burden).[72, 73]

Implicitly, findings from this study underscore the need to broaden the coverage of individuals with mental disorders who complete detailed assessments of symptoms, cognitive and functional status, especially in settings where these assessments are currently reserved for those with high levels of impairment to determine guardianship and placement issues.[74]

There are several limitations to be considered in the interpretation of this study. The study design was cross sectional, limiting inferences on the longitudinal trajectory of functional outcome. This was an exploratory study; hence we did not correct for multiple testing. The control and MDD samples were not matched on age or gender to the schizophrenia cohort, albeit we included these factors as covariates to address this limitation. Furthermore, we mapped scores from the original symptom measures to generic severity groups, with some potential loss of information. Notwithstanding, the method used in this study offers promise for comparison across samples in future studies. Finally, the cross-sectional assessments of function using the FAST may be impacted by patient self-report of daily activities and coping and overestimate function in those with cognitive impairment or other reporting biases. Performance based measures (e.g., Personal and Social Performance scale [PSP], University of California San Diego [USCD]-Performance-

Based Skills Assessment, Direct Assessment of Functional Status [DAFS], Maryland Assessment of Social Competence [MASC], and Social Skills Performance Assessment [SSPA], etc.) are time intensive but may provide a more accurate indication of day to day function.[75] Future prospective studies that are adequately powered with robust sample sizes are indicated to address the limitations identified in the present study.

Conclusion

Improved functional status and QoL remains a major treatment goal for people with schizophrenia and MDD. We found differential patterns of impairment in function and quality of life in MDD and schizophrenia depending on standardized illness severity. While attention and immediate memory were directly predictive of aspects of QoL, there was no direct effect of cognitive function on general function measured by the FAST over that of symptom burden. However, there was an indirect effect of symptoms through cognition on FAST. There were complex differential mediated effects of symptoms via cognition on mental and physical QoL. To improve function and QoL optimal symptom treatment is primary while successful cognitive interventions may have mixed effects related to illness insight. Although, these results are exploratory, they support the use of standardized illness severity measures in studies of cognition and function, allowing the integration of data sets across diagnoses and scales. Optimally, interventions targeted at improving cognitive deficits (such as cognitive remediation, neurocognitive enhancement therapy, work therapy, and verbal memory task based on dichotic listening, etc) can have direct benefits on functional outcomes, and indirect positive effects as a mediating factor on the relationship between symptom or illness severity and psychosocial function. Future prospective studies should consider the use of performance measures of general function to reduce the influence of patient reporting biases and collect robust data on physical comorbidity to validate perceptions of physical health and its impact on day to day function.

Conflict of interest

No conflict of interest to declare

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Table 1: Mapping of symptom measures in schizophrenia and major depressive disorder to illness severity using CGI

Diagnostic Categories	Illness severity [CGI]		
	Normal[#]	Mild	Moderate
Schizophrenia (PANSS score)	<54	54-74	75-94
Major depressive disorder (HAMD score)	0-8	9-16	17-23

#= below illness threshold, CGI- Clinical Global Impression (CGI) rating scale,
PANSS- Positive and Negative Symptom's Scale, HAMD= Hamilton Depression Rating Scale.
Adapted from Leucht et al. [48, 49]

Table 2: Characteristics of people with schizophrenia, major depression and healthy controls

Variables	Schizophrenia (n=56)	Major Depression (n=66)	Controls (n=34)	TOS	p-value
Sex n (%)					
Male	38(50.0)	23(30.3)	15(19.7)	$\chi 2$ =13.58	0.001
Female	18(22.5)	43(53.8)	19(23.8)		
Age in yrs, mean (SD)	37.91(11.41)	31.06(14.09)	28.68(15.09)	F=6.193	0.003
Yrs of education, mean (SD)	11.69(2.77)	13.03(1.94)	13.38(1.58)	F=8.140	<0.001
HAMD score, mean (SD)	n/a	9.84(5.76)	2.85(2.03)	t= 6.99	<0.001
PANSS score, mean (SD)	54.53(13.61)	n/a	n/a	--	--
*Illness severity, n (%)					
Normal[#]	26(28.2)	32(34.8)	34(37.0)	$\chi 2$ =32.97	<0.001
Mild	25(52.1)	23(47.9)	-		
Moderate	5(31.2)	11(68.8)	-		
Cognition(RBANS)					
Immediate memory	73.84(19.24)	101.14(16.23)	101.53(16.29)	F=44.687	<0.001
Spatial cognition	82.02(15.27)	87.00(15.98)	93.88(16.01)	F=6.031	0.003
Semantic memory	86.25(13.38)	100.45(15.38)	94.58(17.24)	F=13.372	<0.001
Attention	78.82(17.92)	103.21(16.34)	102.56(16.48)	F=36.488	<0.001
Delayed memory	77.38(17.42)	92.23(11.16)	95.50(8.47)	F=26.451	<0.001
FAST-domain, mean (SD)					
Total score	24.36(13.43)	11.92(11.55)	3.44(3.04)	F=40.639	<0.001
Autonomy	3.36((3.08)	1.18(2.04)	0.12(0.41)	F=24.644	<0.001
Occupational Functioning	7.11(4.64)	2.68(3.58)	1.00(1.39)	F=35.275	<0.001
Cognitive Function	5.46(3.42)	4.06(3.37)	1.32(1.29)	F=19.334	<0.001
Financial Issues	1.14(1.59)	0.38(0.98)	0.18(0.52)	F=9.346	<0.001
Inter-personal Relationship	5.64(4.01)	2.85(4.09)	0.59(1.54)	F=21.308	<0.001
Leisure	1.64(1.67)	(0.78(1.17)	0.24(0.49)	F=14.128	<0.001
SF-36 composite, mean (SD)					
Mental health	38.13(12.72)	33.24(13.93)	49.41(9.44)	F=10.379	<0.001
Physical Health	46.49(12.39)	54.37(8.26)	51.92(6.15)	F=18.376	<0.001

%-percent, FAST- function assessment short test, HAMD- Hamilton depression rating scale, HC-healthy controls, n-frequency, n/a-not applied, PANSS- positive and negative symptoms scale, R-BAN= Repeatable Battery for the Assessment of Neuropsychological Status, *Severity of illness was derived by mapping HAMD/PANSS scores with CGI severity categories adapted from Leucht et al., [48,49] #-below illness threshold

Table 3: Linear regression of functional status (FAST) by cognitive function in schizophrenia, major depressive disorder and healthy controls, controlling for clinico-demographic confounders

Outcome FAST-domain	Predictors	Sub-group pairwise comparison	Beta [95% Confidence Interval]	P-value comparison	P-value global
Total	Diagnosis	HC vs Scz	-11.90[-16.98, -6.83]	<0.001*	<0.001*
		HC vs MDD	-3.38[-7.41, 0.65]	0.10	
		MDD vs Scz	-8.52[-12.99, -4.047]	<0.001*	
	Illness severity	Normal vs mild	-7.16[-10.62, -3.70]	<0.001*	<0.001*
		Normal vs moderate	-15.45[-20.73, -10.17]	<0.001*	
		Mild vs moderate	-8.29[-13.53, -3.05]	<0.001*	
	Sex	Male vs Female	2.26[-0.71, 5.23]		0.136
	Age(years)		0.11[-0.006, 0.220]		0.063
	Education (years)		-0.49[-1.19, 0.22]		0.177
	Immediate memory		-0.06[-0.17, 0.050]		0.297
	Spatial cognition		0.03[-0.08, 0.13]		0.632
	Semantic memory		-0.001[-0.11, 0.10]		0.981
	Attention		-0.009[-0.10, .084]		0.848
	Delayed memory		-0.02[-0.16, 0.12]		0.773
	Overall Model=[F = 9.89, p< 0.001, R^2= 0.51]				
Autonomy	Diagnosis	HC vs Scz	-1.49[-2.59, -0.39]	0.008*	0.009*
		HC vs MDD	-0.04[-0.93, 0.85]	0.93	
		MDD vs Scz	-1.44[-2.42, -0.47]	0.004*	
	Illness severity	Normal vs mild	-1.65[-2.39, -0.89]	<0.001*	<0.001*
		Normal vs moderate	-2.91[-4.07, -1.75]	<0.001*	
		Mild vs moderate	-1.27[-2.41, -0.12]	0.003*	
	Sex	Male vs Female	0.35[-0.29, 1.002]		0.288
	Age(years)		0.02[-.006, .043]]		0.145
	Education (years)		-0.13[-0.28, 0.024]		0.098
	Immediate memory		-0.02[-0.04, 0.006]		0.142
	Spatial cognition		0.01[-0.01, 0.035]		0.275
	Semantic memory		-0.01[-0.03, .014]		0.488
	Attention		0.01[-0.01, 0.03]		0.346
	Delayed memory		-0.006[-0.04, 0.02]		0.706
	Overall Model=[F = 6.32, p< 0.001, R^2 = 0.38]				

Table 3: Continued

Outcome FAST-domain	Predictors	Sub-group pairwise comparison	Beta [95% Confidence Interval]	P-value comparison	P-value global
Occupational Functioning	Diagnosis	HC vs Scz	-4.04[-5.89, -2.19]	<0.001	<0.001*
		HC vs MDD	-0.78[-2.25, 0.68]	0.297	
		MDD vs Scz	-3.26[-4.89, -1.63]	<0.001	
	Illness severity	Normal vs mild	-1.26[-2.50, -0.01]	0.048	0.008*
		Normal vs moderate	-2.88[-4.80, -0.96]	0.003	
		Mild vs moderate	-1.62[-3.53, 0.28]	0.095	
	Sex	Male vs Female	0.55[-.53, 1.63]		0.315
	Age(years)		0.027[-.015, 0.068]		0.206
	Education (years)		-0.13[-.391, 0.126]		0.314
	Immediate memory		-0.03[-0.073, 0.005]		0.085
	Spatial cognition		0.001[-0.037, 0.039]		0.953
	Semantic memory		-0.01[-0.048, .028]		0.609
	Attention		-.002[-0.036, .032]		0.910
	Delayed memory		.026[-0.023, .076]		0.298
	Overall Model=[F =6.69 , p= 0.009, R^2 =0.40]				
Cognitive Function	Diagnosis	HC vs Scz	-1.54[-3.003, -0.080]	0.039*	0.019*
		HC vs MDD	-1.63[-2.81, -0.46]	0.007	
		MDD vs Scz	0.091[-1.202, 1.39]	0.890	
	Illness severity	Normal vs mild	-1.82[-2.81, -0.82]	<0.001*	<0.001*
		Normal vs moderate	-2.109[-3.65, -.5689]	0.007*	
		Mild vs moderate	-0.29[-1.82, 1.24]	0.708	
	Sex	Male vs Female	-0.27[-1.13, 0.59]		0.541
	Age(years)		0.029[-0.004, 0.062]		0.081
	Education (years)		-0.08[-0.286, 0.122]		0.431
	Immediate memory		-0.02[-0.051, .010]		0.188
	Spatial cognition		<0.001[-0.03, 0.03]		0.989
	Semantic memory		0.01[-0.019, 0.041]		0.459
	Attention		-.006[-0.033, 0.02]		0.652
	Delayed memory		-0.03[-0.071, 0.009]		0.124
	Overall Model=[F =4.79 , p< 0.001, R^2 =0.31]				

Table 3: Continued

Outcome FAST-domain	Predictors	Sub-group pairwise comparison	Beta [95% Confidence Interval]	P-value comparison	P-value global
Financial Issues	Diagnosis	HC vs Scz	-0.56[-1.183, .06]	0.077	0.05*
		HC vs MDD	0.11[-0.39, 0.613]	0.658	
		MDD vs Scz	-0.67[-1.22, -0.12]	0.016*	
	Illness severity	Normal vs mild	-0.51[-0.93, -0.08]	0.019*	0.007*
		Normal vs moderate	-0.94[-0.94, -1.59]	0.005*	
		Mild vs moderate	-0.43[-1.08, 0.22]	0.194	
	Sex	Male vs Female	0.45[.08, 0.82]		0.016
	Age(years)		0.06[-.008, .020]		0.424
	Education (years)		-.024[-0.11, 0.063]		0.593
	Immediate memory		.003[-0.010, .016]		0.615
	Spatial cognition		-.001[-.013, 0.012]		0.929
	Semantic memory		-.009[-0.021, 0.004]		0.186
	Attention		.001[-.010, .012]		0.848
	Delayed memory		-.005[-.022, .012]		0.559
	Overall Model= [F =2.84, p=0.004, R^2 = 0.17]				
Interpersonal relationship	Diagnosis	HC vs Scz	-3.03[-4.73, -1.34]	<0.001*	0.02*
		HC vs MDD	-3.031[-2.205, 0.511]	<0.001*	
		MDD vs Scz	-2.18[-3.68, -0.69]	0.004*	
	Illness severity	Normal vs mild	-1.49[-2.65, -0.33]	0.012	<0.001*
		Normal vs moderate	-5.290[-7.07, -3.51]	<0.001*	
		Mild vs moderate	-3.804[-5.56, -2.04]	<0.001*	
	Sex	Male vs Female	1.299[0.3005, 2.297]		0.011*
	Age(years)		0.033[-0.005, 0.07]		0.093
	Education (years)		-.178[-0.413, 0.058]		0.139
	Immediate memory		0.005[-0.031, 0.041]		0.787
	Spatial cognition		0.006[-0.029, 0.042]		0.729
	Semantic memory		.008[-0.026, 0.043]		0.634
	Attention		-.003[-0.034, .028]		0.829
	Delayed memory		-.006[-0.052, .040]		0.798
	Overall Model=[F =5.37, p=0.003, R^2 =0.422]				

Table 3: Continued

Outcome FAST-domain	Predictors	Sub-group pairwise comparison	Beta [95% Confidence Interval]	P-value comparison	P-value global
Leisure	Diagnosis	HC vs Scz	-1.111[-1.773, -0.449]	0.001*	0.002*
		HC vs MDD	-0.196[-0.729, 0.337]	0.472	
		MDD vs Scz	-0.915[-1.502, -0.329]	0.002*	
	Illness severity	Normal vs mild	-.453[-0.904, -0.003]	0.049*	0.002*
		Normal vs moderate	-1.220[-1.918, -0.522]	0.001*	
		Mild vs moderate	-.7668 [-0.767, -0.074]	0.030*	
	Sex	Male vs Female	-0.147[-0.5380, .2437]		0.461
	Age(years)		-.002[-0.016, 0.013]		0.840
	Education (years)		.024[-0.069, 0.116]		0.614
	Immediate memory		.003[-0.017, .011]		0.666
	Spatial cognition		.005[-0.009, 0.018]		0.505
	Semantic memory		.004[-0.009, 0.018]		0.546
	Attention		-.003[-0.015, 0.009]		0.572
	Delayed memory		.007[-0.011, 0.025]		0.465
	Overall Model=[F =2.59 , p< 0.001, R^2 =0.16]				

*significant global p<=0.05; F= overall model stat FAST=Functional assessment short test, MDD= major depressive disorder, Scz=schizophrenia. Linear regression results presented as standardized Beta coefficients [95% confidence interval] and p value in parentheses, R^2= R-squared (coefficient of determination)

Table 4: Linear regression of quality of life (SF-36) by cognitive function in schizophrenia versus major depressive disorder and healthy controls

Outcome SF-36	Predictors	Sub-group pairwise comparison	Beta [95% Confidence Interval]	P-value comparison	P-value global
Mental Health	Diagnosis	HC vs Scz	7.031[0.882, 13.181	0.025	0.001*
		HC vs MDD	9.825[4.792, 14.857]	<0.001*	
		MDD vs Scz	-2.794[-8.226, 2.639]	0.314	
	Illness severity	Normal vs mild	10.747[6.519, 14.975]	<0.001*	<0.001*
		Normal vs moderate	15.556[8.838, 22.275]	<0.001*	
		Mild vs moderate	4.809[-1.934, 11.552]	0.162	
	Sex	Male vs Female	-1.521[-5.277, 2.235]		0.427
	Age(years)		0.166[.023, 0.310]		0.023*
	Education (years)		0.325[-0.620, 1.269]		0.500
	Immediate memory		.068[-0.063, 0.200]		0.309
	Spatial cognition		0.031[-0.098, 0.161]		0.638
	Semantic memory		-0.037[-0.161, 0.088]		0.561
	Attention		-0.125[-0.239, 0.011]		0.032*
	Delayed memory		-0.036[-0.204, 0.132]		0.677
	Overall Model=[F =5.19 , p< 0.001, R^2 =0.42]				
Physical Health	Diagnosis	HC vs Scz	3.2807[-1.788, 8.349]	0.205	0.009
		HC vs MDD	-3.528[-7.676, 0.619]	0.095	
		MDD vs Scz	6.809[2.331, 11.286]	0.003	
	Illness severity	Normal vs mild	1.160[-2.324, 4.645]	0.514	0.696
		Normal vs moderate	2.038[-3.500, 7.575]	0.471	
		Mild vs moderate	.877[-4.680, 6.435]	0.757	
	Sex	Male vs Female	3.602[0.507, 6.698]		0.023*
	Age(years)		-0.124[-0.242, -0.005]		0.040*
	Education (years)		-0.960[-1.739, -0.182]		0.016*
	Immediate memory		0.014[-0.094, 0.123]		0.794
	Spatial cognition		0.002[-0.105, 0.109]		0.974
	Semantic memory		-0.022[-0.124, 0.081]		0.675
	Attention		0.114[0.020, 0.208]		0.017*
	Delayed memory		-.011[-0.149, 0.128]		0.879
	Overall Model=[F =2.12, p=0.006, R^2 =0.12]				

*significant global p<=0.05; SF-36= 36-item short form survey, MDD= major depressive disorder, Scz=schizophrenia. Linear regression results presented as standardized Beta coefficients [95% Confidence interval] and p values in parentheses, R^2= R-squared (coefficient of determination)

Table 5: Investigating transdiagnostic mediation effects of cognitive domains on the relationship between illness severity and functional outcome and QoL in all participants

Mediation models[#]		**Direct effect (symptoms) Mean [95% CI]**	**Indirect effect (cognition) Mean [95% CI]**	**Total effect mediated [%]**
Dependent variable [DV]	*Mediators* (Cognitive domains)			
FAST total	Global (RBANS total)	11.22[7.95, 13.91]*	2.07[0.83, 3.98]*	15
	Immediate memory	11.29[8.08, 13.95]*	1.99[0.72, 3.93]*	15
	Spatial cognition	12.15[8.59, 15.08]*	1.13[0.10, 2.53]*	9
	Semantic memory	13.27[9.86, 16.09]*	-0.07[-0.76, 0.75]	-1
	Attention	11.64[8.29, 14.39]*	1.64[0.59, 3.39]*	12
	Delayed memory	11.98[8.67, 14.70]*	1.29[0.27, 2.91]*	9
SF-36 Mental Health	Global (RBANS total)	-14.59[-18.41, -11.45]*	0.52[-0.26, 1.67]	-3.5
	Immediate memory	-14.30[-18.10, -11.17]*	0.19[-0.53, 1.11]	13
	Spatial cognition	-13.82[-17.73, -10.61]*	-0.25[-.1.46,0.97]	1.8
	Semantic memory	-14.17[-17.89, -11.11]*	0.03[-0.42, 0.68]	-0.2
	Attention	-14.92[-18.67, -11.82]*	0.84[0.04, 2.09]*	-5
	Delayed memory	-14.13[-17.93, -11.01]*	0.02[-0.71, 0.78]	-0.1
SF-36 Physical Health	Global (RBANS total)	-0.65[-3.83, 1.98]	-0.93[-1.94, -1.99]*	44
	Immediate memory	-0.87[-4.04, 1.73]	-0.71[-1.60, -0.11]*	34
	Spatial cognition	-1.46[-4.78, 1.27]	-0.07[-1.06, 1.01]	3
	Semantic memory	-1.62[-4.78, 0.97]	0.01[-0.41, 0.37]	-0.3
	Attention	-0.60[-3.72, 1.96]	-0.99[-1.99, -0.27]*	45
	Delayed memory	-1.29[-4.49, 1.35]	-0.28[-1.02, 0.23]	14

[#]Independent variable [IV] in all models is illness severity, *significant at p≤0.05, 95% CI= 95% Confidence interval, R-BANS= Repeatable Battery for the Assessment of Neuropsychological Status

Chapter 7

General Discussion and Future Perspectives

General discussion

The introduction of antipsychotics to treat mental illnesses in the 1950s is considered a landmark breakthrough in psychiatry.[1-3] The successful treatment of people with severe mental illnesses (the majority of them were diagnosed with schizophrenia) with antipsychotics paved the way for the "deinstitutionalization" of many hospitalized patients,[2,3] and promoted community care of individuals with schizophrenia.[3] Several benefits of deinstitutionalization and community care (e.g., improvement in independence, socialization, and adaptation to life outside the hospital environment) have been identified in people with schizophrenia and other severe mental illnesses.[1-6] While antipsychotics have shown good efficacy for symptom remission in schizophrenia and enhanced community reintegration, impaired function and disability are still major concerns in a proportion of individuals with schizophrenia.[6-8,10] In fact, schizophrenia is ranked among the top causes of disability globally.[5, 10-12]

To promote functional recovery, evidence-based multi-modal psychosocial therapies (e.g., cognitive behavioural therapy, cognitive remediation, psychosocial rehabilitation, illness self-management training, and family support) are recommended in clinical guidelines as adjunct treatments for people with schizophrenia,[12,13] although success in this area has been modest.[14,15]. Hence, exploration for interventions to improve impaired function and disability in schizophrenia is recognized as a topical area of research.[14,15] The heterogeneity in functional deficits across patients and the limited evidence on the predictors of functional outcome are often highlighted as major challenges in research exploring functional outcomes in schizophrenia.[15] For example, while a wide range of correlates has been linked with functional outcomes in individuals with schizophrenia, findings on their roles as putative explanatory factors for the variability in functional outcome are imprecise and mixed.[15-21] Specifically, the factors associated with functional outcomes vary, and individually do not account for a large percentage of the variance in functional outcomes.[15, 18] For instance, in their study, Joseph et al. reported that less than 30% of the variance in functional outcome measured with the assessment of lifespan functioning attainment scale was explained by the multiple factors investigated.[18]

Similar to schizophrenia, impairment in psychosocial function is common in mood disorders, especially major depressive disorder.[12] In particular, an overlap in cognitive and functional impairment has been reported across these disorders, albeit people with schizophrenia are generally

thought to have more prominent deficits in comparison to MDD.[12] However, few studies have systematically explored the differences in the deficits in specific domains of psychosocial function between these disorders. Such comparative analyses of deficits in psychosocial function between schizophrenia and MDD can help establish if the well-developed rehabilitation interventions for individuals with schizophrenia can be applied or adapted for individuals with MDD.

In light of the above, this thesis is premised on the need to better understand the functional difficulties experienced by individuals with schizophrenia across multiple areas and their recovery process. Furthermore, the thesis delved into expanding current knowledge on the similarities and differences in the degree of severity and the domains of functional deficits in individuals with schizophrenia compared with MDD and healthy controls. This is a necessary step for meaningful discussion with clients and planning appropriate treatment to promote functional recovery. If functional deficits in individuals with schizophrenia and the associated factors are well characterized, treatment can be refined to target specific deficits along with the risk factors in the individual patient.[22-24] Furthermore, a better knowledge of the factors associated with functional deficits in schizophrenia can inform the stratification of patients for psychosocial rehabilitation and interventions to improve functional outcomes.[22] On a broader note, the outcome of comparative analyses of deficits in psychosocial function in people with schizophrenia and MDD can help inform the adaptation of the well-developed rehabilitation interventions for people with schizophrenia to individuals with MDD.

In this thesis, we included meta-analytic and original studies that were conducted to shed more light on the predictors of psychosocial function in individuals with schizophrenia. In the following sections, we discussed the key findings from each study in the thesis, highlighting their contributions to the field. In **Chapter 1**, a background was provided for this thesis, describing the development and trends in the classification, epidemiology and treatment of people with schizophrenia. Information on deficits in psychosocial function and the associated factors in people with schizophrenia was introduced to set appropriate background for the thesis. An overview of a putative multivariate explanatory model using the work of Schubert, Clark & Baune [23] was included. The model demonstrated the benefits of predicting functional outcome and illness trajectory using the combination of multimodal predictors in patients with schizophrenia. Specifically, they propose that the combination of data on multiple predictors (e.g., clinical, demographic, structural and

functional imaging, electrophysiological and cognitive) compared to a single predictor may better inform the prediction of distinct illness trajectories and functional outcomes in people with schizophrenia.[24,24] Against the background of the value of systematic reviews to evidence-based mental health,[25-27] Chapter 1 was followed by **Chapters 2 and 3** containing two systematic and meta-analytic review papers that synthesized qualitative and quantitative findings on the beneficial effects of antipsychotic medications on impaired function and described the predictors of functional outcome in clinical trial studies conducted on individuals with schizophrenia.

In **Chapter 2**, we examined the benefits of long-acting injectable atypical (LAI-As) antipsychotics on impaired function in people with schizophrenia. To our knowledge, this is the first study to pool the effects of LAI-As compared with placebo or oral antipsychotics on psychosocial function in clinical trials. We focused the review on LAI-A, the recommended first-line treatment for non-adherent individuals with schizophrenia in clinical guidelines.[28-34] As an initial step for the review, we lay a foundation for a multidimensional construct for psychosocial function, including multiple domains of basic-daily function, socio-occupational function, interpersonal relationships, adaptive function, life satisfaction and subjective wellbeing/QoL.[35-37] We argued that this construct allows a more reliable, valid, comprehensive and holistic perspective on multiple aspects of psychosocial function in patients with schizophrenia. Additionally, a qualitative overview of all the functional measures used in the included trials was provided, highlighting a broad composite concept of psychosocial function. The need for uniformity in the construct and measurement of psychosocial function[20,36] through the development of validated, evidence-based and standardized construct in individuals with schizophrenia is promoted.[35]

Across the included trials, LAI-As were superior to placebo (medium effect size) and oral antipsychotic medications (small effect size) for improved psychosocial function. Notably, there was clear evidence of clinically meaningful benefit for LAI-A treatment over placebo, however, the reported absolute differences between oral and LAI-A treatment in terms of percentage of patients achieving good function was small. This benefit is smaller than that reported in mirror-image and some large cohort studies, potentially due to higher levels of oral adherence and underrepresentation of non-compliant patients in selective and closely monitored clinical trials.[35,38]

Importantly, individuals with schizophrenia with more severe symptoms,[37-41]cognitive impairment,[42] and poor insight[43] were less likely to improve in psychosocial function. Our findings

are consistent with the existing evidence of a clear association between cognitive impairment, the severity of psychopathology and poor insight with poor functional recovery.[37] This association is complex but modifiable, such that adherence, less severe psychopathology and functional recovery are associated with better insight, while insight is cognition-dependent, particularly on executive performance and working memory.[35-37] Evidence suggests that insight and cognition can be improved by a wide range of interventions including cognitive behavioural therapy, assertive community treatment and cognitive remediation.[12-15,35] On a different note, our findings underscore the impact of antipsychotics on the overall outcome, and by extension support the benefits of maintenance antipsychotics in patients with schizophrenia. Clinically, a better understanding of the predictive value of factors associated with deficits in psychosocial function can contribute to the current discussion on the use of predictors to decide how to stratify patients who may benefit from adjunct interventions during the course of their care to improve function.

In **Chapter 3**, we replicated the meta-analytic methods described in Chapter 2, examining the benefits of clozapine on functional outcomes in individuals with treatment-resistant schizophrenia (TRS), an important population who are likely to experience significant disability.[44,45] While evidence supports that clozapine has unique beneficial effects on symptoms, no superiority to other antipsychotics on psychosocial function was observed. The findings in this chapter reiterated the clinical relevance of addressing impaired psychosocial function in people with TRS. For example, the limited improvement in psychosocial function following treatment with clozapine may suggest that individuals within clozapine trials are a group with more severe neurodevelopmental pathology and diminished cortical reserve, which limits their margin for recovery with current interventions.[37] Alternatively, delay to clozapine use and associated chronic exposure to antipsychotics has been linked with a decrease in brain volume, limited improvement and worse long-term prognosis.[37] Implicitly, early and targeted interventions to improve functional outcome are indicated in people with TRS. Furthermore, recovery in the context of clozapine pharmacotherapy can become more apparent with incorporation of multi-modal psychosocial therapies that allow learning-training of psychosocial skills.[12-16]

Factors associated with poor functional outcomes for clozapine treatment included the severity of illness, illicit drug use, extrapyramidal side effects, gender and cognition can help predict those who may benefit from clozapine coupled with intensive psychosocial therapies.[37] It is also interesting

that the aggregate effects of the predictors explained greater variability in psychosocial function than individual factors and justifies the recent proposal of a multi-dimensional model for prognostic and trajectory prediction to allow targeted intervention.[23]

Armed with the knowledge from the systematic reviews of clinical trials, it became clear that innovative naturalistic studies are needed to understand the functional difficulties experienced by people with schizophrenia and the predictors of functional outcome. Hence, **Chapter 4** described the Cognitive and Functional Assessment of Psychosis Stratification Study (CoFAPSS).[46] This is the naturalistic study that provided the data on people with schizophrenia to conduct the empirical studies discussed in the next two chapters of the thesis. Individuals with a history of lifetime episode of major depressive disorder and healthy controls were included in the analysis in the two chapters as comparative group for participants with schizophrenia. Data for the comparative groups were derived from the Cognitive Function and Mood study (CoFAMS).[47] We provided an overview of CoFAPSS and CoFAMS under the methods in the next two chapters that present the two empirical studies.[46,47]

These studies (CoFAPSS and CoFAMS)[46,47] are prospective in design and included healthy controls. They are aimed to investigate clinical, cognitive, and biological markers of psychotic and mood disorders that can be integrated with functional measures to improve the prediction of risk and define functional trajectories. Further, the study data are meant to help identify genomic signatures underpinning variation in treatment response and adverse medical outcomes. It is worth mentioning that we utilized the cross-sectional data collected at baseline in these studies to complete the analysis presented in this thesis. Given the scope of these studies, upon completion, would improve the characterization of psychosis/mood disorders and the prediction of symptomatic and functional outcomes by incorporating neurobiological and psychosocial correlates. We hope that the comprehensive description of the methodological underpinnings of CoFAPSS and CoFAMS in open access protocol papers [46,47] will encourage replication of similar studies in diversified settings, and promote international collaboration among investigators. Such collaborative effort is beneficial to advance the field.

Chapter 5 compared patients with schizophrenia with those with lifetime MDD and healthy controls (HC) on multiple aspects of functional status and Quality of Life (QoL), considering the contributions of age, gender, years of education and illness severity on variability. To allow

comparison of symptom load across the diagnostic groups (schizophrenia, MDD and HC), we used a novel approach to map scores from the original symptom measures (PANSS and HAMD) to generate severity groups based on the CGI using a method devised by Leucht et al.[48,49] The method used in this study can be adapted in in future studies to compare samples across diagnostic categories. In this study, patients with schizophrenia reported greater impairment in multiple aspects of functional status (including autonomy, occupational functioning, cognitive functioning, financial issues, leisure and interpersonal relationships) and QoL (mental and physical health composites) followed by MDD compared with HC. While illness severity was significantly related to all the measured aspects of functional status and QoL. Older age was significantly related to higher impairments in global functioning, cognitive function and physical health composite QoL but not related to autonomy, occupational functioning, financial issues, interpersonal relationships and leisure. While having more years of education was positively related to better mental and physical health composite QoL, it was not related to all the aspects of functional status. In general, findings on the relationship between education and psychosocial functioning and outcome in individuals with schizophrenia have been mixed.[50-53] While some studies have indicated that individuals with better education reported worse assessment of their subjective QoL and outcome,[51,52] other studies linked better education with better psychosocial functioning adjustment, improved neurocognitive process, better psychopathological status in the disease evolution, and greater satisfaction with life.[50,53] Finally, males reported greater disability in financial issues and inter-personal relationships but no significant difference between males and females with respect to global functioning, autonomy, occupational functioning, cognitive functioning, leisure and the mental-physical health composite QoL. Although findings on gender differences in psychosocial function and QoL have been mixed, however poorer performance in domains of QoL and psychosocial function in males compared to females with schizophrenia have been associated with the earlier age of onset, poorer premorbid functioning, worse prognosis, and more negative symptoms in males.[54-57] Overall, these study findings indicated that adequate treatment of symptoms is primary and to allow recovery given the significant relationship between illness severity and all aspects of functional status and QoL.

Both meta-analytic papers[35,37]completed in this thesis highlighted cognition as a major predictor of functional outcome in individuals with schizophrenia. In view of the recognition of the central contributions of cognitive process to functional outcome,[35,37,58] we followed up with **Chapter 6,**

investigating impaired function in patients with schizophrenia compared to MDD and healthy controls (HC) focusing on the variation due to multiple aspects of cognitive deficits. Patients with schizophrenia showed the most severe form of deficits across all the measured aspects. Attention was positively related to functional status and negatively related to QoL (direct effect). Despite mixed findings on the relationship between attention and specific aspects of psychosocial function, attention is as an important aspects of cognitive domain deficits (including attention, working memory, verbal learning, and problem solving) that are explanatory of cognitive impairment associated with schizophrenia (CIAS).[59]

Deficits in multiple aspects of cognition showed an indirect effect on psychosocial function, mediating the effects of illness severity on functional status and QoL. Consequently, interventions targeted at improving cognitive deficits (such as cognitive remediation, neurocognitive enhancement therapy, work therapy, and verbal memory task based on dichotic listening, etc) may have direct benefits on functional outcomes, and indirect positive effects as a mediating factor on the relationship between symptom or illness severity and psychosocial function. Clinically, these study results suggest that functional assessments need to be considered in the context of symptom and cognitive burden. Furthermore, multiple aspects of cognitive function and identifiable clinico-demographic factors collectively predicted all the domains of functional status and QoL, with small to medium effect sizes. These findings highlight the need to consider multi-variate explanatory factors for functional status and QoL.[23,24]

Study limitations

We identified several limitations in this thesis, and provided a comprehensive description in each of the chapters. Firstly, psychosocial function was not the primary outcome measure in many original studies that were included in the two meta-analytic reviews. While some trials reported statistical corrections to address potential effects of this limitation on findings, the quality of evidence would be much improved if cofounding effects and study power were considered in relation to psychosocial function a priori. Similar to previous systematic reviews of the literature, we found poor reporting of the randomization process, concealment and sequence generation was common. The oral arms of the trials were not well standardised or monitored. For example, LAI-A were not necessarily compared to the same atypical oral, however, recommended dosing was generally

implemented. Several of the included studies were derived from industry trials, suggesting the risk of industry-sponsored bias. Most of the trials did not look at predictors of psychosocial function and useable data was poorly reported. Future studies that addressed these limitations are indicated.

Concerning the two empirical studies, there is a need for cautious extrapolation of the study findings to other populations of people with schizophrenia and MDD. The studies were conducted at multiple sites in a single metropolitan area of a high-income country which may not exactly reflect the socio-cultural dimensions of psychosocial function in less-resourced settings, particularly low- and middle-income countries. The available resources for psychosocial rehabilitation, community reintegration, and management of patients with schizophrenia differ between advanced and developing contexts. The control and MDD samples were not matched on age or gender to the schizophrenia cohort, albeit we included these factors as covariates to address this limitation.

Future perspectives

Impairment in psychosocial function contributes significantly to disability and the burden of the illness in individuals with schizophrenia.[4-7] However, current treatment modalities have shown limited efficacy on impaired function in individuals with schizophrenia and functional outcome is highly variable. While several factors (including the severity of illness, illicit drug use, extrapyramidal side effects, sex, cognition and insight were identified in this thesis) have been identified as explanatory of functional outcome, a large percentage of variance in psychosocial function is unexplained. The understanding of factors that can enhance recovery-based care in schizophrenia will continue to be an area of interest in clinical practice and research. Although this thesis addressed some pressing issues in this area, several questions and needs for further research are discussed below.

In the meta-analytic papers, we laid the foundation for a multidimensional construct to allow a comprehensive and valid assessment of psychosocial function. However, there is a need for standardized measurement and reporting of psychosocial function using an optimum construct, preferably one that is multidimensional and evidence-based. This will enhance comparative analysis in future meta-analyses or network meta-analyses. Similarly, future trials and naturalistic studies must consider psychosocial function apriori as an outcome to address the concerns noted in

previous trials. Along this line, trials that are modelled to test the efficacy of novel treatments and "pharmaco-psychosocial interventions" in patients with TRS or other clinically relevant groups will be very interesting. Results from such trials can help extend the emerging evidence for the benefits of targeted metacognitive therapy on specific aspects of function.[60-63]

In addition to the abovementioned, drug discovery research to develop a more effective treatment for people with schizophrenia remains a critical area for scientific enquiry. On a positive note, newer treatments with unique mechanisms of action involving the modulations of serotonin, dopamine, and glutamate neurotransmission (e.g., lumateperone) have shown promising results to improve general psychopathology and psychosocial function.[64] Notwithstanding, the search for novel treatment targets that will lead to more effective and safer medications (e.g., with reduced cardiometabolic side-effects) for people with schizophrenia and other psychoses remains important. At least, three novel targets, including trace amine–associated receptors [TAARs] (e.g., ulotaront), muscarinic receptors (e.g., xanomeline plus trospium), and serotonergic receptors (e.g., pimavanserin) showed positive efficacy for both positive and negative symptoms of schizophrenia. The phase 2 trial reports on these medications (e.g., ulotaront, xanomeline, trospium and pimavanserin) showed promising results for beneficial effects of non-D-2 drugs blocking medications to improve symptoms and outcomes in individuals with schizophrenia, especially in those who have not responded to current treatments.[65,66]

While our study findings showed a lack of specific association of the main effect of cognition (mediating effects) on functional status when generic severity is a covariate, future studies to explore the effects of executive function and other domains of cognition as mediators of psychosocial function will be interesting. Some of the interesting associations reported in our study including the mediating effects of attention on QoL and insight on functional status/QoL can stimulate novel hypothesis-driven replication studies. Along this line, the use of pharmacological agents and cognitive remediation therapies to improve cognitive function are supported by research findings exploring opportunities to improve functional outcome. For example, although the results are yet to be posted, the efficacy of BIIB104 (a glutamate receptor modulator molecule) on cognitive function was tested in people with CIAS in a phase 2 trial (NCT03745820) recently completed.[67]

In addition to the development of newer treatments, experts have highlighted the need for greater knowledge of the neurobiology of schizophrenia to inform treatment over the lifespan of the affected individuals.[68,69] This is supported by the hypothesis that schizophrenia is both progressive and increasingly impacted by complex pathophysiology through the course of illness. [68-70] There is evidence to suggest that treatments might have better efficacy for symptoms and improved outcomes if informed by the knowledge of the illness phase (e.g., mGluR2 agonist showed better efficacy during the early phase of the illness when target signalling mechanisms intrinsic to cortical microcircuits are expressed).[68,71] Future research to better account for the development of these circuits and signalling mechanisms in the course of the illness would be interesting.

Although several predictors of psychosocial function were identified in this thesis, a significant percentage of variance was unexplained, highlighting the benefits of a multi-variate paradigm. Similar to CoFAPSS and CoFAMS,[46,47, 72] novel prospective studies that integrate biological markers (e.g., genomics, proteomics, metabolomics, and neuroimaging) may help improve the predictive performance in multi-modal model and help advance personalize care. Furthermore, successful replication of similar studies, with a comparison of major psychiatric disorders will lend strong support to the growing interest in transdiagnostic psychiatry. Importantly, the collection of novel data using similar and validated measures across psychiatric diagnostic groups can provide better insight into any overlap or differences in deficits in psychosocial function across these disorders and inform the transdiagnostic adaptation or application of psychosocial intervention.

In light of the above, recent advancements in computer and data science provide opportunities to combine markers in novel ways to address the current limitations of prediction models. For instance, predictive algorithms, and supervised machine learning methods using supported vector learning [SVL] are some of the techniques that can be explored to push the frontier of modelling of functional trajectory.[73,74] Such predictive models (regression and SVL) can be operationalized to test the performance of a multi-modal paradigm in prognosticating functional outcomes.

Finally, improving the psychosocial function and quality of life of individuals with schizophrenia requires policy actions and scalable programs to support the social integration and recovery of the affected individuals. For instance, there is a need for policies and programs to promote equitable access to evidence-based integrated care.[75] Adequate funding and support for social services and employment can enhance opportunities for patients to learn social skills and provide a stimulating

environment for interpersonal relationships and skills. Educational programs and support for families and caregivers, active engagement of stakeholders to ensure the implementation of best practices, and support for research to develop novel treatments are important action plans needed to promote recovery in individuals with schizophrenia.[75-77]

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