UNIVERSITAT DE BARCELONA

Testing Hypotheses in Schizophrenia and Related Psychoses: From Genetic Underpinnings to Real-World Evidence

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Testing Hypotheses in Schizophrenia and Related Psychoses: From Genetic Underpinnings to Real-World Evidence.

Doctoral thesis dissertation presented by **Justo Emilio Pinzón Espinosa** to apply for the degree of doctor at the University of Barcelona

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Table of Contents

List of articles in the thesis

Thesis in compendium of publications format. The thesis consists of five objectives and five articles. *(*) Denotes shared first authorship*.

1. Lin BD*, **Pinzón-Espinosa J***, Blouzard E, van der Horst MZ, Okhuijsen-Pfeifer C, van Eijk KR, Guloksuz S, Peyrot WJ, Luykx JJ; Genetic Risk and Outcome of Psychosis (GROUP) and Clozapine International Consortium (CLOZIN) Investigators. Associations Between Polygenic Risk Score Loading, Psychosis Liability, and Clozapine Use Among Individuals With Schizophrenia. *JAMA Psychiatry*. 2023 Feb 1;80(2):181-185.

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Resum

Títol: Posant a Prova Hipòtesis a l'Esquizofrènia i Psicosi Relacionades: Des de les Bases Genètiques fins a l'Evidència del Món Reial.

Introducció: L'esquizofrènia és una de les malalties mentals més complexes i severes, afectant aproximadament l'1% de la població mundial. Caracteritzada per una diversitat de símptomes i un curs crònic que sovint resulta en deteriorament funcional significatiu, l' esquizofrènia planteja desafiaments particulars tant en termes de diagnòstic com de tractament. Malgrat extenses investigacions, els mecanismes patofisiològics precisos encara no es comprenen completament, i els tractaments actuals són sovint subòptims.

Hipòtesis:

1. Els individus amb més càrrega de puntuació de risc poligènic (PRS) per a esquizofrènia presentaran símptomes clínics més greus i una major probabilitat de requerir tractament amb clozapina.
2. La majoria dels pacients amb esquizofrènia en el món real no serien elegibles per participar en assajos clínics aleatoritzats (RCTs) estàndard a causa de criteris d'exclusió comuns, i aquests pacients exclosos tindran pitjors resultats en el curs de la seva malaltia.
3. Els antipsicòtics injectables d' acció prolongada tenen una major efectivitat en la prevenció de recaigudes en entorns del món real en comparació amb les formulacions orals.
4. La prevalença d'alteracions neuroimaginològiques en pacients amb trastorns psicòtics d'inici primerenc (<18 anys) és més gran que en controls comunitaris.
5. Les persones amb trastorns mentals se sotmeten a proves de COVID-19 amb menys freqüència que les persones sense trastorns mentals, i resultarien positiu més sovint en comparació amb persones sense trastorns mentals.

Objectius:

1. Examinar si el PRS per a esquizofrènia pot estratificar els pacients amb esquizofrènia i psicosi relacionades basant-se en la seva gravetat clínica.
2. Descriure les característiques de la població amb esquizofrènia del món real que no està representada en els RCTs tradicionals a causa de criteris d' exclusió i comparar els seus resultats clínics amb els de pacients elegibles per a RCTs.
3. Comparar l' eficàcia i efectivitat dels antipsicòtics per a la prevenció de recaigudes en esquizofrènia, sintetitzant dades de RCTs i evidència del món real, amb un enfocament particular en formulacions d' acció prolongada versus les seves formulacions orals.
4. Avaluar la prevalença i significança d'alteracions en imatges per ressonància magnètica (MRI) cerebral en pacients amb psicosi d'inici primerenc (<18 anys) en comparació amb controls comunitaris.

5. Descriure l'associació entre la freqüència de proves de COVID-19 i taxes de positivitat en individus amb trastorns mentals comparat amb aquells sense trastorns mentals.

Mètodes: La tesi empra una combinació d'estudis d'associació de PRS, observacionals basat en registres, meta-anàlisi de xarxes que combinen evidència d'assajos controlats aleatoris i dades del món real, estudis controlats de troballes neuroimaginològiques en joves amb psicosi d'inici primerenc, i estudi d'associació poblacional entre trastorns psiquiàtrics, probabilitat de realització de proves de COVID-19 i els seus resultats.

Resultats Principals:

1. Les persones amb un PRS més alt presenten una major gravetat clínica i una major probabilitat de necessitar clozapina.
2. Gairebé el 80% de les persones amb esquizofrènia en el món real seria inelegible per participar en RCTs, i aquests solen tenir pitjors resultats de salut.
3. Els antipsicòtics injectables d'acció prolongada són més efectius en la prevenció de recaigudes en comparació amb les formulacions orals en un context de món real.
4. Les alteracions en les MRI cerebrals són més prevalents en joves amb psicosi d'inici precoç en comparació amb controls, suggerint una trajectòria neurobiològica distinta per a la psicosi d'inici precoç.
5. Les persones amb trastorns mentals, especialment aquells amb trastorns per ús de substàncies, han estat sotmesos a proves de COVID-19 amb més freqüència i presenten menors probabilitats de tenir resultats positius, desafiant estigmes sobre el compliment de mesures de contenció i accés a l'atenció sanitària.

Conclusions: Les nostres troballes destaquen la necessitat d'integrar el PRS i altres biomarcadors genètics en el maneig clínic de l'esquizofrènia, estratificant poblacions per potencialment millorar la personalització del tractament. A més, ressalta les limitacions dels assajos clínics aleatoritzats per reflectir la diversitat i complexitat de la població de pacients amb esquizofrènia en el món real i suggereix la necessitat d'incorporar més evidència del món real en les guies de pràctica clínica per informar millor les guies i decisions terapèutiques. S'afegeix evidència a la necessitat de realitzar estudis de neuroimatge en primers episodis d'inici primerenc per descartar patologies orgàniques subjacents; se suggereix la possibilitat que hi hagi una trajectòria de neurodesenvolupament diferent en la psicosi d'inici primerenc. Finalment, també proporciona evidència crucial per reduir l'estigma associat amb els trastorns mentals en el context de la pandèmia de COVID-19.

Resumen

Título: Poniendo a Prueba Hipótesis en la Esquizofrenia y Psicosis Relacionadas: Desde las Bases Genéticas hasta la Evidencia del Mundo Real.

Introducción: La esquizofrenia es una de las enfermedades mentales más complejas y severas, afectando a aproximadamente el 1% de la población mundial. Caracterizada por una diversidad de síntomas y un curso crónico que a menudo resulta en deterioro funcional significativo, la esquizofrenia plantea desafíos particulares tanto en términos de diagnóstico como de tratamiento. A pesar de múltiples investigaciones, los mecanismos fisiopatológicos precisos aún no se comprenden completamente, y los tratamientos actuales son a menudo subóptimos.

Hipótesis:

1. Los individuos con mayor carga de puntaje de riesgo poligénico (PRS) para esquizofrenia presentarán síntomas clínicos más graves y una mayor probabilidad de requerir tratamiento con clozapina.
2. La mayoría de los pacientes con esquizofrenia en el mundo real no serían elegibles para participar en ensayos clínicos aleatorizados (RCTs) estándar debido a criterios de exclusión comunes, y estos pacientes excluidos tendrán peores resultados en el curso de su enfermedad.
3. Los antipsicóticos inyectables de acción prolongada tienen una mayor efectividad en la prevención de recaídas en entornos del mundo real en comparación con las formulaciones orales.
4. La prevalencia de alteraciones neuroimaginológicas en pacientes con psicosis de inicio temprano (<18 años) es mayor que en controles comunitarios.
5. Las personas con trastornos mentales se someten a pruebas de COVID-19 con menos frecuencia que las personas sin trastornos mentales.

Objetivos:

1. Examinar si el PRS para esquizofrenia puede estratificar a los pacientes con esquizofrenia y psicosis relacionadas basándose en su gravedad clínica.
2. Describir las características de la población con esquizofrenia del mundo real que no está representada en los RCTs tradicionales debido a criterios de exclusión y comparar sus resultados clínicos con los de pacientes elegibles para RCTs.
3. Comparar la eficacia y efectividad de los antipsicóticos para la prevención de recaídas en esquizofrenia, sintetizando datos de RCTs y evidencia del mundo real, con un enfoque particular en formulaciones de acción prolongada versus sus formulaciones orales.

4. Evaluar la prevalencia y significancia de alteraciones en imágenes por resonancia magnética (MRI) cerebral en pacientes con psicosis de inicio temprano (<18 años) en comparación con controles comunitarios.
5. Las personas con trastornos mentales se someten a pruebas de COVID-19 con menos frecuencia que las personas sin trastornos mentales, y dan positivo más a menudo en comparación con personas sin trastornos mentales.

Métodos: La tesis emplea una combinación de estudios de asociación de PRS, observacionales basado en registros, meta-análisis en red que combinan evidencia de ensayos controlados aleatorios y datos del mundo real, estudios controlados de hallazgos neuroimaginológicos en jóvenes con psicosis de inicio temprano, y estudio de asociación poblacional entre trastornos psiquiátricos, probabilidad de realización de pruebas de COVID-19 y sus resultados.

Resultados Principales:

1. Los individuos con un PRS más alto presentan una mayor gravedad clínica y una mayor probabilidad de necesitar clozapina.
2. Casi 80% de los individuos con esquizofrenia en el mundo real sería inelegible para participar en RCTs, y estos suelen tener peores resultados de salud.
3. Los antipsicóticos inyectables de acción prolongada son más efectivos en la prevención de recaídas en comparación con formulaciones orales en un contexto de mundo real.
4. Las alteraciones en las MRI cerebrales son más prevalentes en jóvenes con psicosis de inicio temprano en comparación con controles, sugiriendo una trayectoria neurobiológica distinta para la psicosis de inicio temprano.
5. Las personas con trastornos mentales, especialmente aquellos con trastornos por uso de sustancias, han sido sometidos a pruebas de COVID-19 con mayor frecuencia y presentan menores probabilidades de tener resultados positivos, desafiando estigmas sobre el cumplimiento de medidas de contención y acceso a la atención sanitaria.

Conclusiones: Nuestros hallazgos destacan la necesidad de integrar el PRS y otros biomarcadores genéticos en el manejo clínico de la esquizofrenia, estratificando poblaciones para potencialmente mejorar la personalización del tratamiento. Además, resaltan las limitaciones de los RCTs para reflejar la diversidad y complejidad de la población de pacientes con esquizofrenia en el mundo real y sugieren la necesidad de incorporar más evidencia del mundo real en las guías de práctica clínica para informar mejor las guías y decisiones terapéuticas. Se refuerza la necesidad de estudios de neuroimagen en episodios tempranos para descartar patologías orgánicas subyacentes; se sugiere una posible trayectoria de neurodesarrollo diferente en la psicosis de inicio temprano. Por último, se proporciona evidencia crucial para reducir el estigma asociado con los trastornos mentales en el contexto de la pandemia de COVID-19.

Introduction

A. Introduction to Schizophrenia

I. What is Schizophrenia? — An Overview

Schizophrenia is a complex and severe psychiatric disorder that affects various domains of cognitive, affective, and behavioral functioning (1–3). It is characterized by a heterogeneous spectrum of symptoms and has a multifactorial etiology, involving genetic and environmental risk and protective factors (4,5). Despite significant research efforts, the exact mechanisms underlying schizophrenia remain elusive, and available pharmacological and psychosocial treatments often fail to achieve optimal outcomes.

Schizophrenia has a global prevalence of approximately 1%, rendering it one of the most common severe mental illnesses worldwide (3,6). Even though it is relatively uncommon, it remains one of the most complex and challenging psychiatric disorders due to its significant impact on individuals and society. It is characterized by a heterogeneous constellation of symptoms, including positive (hallucinations, delusions), negative (disorganized thinking, avolition, flat affect), mood, and cognitive impairments, all of which contribute to a substantial burden on affected individuals, their families, and society as a whole (1–3,7). It usually emerges in late adolescence or early adulthood and follows an often chronic and deteriorating course, with many patients experiencing substantial functional impairment over time (1,8). The latter leads to long-term disability, loss of quality of life, and economic costs (9), not only due to factors directly associated with the disorder, but also to somatic side effects of current approaches and comorbidities.

Schizophrenia is associated with high morbidity, mortality, and socioeconomic burden (2,7). Individuals with schizophrenia are at increased risk of various somatic comorbidities, such as cardiovascular disease, diabetes, and respiratory disorders, which account for a reduced life expectancy of 10-25 years compared to the general population (2,10). The complexity of schizophrenia is further exacerbated by its marked heterogeneity; the disorder is characterized by a diverse range of symptoms and outcomes, presenting significant challenges for diagnosis, treatment, and research.

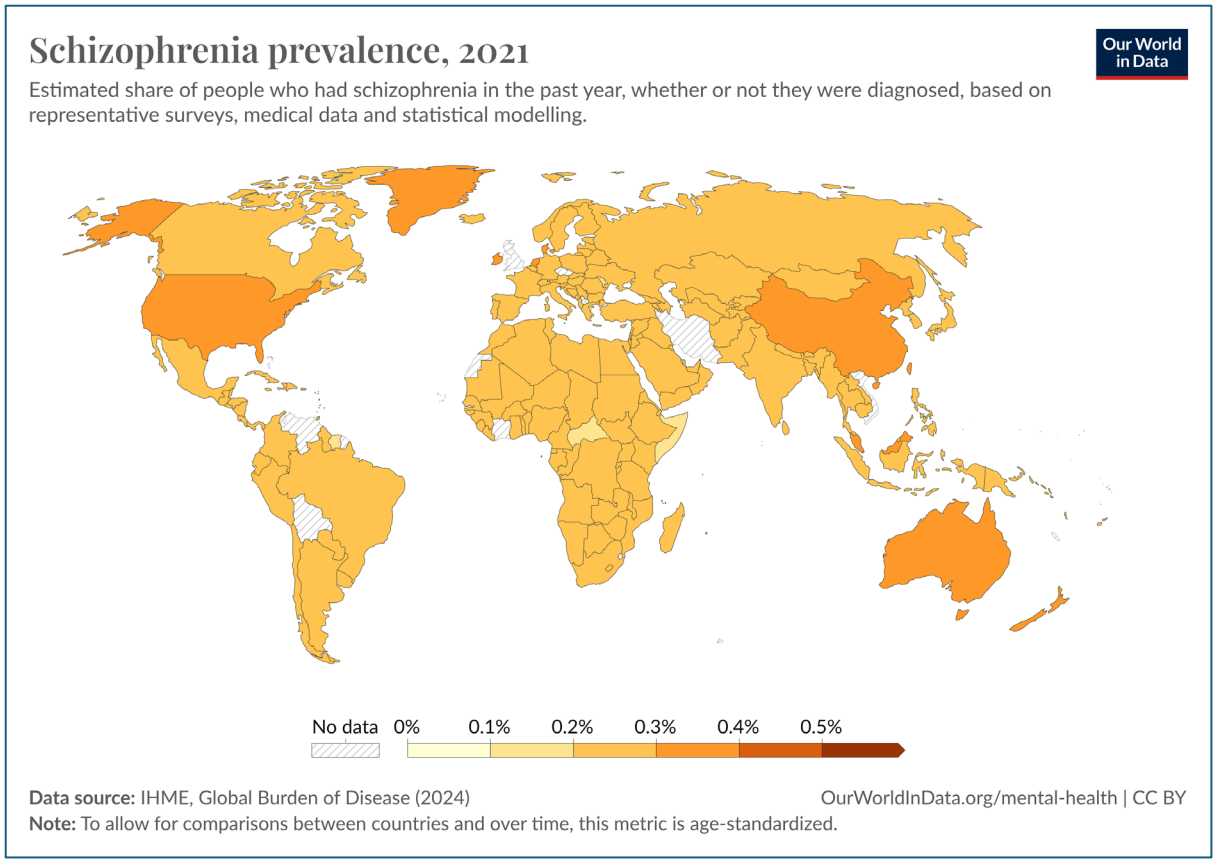


Figure 1. Age-standardized estimated prevalence of people living with schizophrenia in the past year by country. Source: IHME, Global Burden of Disease (2024) – with major processing by Our World in Data (11).

Schizophrenia involves the dysregulation of neurodevelopmental and neurochemical processes, particularly that affecting the dopamine, glutamate, and serotonin systems (3,7,12,13). It is characterized by positive symptoms (hallucinations, delusions), negative symptoms (social withdrawal, flat affect), and cognitive impairments (learning and attention deficits) (2,7,8,13,14). These symptoms can vary considerably in their manifestation and severity among individuals (1–3). Cognitive impairments often precede the onset of psychosis by several years (8).

Current treatments mainly consist of antipsychotic medications that modulate mainly dopamine receptors, but although these are efficacious in improving positive symptoms, their overall effectiveness has been questioned and are also often limited by adverse effects (2,3,7,13,15). Psychosocial interventions are essential to manage negative symptoms and improve functional outcomes, but access to these interventions is limited (1–3). Advances in elucidating the neurobiological mechanisms of

schizophrenia are promising, but more research and efforts to translate its findings into clinical practice are still needed.

The economic burden of schizophrenia is profound, encompassing both direct and indirect costs. Direct costs involve expenditures related to medical care, hospitalization and rehabilitation, while indirect costs are associated with lost productivity, both of patients and caregivers, and the social implications of long-term disability. In particular, a systematic review highlighted that indirect costs, such as productivity losses and disability compensation, can constitute up to 85% of the total economic burden (16). Beyond its economic and clinical dimensions, schizophrenia profoundly affects the quality of life of those affected. Frequent relapses, multiple hospitalizations, and poor adherence to treatment worsen the decline in quality of life. Therefore, regular follow-up and adherence to treatment are crucial to mitigate these declines and improve general well-being (17).

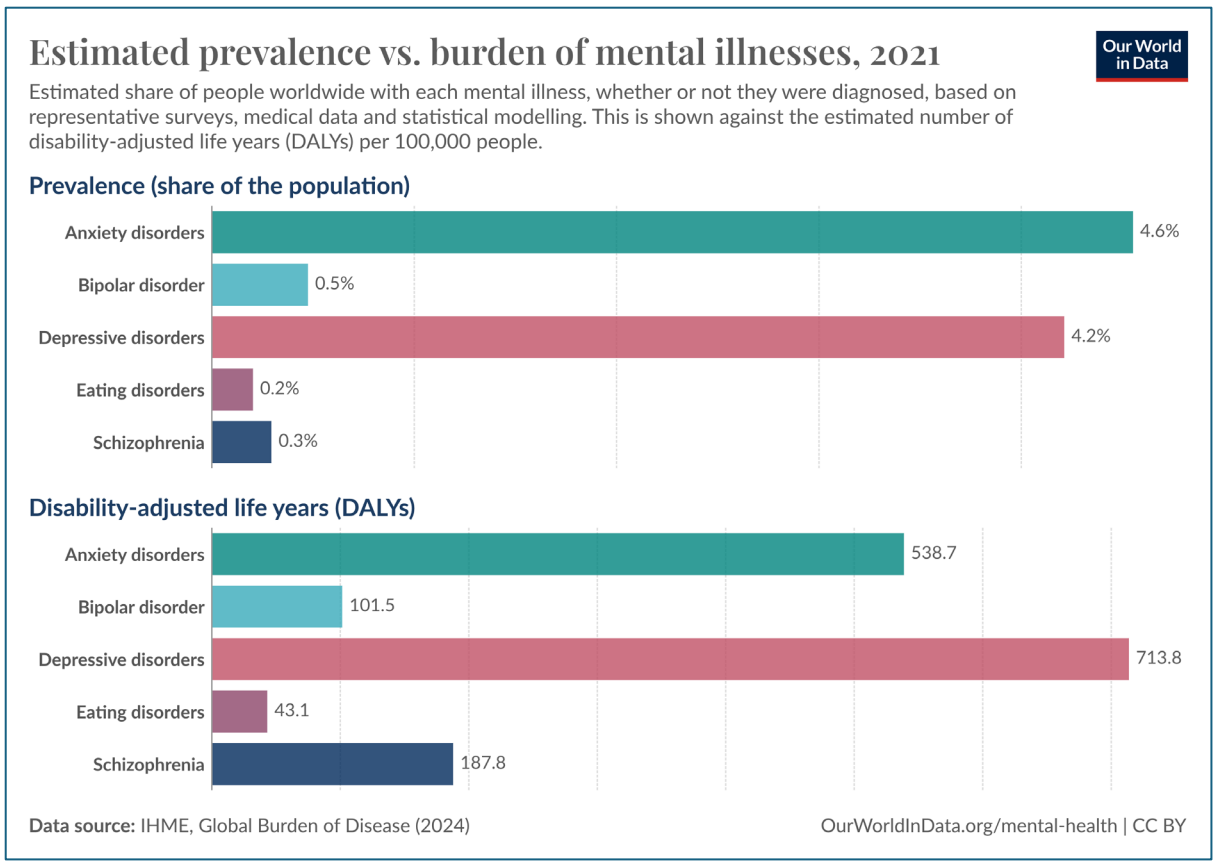


Figure 2. Estimated prevalence of people living with each mental disorder compared to estimated number of disability-adjusted life years (DALYs) per 100 000 people. Source: IHME, Global Burden of Disease (2024) – with major processing by Our World in Data (11).

Moreover, the humanistic burden of schizophrenia deserves mention; this includes the emotional, social, and psychological challenges faced by individuals and caregivers. The stigma associated with mental illness and schizophrenia, coupled with the adverse effects of treatment and the emotional burden on caregivers, adds another layer of complexity to treating the disorder. Moreover, comorbid anxiety, common among people with schizophrenia, further exacerbate this burden. They are associated significantly lower quality of life compared to those without such comorbidities, highlighting the need for comprehensive treatment approaches that address both schizophrenia and its associated anxiety disorders (18).

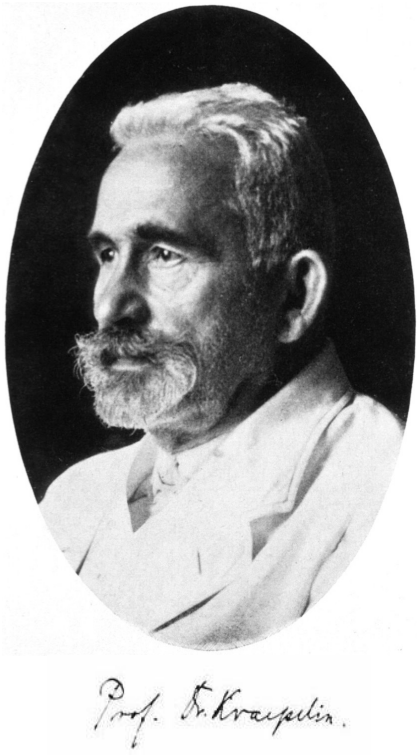
Addressing these multidimensional challenges is essential for a comprehensive approach to care, one that transcends mere symptom management and strives to improve the overall quality of life of individuals affected by schizophrenia (19). To achieve this goal, all three basic, translational, and clinical research remain of paramount importance and perhaps even a moral duty (20).

II. How Did Schizophrenia Become a Spectrum? — Conceptual Evolution and Understanding of Schizophrenia over Time

The understanding and diagnosis of schizophrenia have evolved considerably since its initial description in the late 19th century. Originally conceptualized by Emil Kraepelin as "*dementia praecox*," the disorder was distinguished from mood disorders by its early onset and chronic, deteriorating course (21). This foundational perspective laid the groundwork for contemporary diagnostic criteria, emphasizing the presence of psychotic symptoms such as delusions, hallucinations, and disorganized thinking, coupled with significant declines in social or occupational functioning (22).

Over time, the conceptualization of schizophrenia has shifted from an emphasis on specific subtypes—such as paranoid, disorganized, and catatonic schizophrenia—to a more dimensional approach that acknowledges the disorder's spectrum nature (2). This change signifies a growing awareness that psychotic symptoms can appear in multiple conditions, and the distinctions between various psychotic disorders are often

fluid. This emerging viewpoint has substantial repercussions for both research and clinical practice, questioning conventional categorical separations and highlighting the need for personalized treatment plans tailored to each individual patient's unique requirements.



Picture 1. Emil Kraepelin, ca. 1926.

The term "schizophrenia" was first introduced by Eugen Bleuler in 1911, yet it was Kraepelin's earlier description of "dementia praecox" that initially framed the disorder (23). Kraepelin’s observations of young adults who exhibited symptoms such as hallucinations, delusions, and cognitive decline—leading to progressive functional deterioration—differentiated schizophrenia from mood disorders, which were viewed as episodic and potentially reversible (24). His focus on the chronic and deteriorating nature of schizophrenia heavily influenced early 20th-century conceptions of the disorder (21).

However, Bleuler expanded upon Kraepelin's work by offering a more nuanced understanding of schizophrenia, rejecting the strict focus on early onset and deterioration. Instead, he emphasized the "splitting" of mental functions as the core feature of the disorder (23,25,26). This shift in perspective led to the coining of the term "schizophrenia" and paved the way for a more inclusive and flexible diagnostic approach, recognizing the disorder's potential to manifest in various ways (26). This broader understanding laid the foundation for modern diagnostic criteria and significantly influenced the field’s subsequent development (27).

As psychiatry advanced into the latter half of the 20th century, the advent of standardized diagnostic manuals such as the American Psychiatric Association’s Diagnostic and Statistical Manual (APA, DSM) and World Health Organization’s International Classification of Diseases (WHO, ICD) further refined the criteria for diagnosing schizophrenia. These manuals aimed to bring greater clarity and consistency

to psychiatric diagnoses. The DSM-III, introduced in 1980, marked a pivotal shift towards symptom-based, operationalized criteria, which have continued to shape subsequent editions, up to and including the DSM-5 (27).

The current diagnostic criteria for schizophrenia, as outlined in the DSM-5 and ICD-11, represent the culmination of over a century of clinical observation and research. The APA and the WHO define schizophrenia by the presence of at least two key symptoms—delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms like affective flattening or avolition—present for a significant portion of time during a one-month period. To meet the diagnostic criteria, these symptoms must persist for at least six months, with a minimum of one month involving active-phase symptoms (28–30). In recent decades, the conceptualization of schizophrenia has continued to evolve, moving away from rigid subtypes toward a more dimensional and spectrum-based approach. This shift acknowledges that psychotic symptoms can occur across a broad range of psychiatric disorders, and that the boundaries between these disorders are often fluid (31).This approach has significant implications for both research and clinical practice, emphasizing the importance of personalized treatment strategies tailored to the specific symptoms and needs of each patient (2).

Picture 2. Eugen Bleuler, ca. 1900

Complementing this shift, the Research Domain Criteria (RDoC) framework introduced by the National Institute of Mental Health (NIMH) represents a further evolution in the understanding of schizophrenia. Unlike traditional diagnostic systems, which are based on symptom clusters, RDoC is built on a dimensional approach that focuses on fundamental behavioral dimensions and their associated neural circuits. This framework integrates genetics, neuroscience, and cognitive science to better understand the underlying mechanisms of mental disorders, aiming to move beyond categorical diagnoses (32). For schizophrenia, the RDoC framework encourages research that cuts

across traditional diagnostic boundaries, exploring domains such as cognitive systems, negative valence systems, and social processes. This approach not only challenges existing diagnostic paradigms but also holds the promise of more precise, targeted treatments (33). Despite some criticisms of RDoC as potentially reductionistic, its focus on integrating neural data with behavioral and psychological assessments provides a comprehensive model that could significantly advance the field of psychiatry (27).

"I call dementia praecox schizophrenia because, as I hope to show, the splitting of the different psychic functions is one of its most important features. In each case there is a more or less clear splitting of the psychological functions: as the disease becomes distinct, the personality loses its unity (34)." –Eugen Bleuler

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Understanding the evolving conceptualizations of schizophrenia is crucial for recognizing the critical role of contemporary neurobiological research, particularly advancements in genetics and neuroimaging. Research in these fields is essential for understanding the intricate mechanisms underlying schizophrenia, which is now widely considered as arising from a complicated interplay of genetic and environmental factors. As the scientific community delves deeper into the genetic architecture of schizophrenia, the potential to transcend traditional, descriptive diagnostic frameworks grows, paving the way for a more mechanistic and individualized understanding of the disorder. This genetic-centric approach not only promises to enhance diagnostic precision but also heralds the development of more targeted therapeutic interventions.

However, despite these promising advances, significant unmet needs remain in schizophrenia research, particularly in the areas of treatment resistance, real world long-term outcomes, and the effectiveness of current therapeutic strategies. Addressing these challenges is essential for translating these neurobiological insights into real-world clinical benefits, thereby offering renewed hope to individuals grappling with schizophrenia.

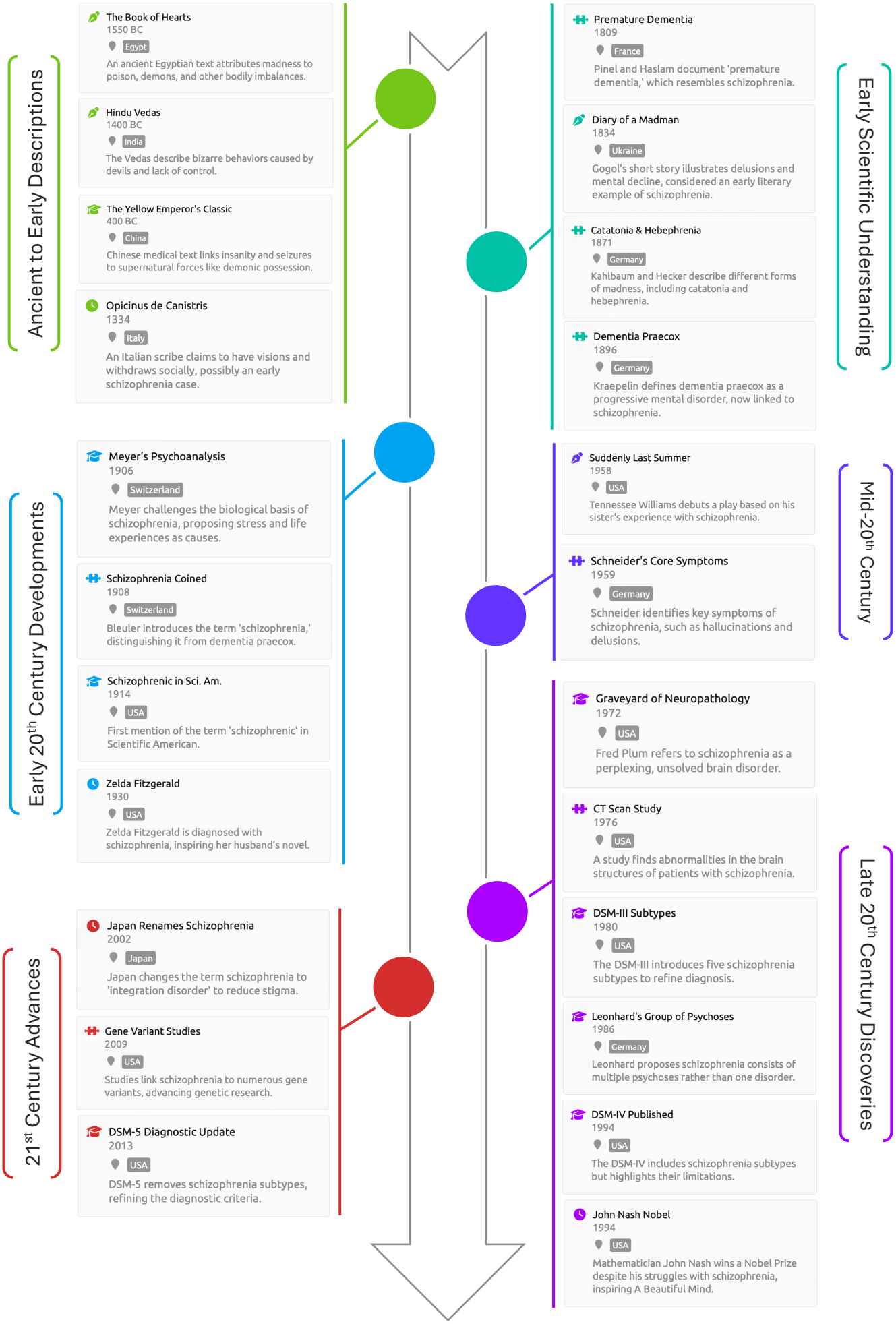

Figure 3. How has the concept of schizophrenia evolved over time? Own creation with data from (35).

B. What Are We Missing?—Identifying Gaps and Unmet Needs

I. Diagnosis, Characterization, and Biomarkers

Schizophrenia has a complex nature, with multiple, heterogeneous genetic, neurobiological, and environmental risk and protective factors interacting (1,5) which sometimes culminate presenting diverse phenotypical profiles in the clinic (36,37). Therefore, substantial unmet needs remain in clinical research for diagnostic and treatment biomarkers. These gaps significantly impede the development of precise diagnostic tools and personalized effective and safe treatments.

A critical issue lies in the validation of biomarkers for schizophrenia, as most candidate biomarkers have not yet been sufficiently reliable or useful for clinical adoption (38–40). Despite numerous identified candidates, none have been validated for clinical use, which underscores the need for more robust and reliable biomarkers (39–41). Genetic and environmental interactions that contribute to schizophrenia introduce considerable disease heterogeneity, further complicating the identification of specific biomarkers (39,42,43). Additionally, the overlap in symptoms, genetic variations, and brain alterations with other psychiatric disorders adds another layer of complexity, making it difficult to determine disease-specific effects (42,44).

Neuroimaging, while promising for the development of biomarkers through the capture of phenotypic variations in brain circuits, still lacks effective biomarkers (41,45). Although multivariate pattern recognition approaches in neuroimaging have shown potential, they are not ready to be applied clinically (45).

Advances in genetic analysis techniques, such as genome-wide association studies (GWAS) and polygenic risk scores (PRS), have enriched our understanding of schizophrenia. However, these have yet to be translated into reliable clinical biomarkers (44,46). There remains a pressing need for biomarkers that can predict the transition to schizophrenia in high-risk individuals, with current research focusing on genetic and imaging markers (43,46). Combining different types of biomarkers—genetic, neuroimaging, and peripheral markers—may enhance the classification and diagnosis of schizophrenia (39,40). To advance biomarker development, collaborative efforts are

essential, particularly those that integrate biosystems beyond genetics and neuroimaging (38,40).

II. Timely, Personalized Pharmacological Treatments

It goes without saying that even though early diagnosis is essential to improve care for individuals with schizophrenia (47), little can be done with the diagnosis alone. Effective and safe treatment options are necessary to prevent relapses (48)—and consequently cognitive decline (49)—, minimize long-term adverse effects, maintain healthy social relationships and functioning, and lead an overall fulfilling life (15,17).

Despite significant advancements, several critical unmet needs persist in the pharmacological treatment of schizophrenia, highlighting the limitations of current therapeutic approaches. The treatment of negative symptoms (50) and cognitive impairments (51) represent significant gaps in the treatment landscape, as current medications have limited efficacy in addressing these, which contribute to functional impairment in patients (50,52,53). The limited efficacy of available treatments for negative and cognitive symptoms underscores the necessity to develop antipsychotics with novel mechanisms of action that can effectively target the full spectrum of schizophrenia symptoms while reducing adverse effects (50,54,55). Research into non-dopaminergic targets, such as NMDA receptor modulators, offers potential new avenues for treatment, although these approaches are still in exploratory stages (51,52). Promising areas include muscarinic receptor agonism, trace amine-associated receptor 1 agonism, serotonin receptor antagonism/inverse agonism, and glutamatergic modulation (54,56).

The effectiveness and safety of antipsychotic medications also remain a critical focus. While several antipsychotics are available, particularly for early-onset schizophrenia (EOS) where positive symptoms predominate, the side effects associated with these drugs—such as weight gain and metabolic syndrome mainly with second-generation antipsychotics and extrapyramidal symptoms with first-generation antipsychotics—continue to pose significant challenges (57). In treating early-onset

psychosis (EOS), there is a notable gap in addressing outcomes related to cognition, functioning, quality of life, suicidal behavior, mortality, and cost-effectiveness, highlighting the necessity for future long-term trials (57). Moreover, despite ongoing efforts, there remains insufficient evidence to support recommendations for several psychopharmacologic and psychosocial treatments (58,59). This insufficiency is compounded by methodological challenges in clinical trials, such as inconsistent results and small sample sizes, which hinder the assessment of the efficacy of current treatments, particularly for negative symptoms (50,60).

In translating research evidence into clinically relevant long-term outcomes, there is a clear deficit in effective long-term outcome measures that map onto functional outcomes. The need to transfer measurement-based approaches from research to clinical practice is evident (56,61). The focus of current pharmacological strategies on short-term symptom control, with insufficient emphasis on long-term outcomes such as cognitive function, overall functioning, quality of life, and cost-effectiveness, further complicates treatment. The lack of longitudinal studies in these areas leaves clinicians with limited guidance on optimizing treatment over the course of a patient's life, a significant concern given the chronic nature of schizophrenia (56,61,62). A more comprehensive understanding of these long-term outcomes is essential for improving the quality of care and ensuring that treatments provide sustained benefits.

III. Treatment Resistant Schizophrenia and Improving Prognosis

Treatment-resistant schizophrenia (TRS), affecting approximately 30% of individuals diagnosed with schizophrenia, presents one of the most formidable challenges in psychiatric practice (62). Characterized by the failure to respond to standard antipsychotic treatments, TRS is associated with a substantial burden on patients, caregivers, and healthcare systems. The heterogeneity in clinical courses and treatment responses highlights the inadequacy of a one-size-fits-all approach, underscoring the need for more personalized treatment strategies (63,64).

A significant unmet need in managing TRS lies in the absence of standardized, evidence-based diagnostic criteria, which complicates timely identification and treatment (62–66). Current definitions vary widely, leading to inconsistencies in both diagnosis and therapeutic approaches. Even with the most effective pharmacological option, clozapine, many patients fail to achieve adequate symptom control due to severe side effects and the necessity of rigorous monitoring, limiting its broader application (57,62,64,67). This underscores the pressing need for the development of safer and more effective pharmacological treatments, particularly for patients unable to tolerate current therapies (68).

Promising non-pharmacological interventions, including psychotherapy and psychosocial treatments, remain under-researched and insufficiently implemented (69–71). Additionally, caregivers face considerable challenges, including emotional, physical, and financial strain, due to the severe and persistent symptoms associated with TRS (70,72). Addressing these gaps not only highlights the need for improved treatment strategies but also sets the stage for personalized psychiatry, where interventions are tailored to the unique clinical profiles, biomarkers, and treatment responses of individuals with TRS. This shift toward stratified care offers the potential for more precise and effective therapeutic outcomes.

IV. Personalized Medicine or Stratified Psychiatry

Stratified psychiatry represents a pivotal step toward precision psychiatry, focusing on improving treatment outcomes by categorizing patients with similar biomarker profiles. By identifying biomarkers that indicate a patient's likelihood to respond to a particular treatment, stratified psychiatry aims to enhance clinical outcomes by assigning patients to established, on-label treatments based on these profiles (73). This approach differs from personalized psychiatry, which tailors interventions to each individual patient based on unique, replicable markers. While stratified psychiatry groups patients with similar profiles to increase the likelihood of a

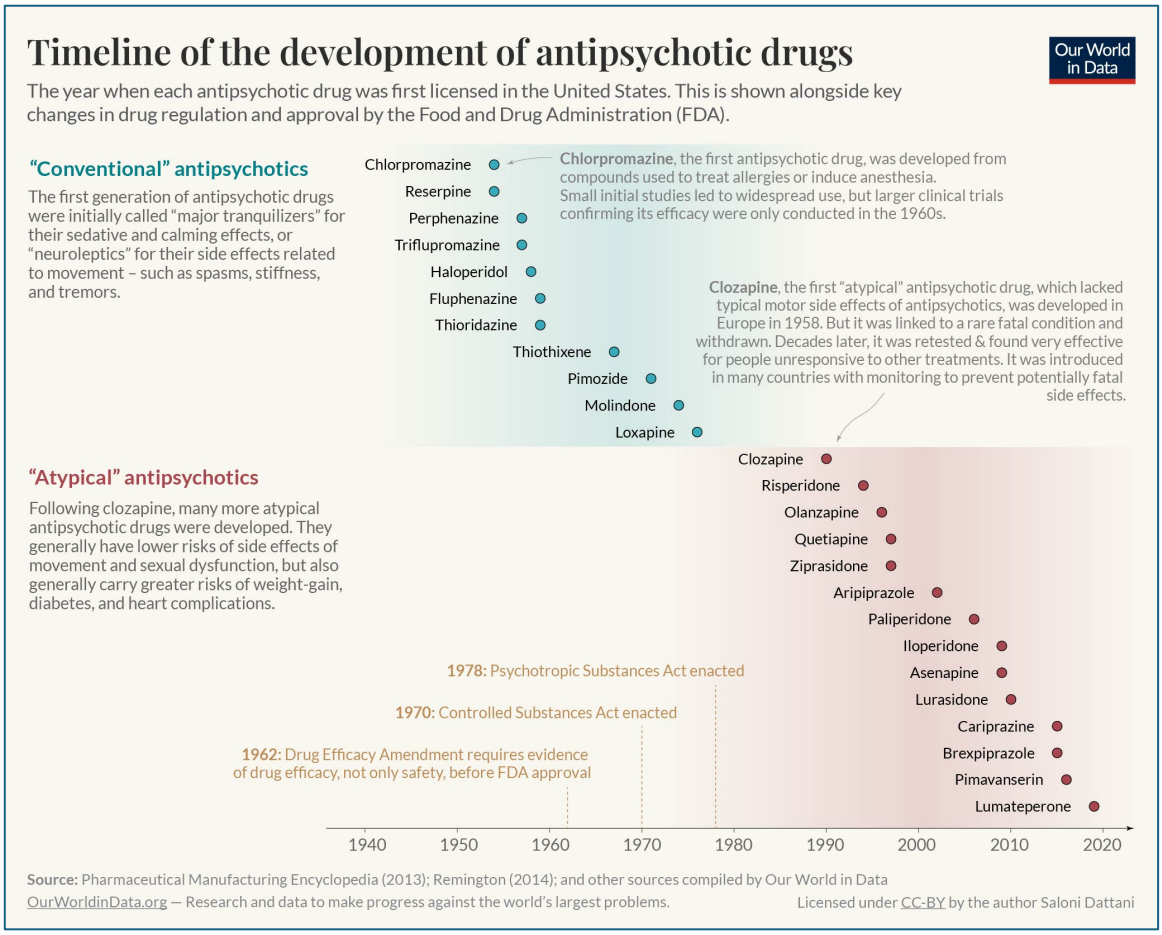

Figure 4. Timeline of the development of antipsychotic drugs. Source: Our World in Data (74).

positive response to established treatments, personalized psychiatry focuses on the nuances of individual variability (73).

Advances in technologies like genotyping and pharmacogenetics are integral to the development of stratified psychiatry, as they allow for more accurate selection of psychopharmacologic agents based on individual metabolic and clinical profiles (75). Techniques such as EEG, fMRI, and DTI, when combined with pharmacogenetics, offer new insights into psychiatric disorders and enable more refined treatment approaches (75). Digital tools, including structured diary applets and Ecological Momentary Interventions (EMIs), further support these advancements by involving patients in real-time data collection, allowing for more dynamic and tailored care (76).

Although stratified psychiatry brings us closer to precision psychiatry, personalized medicine continues to play a crucial role in addressing the substantial variability in treatment responses and disease progression seen in schizophrenia and

psychosis (77). Despite the promise of precision approaches, the treatment of schizophrenia largely remains reliant on a “trial-and-error” approach, lacking the precision seen in fields like oncology (78). Standard treatments, such as second-generation antipsychotics, are often prescribed based on clinician preference rather than being tailored to individual patient needs (36,79). Despite advances in neurobiological research, reliable biomarkers for diagnosis and treatment have yet to become available, further highlighting the need for individualized strategies (78).

Significant challenges remain in the current landscape of schizophrenia treatment, particularly in the underutilization of psychosocial interventions and cognitive behavioral therapies, despite their proven efficacy (36). Cognitive deficits in schizophrenia require interventions such as personalized cognitive remediation (CR), which must be tailored to each patient’s cognitive, psychological, and biological profile in order to improve outcomes (80,81). Early detection and intervention in high-risk youth are also crucial for improving long-term outcomes, emphasizing the importance of expanding early psychosis initiatives (80).

Looking ahead, identifying at-risk genes and neuroimmunological markers offers a promising direction for developing targeted treatments (78). However, translating these findings into clinical practice remains a significant challenge. Personalized interventions, such as tailored metacognitive therapy, have shown potential in improving symptoms and social functioning by focusing on real-world issues that patients encounter in their daily lives (82,83). Additionally, individualized treatment approaches must consider current symptoms, comorbid conditions, past therapeutic responses, adverse effects, and patient preferences to effectively address the variability in therapeutic outcomes (56,61). Pharmacogenomic strategies, in particular, are vital in addressing the wide variability in therapeutic effects and side effects among patients (84,85).

Patient perspectives are central to the future of schizophrenia treatment. Patients often prioritize social and functional recovery over mere symptom control, which underscores the importance of aligning treatment goals with their holistic view of recovery (15). Incorporating these perspectives into treatment plans not only enhances

engagement but also ensures that interventions are relevant to the patient's unique needs and experiences.

There are calls for more individualized treatment plans that consider the clinical characteristics of each patient (56,79,86). Before that, stratified psychiatry marks significant progress towards more effective treatment strategies for schizophrenia by grouping patients with similar biomarker profiles and can be considered a segue to personalized psychiatry. The integration of emerging technologies such as PRS, pharmacogenetics, along with patient-centered approaches, will be essential in translating these advances into clinical practice. Overcoming the current challenges in implementing stratified and personalized treatment strategies will be key to realizing their full potential in improving outcomes for individuals with schizophrenia.

V. Stigma and Discrimination

Schizophrenia is widely recognized as a mental disorder heavily impacted by stigma and discrimination, which significantly hinders the recovery and social integration of those affected. Research consistently demonstrates that individuals with schizophrenia face extensive negative discrimination across multiple domains of life, including social interactions, healthcare, and employment (87–89). Reports of verbal abuse, humiliation, and exclusion are common, reflecting the widespread nature of this discrimination across different cultural contexts.

Discrimination in healthcare settings is particularly troubling, as individuals with schizophrenia frequently report experiences of disrespect and inadequate care from healthcare providers (88,90). Mental health professionals themselves, though trained to provide support, may still harbor stigmatizing attitudes, which can further undermine the quality of care and reinforce negative experiences for patients (90,91). This pervasive stigma within healthcare settings not only affects immediate treatment but also reduces long-term health outcomes, as patients become less likely to seek help or adhere to prescribed treatments. Internalized stigma represents another significant barrier to recovery for individuals with schizophrenia. Many individuals internalize society's

negative attitudes, which leads to feelings of alienation, low self-esteem, and negative self-perception (87,92). This self-stigmatization exacerbates symptoms, diminishes quality of life, and discourages help-seeking behaviors (92,93), thereby creating a vicious cycle that further entrenches the individual in their illness.

The social consequences of stigma are equally damaging. Individuals with schizophrenia often struggle with forming and maintaining relationships, resulting in social isolation and impaired social functioning (90,93,94). This stigma-induced isolation not only hinders recovery but also limits access to crucial social support networks. However, community-based interventions aimed at reducing stigma have shown promise in improving social functioning and reducing the anticipation of discrimination (93), offering hope for more effective integration strategies.

Comparatively, schizophrenia is often more stigmatized than other mental health disorders, such as anxiety or affective disorders. Individuals with schizophrenia are frequently perceived as more dangerous or unpredictable, contributing to greater social distance and fear from others (91,94,95). This heightened stigma further marginalizes people with schizophrenia, reinforcing societal barriers that impede their ability to engage fully in community life.

C. How Do We Know What We Know? —Epistemological Approach to Hypothesis Testing

Scientific inquiry, particularly in fields as complex and multifaceted as psychiatry, hinges on a robust understanding of the underlying epistemological frameworks that guide research. Central to this endeavor is the formulation, testing, and potential refutation of hypotheses, which serve as the cornerstone of scientific advancement. This thesis, titled *Testing Hypotheses in Schizophrenia and Related Psychoses*, reflects a deliberate focus on employing rigorous hypothesis testing methodologies to explore key questions in the field. The approach adopted here is grounded in the principles of

scientific epistemology, particularly those articulated by Karl Popper, who argued that the falsifiability of hypotheses is the defining characteristic of scientific progress (96).

Popper's philosophy of science emphasizes that scientific theories cannot be conclusively proven; rather, they must be subjected to rigorous testing and remain open to refutation. This idea has profound implications for research in psychiatry, where the complexity of disorders like schizophrenia necessitates a flexible, iterative approach to hypothesis testing. Psychiatry, unlike more deterministic fields such as physics or chemistry, deals with a wide range of variables—including genetic, neurobiological, and environmental factors—that interact in complex, often unpredictable ways (97). As such, it is vital that hypotheses in psychiatric research are structured in a way that allows them to be tested empirically and, if necessary, refuted or revised considering new evidence.

This thesis applies these epistemological principles across several domains of schizophrenia research. Each chapter represents a distinct research initiative, but all are unified by a commitment to rigorous hypothesis testing. By integrating data from genetics, neuroimaging, real-world clinical outcomes, and randomized controlled trials (RCTs), this work tests a range of hypotheses related to the neurobiology, treatment, and clinical management of schizophrenia. Importantly, this approach acknowledges the provisional nature of scientific knowledge in psychiatry—findings are not definitive but serve as steppingstones toward a deeper understanding of this complex disorder.

I. The Role of Hypothesis Testing in Schizophrenia Research

In psychiatric research, hypothesis testing takes on particular importance due to the heterogeneity of disorders such as schizophrenia. The variability in symptom presentation, disease progression, and treatment response necessitates a multifaceted approach to research. Hypotheses in this field must be crafted to accommodate this variability while remaining amenable to empirical testing. For instance, one of the central hypotheses in this thesis investigates the role of polygenic risk scores (PRS) in predicting clinical outcomes in schizophrenia. The hypothesis posits that individuals with higher PRS for schizophrenia will exhibit more severe clinical symptoms and a greater likelihood

of requiring treatment with clozapine, a medication often reserved for treatment-resistant cases. This hypothesis, like others in this work, is grounded in existing literature but remains open to refutation based on the evidence gathered through empirical testing (98–101).

The iterative nature of hypothesis testing in psychiatry is also reflected in the analysis of real-world data versus randomized controlled trial (RCT) data. A persistent issue in psychiatric research has been the disconnect between the highly controlled environments of RCTs and the more chaotic realities of clinical practice (102). Hypotheses about treatment efficacy derived from RCTs may sometimes be perceived by clinicians as failing to hold up in real-world settings, where patient adherence, comorbidities, and other factors complicate the outcomes. This thesis addresses these discrepancies by testing the hypothesis that antipsychotic medications, particularly long acting injectables (LAIs), may perform differently in real-world settings compared to the controlled conditions of RCTs. Through the integration of real-world evidence from national registries in Sweden and Finland, this work tests whether the efficacy of antipsychotics observed in clinical trials can be replicated in broader, more representative patient populations (103–105).

II. Epistemological Implications of Multi-Domain Hypothesis Testing

The title of this thesis, *Testing Hypotheses in Schizophrenia and Related Psychoses*, underscores the importance of applying a structured, epistemologically sound approach to psychiatric research. Schizophrenia, as a disorder, does not lend itself easily to simple, linear hypotheses. Its multifactorial nature requires hypotheses that are both specific enough to be testable and flexible enough to accommodate the complexity of the disorder. For example, the hypothesis that early-onset psychosis has a more pronounced neurobiological basis than adult-onset psychosis is grounded in neuroimaging studies that show higher rates of brain abnormalities in younger patients (106). This hypothesis reflects the interplay between developmental neurobiology and

clinical presentation, suggesting that different subtypes of psychosis may have distinct etiological pathways. However, this hypothesis remains open to revision or rejection based on further empirical evidence, in keeping with the epistemological principles that guide this thesis.

The application of polygenic risk scores (PRS) in predicting treatment outcomes is another example of how hypothesis testing in this thesis builds upon existing scientific knowledge while remaining open to falsification. Although previous studies have suggested a link between genetic risk and clinical severity in schizophrenia, the precise nature of this relationship remains uncertain (107). By testing the hypothesis that PRS can stratify patients based on their clinical severity, this work aims to contribute to the ongoing debate about the utility of genetic information in psychiatric treatment planning. Importantly, the hypothesis is structured in such a way that it can be refuted or modified based on the results of empirical testing, in line with Popper's criteria for scientific progress.

Similarly, the hypothesis that most real-world schizophrenia patients would not qualify for inclusion in traditional RCTs due to exclusion criteria is both a reflection of the current limitations of clinical research and an attempt to push the field forward by advocating for more inclusive study designs. This hypothesis is tested by comparing real-world patient outcomes with those of patients who meet the stringent inclusion criteria of RCTs, thereby providing a more accurate picture of how schizophrenia treatments perform across different patient populations (108). The findings from these comparisons have the potential to reshape how clinical trials are designed and how treatment guidelines are developed, ensuring that they are more representative of the real-world populations they aim to serve.

The epistemological approach to hypothesis testing adopted in this thesis is grounded in the recognition that scientific knowledge in psychiatry is provisional, evolving as new evidence emerges. By testing hypotheses across multiple domains—genetics, neuroimaging, clinical outcomes, and real-world evidence—this work exemplifies the iterative process of scientific inquiry in psychiatry. The title, *Testing Hypotheses in Schizophrenia and Related Psychoses*, reflects the centrality of this

approach, emphasizing the importance of subjecting theories to rigorous empirical scrutiny while remaining open to the possibility of refutation and revision. Ultimately, this thesis contributes to the ongoing effort to refine our understanding of schizophrenia and related psychoses, offering new insights into the etiology and treatment of these complex disorders while adhering to the foundational principles of scientific epistemology.

D. Genetic Architecture of Schizophrenia

The genetic architecture of schizophrenia exemplifies the intricate interplay between biological, psychological, and environmental factors—a complexity that the RDoC framework seeks to elucidate. Schizophrenia is widely recognized as a highly heritable disorder, with genetic factors contributing to approximately 60-80% of the risk for developing the condition (109). Early twin and family studies provided compelling evidence supporting this genetic basis, revealing that individuals with a first-degree relative diagnosed with schizophrenia face a significantly elevated risk of developing the disorder themselves (110). Importantly, schizophrenia is not driven by a single gene; rather, it is a polygenic disorder, influenced by the cumulative effects of numerous genetic variants, each exerting a modest impact on overall risk (98,99).

The advent of GWAS has markedly expanded our understanding of the genetic architecture of schizophrenia. These studies have identified over 100 genetic loci associated with the disorder, implicating a range of biological processes, including synaptic function, neurotransmitter signaling, and immune response (98). For example, the association between schizophrenia and the major histocompatibility complex region on chromosome 6, which has been linked to both immune function and neurodevelopment, exemplifies the multiple factors at play in the genetic architecture of schizophrenia (111).

PRS have emerged as a significant tool for quantifying an individual's genetic susceptibility to schizophrenia. Calculated by summing the effects of multiple genetic variants, each weighted by its association with the disorder, PRS reflect the cumulative

genetic risk (112–114). The potential applications of PRS extend beyond psychiatry, demonstrating significant promise across various medical disciplines. For example, in cardiology, the integration of PRS into cardiovascular disease risk assessments has enhanced the accuracy of risk predictions, enabling more targeted preventive measures (115–117). In oncology, PRS have proven instrumental in managing breast cancer risk, promoting adherence to preventive strategies without increasing patient anxiety (118). These examples underscore the broader potential of PRS in improving clinical outcomes across different medical fields. In neuroscience, PRS have demonstrated potential in predicting the risk of neurodegenerative diseases such as Alzheimer's disease. Research suggests that PRS can identify individuals at higher risk for Alzheimer's even before symptoms manifest, potentially leading to earlier, more effective interventions (119,120).

Additionally, in psychiatry, PRS are increasingly recognized for their role in predicting the onset and progression of disorders like schizophrenia and bipolar disorder, offering opportunities for early intervention that could mitigate disease severity (114,121). They are increasingly being studied as a tool for personalizing psychiatric treatment by predicting individual responses to medications. Recent studies have underscored the utility of PRS in the context of treatment-resistant schizophrenia (TRS) and major depressive disorder (MDD), highlighting the potential of these scores to enhance clinical outcomes by tailoring treatments based on genetic risk profiles. In the treatment of severe major depressive episodes (MDEs), electroconvulsive therapy (ECT) is considered the most effective intervention, yet patient responses vary significantly.

A study led by Luykx's group investigated the role of PRS for schizophrenia (PRS-SCZ) in predicting ECT outcomes in patients with MDEs. This multinational study, involving 288 patients across Ireland, Belgium, and the Netherlands, revealed a significant positive association between higher PRS-SCZ and greater reductions in Hamilton Depression Rating Scale (HDRS) scores post-ECT (122). Notably, this association persisted across various subgroups, including patients with non-psychotic and unipolar depression. These findings suggest that PRS-SCZ could serve as a valuable predictor of ECT response in MDD, potentially guiding clinicians in identifying patients –

independent of current diagnostic criteria – who are more likely to benefit from this biological, non-pharmacological treatment.

Further expanding the scope of PRS in psychiatry, another study examined its role in predicting treatment outcomes in patients with TRS treated with clozapine—the gold standard for TRS management. The study, which included 684 patients with schizophrenia spectrum disorders after quality control, explored the association between PRS-SCZ and symptom severity, alongside genotype-predicted cytochrome P450 enzyme activities (123). Results indicated that patients with higher PRS-SCZ experienced lower symptom severity, suggesting a more favorable response to clozapine. Additionally, the study found that higher genotype-predicted CYP2C19 enzyme activity was independently associated with reduced symptom severity, highlighting the potential for integrating pharmacogenomics with PRS to further refine treatment strategies for TRS. While no single genetic locus reached genome-wide significance, the identification of suggestive associations provides a foundation for future research aimed at uncovering the genetic underpinnings of clozapine response variability.

Beyond common variants identified through GWAS, the genetic architecture of schizophrenia also involves rare variants and copy number variations (CNVs), which contribute to the disorder's complexity. Rare coding variants, particularly those identified through large-scale sequencing efforts such as the SCHEMA consortium, have shown substantial effects on schizophrenia risk. These variants are often found in genes related to synaptic function and neurodevelopment, suggesting that rare, highly penetrant mutations may underlie more severe cases of the disorder (124). CNVs, which involve large deletions or duplications of genomic segments, have also been strongly associated with schizophrenia. For instance, duplications at 16p11.2 and deletions at 22q11.2 are among the most well-established CNVs linked to the disorder, highlighting the importance of structural genomic variation in schizophrenia risk (125).

Epigenetic modifications, including DNA methylation and histone modifications, further complicate the genetic architecture of schizophrenia. These heritable changes in gene expression, which do not alter the underlying DNA sequence, can be influenced by

both genetic and environmental factors. Studies have shown that differential DNA methylation patterns across various brain regions are significantly associated with schizophrenia, suggesting that epigenetic mechanisms may play a critical role in the disorder's pathophysiology (126). Moreover, recent findings indicate that genetic risk variants for schizophrenia often co-localize with differentially methylated regions, implying that these variants may exert their effects by altering the epigenetic regulation of gene expression (126). Integrating genetic and epigenetic data proves again important to gain a more comprehensive understanding of schizophrenia's etiology.

However, despite the promising potential of PRS in predicting schizophrenia risk, they currently account for only a portion of the variance in disease susceptibility. This highlights the need for larger GWAS datasets, more advanced statistical techniques, and a greater focus on rare variants and CNVs to fully capture the extent of genetic liability (127). Ongoing research is crucial for refining PRS and determining how they can be effectively integrated into clinical practice, particularly in identifying individuals at high risk and guiding stratified treatment strategies.

In summary, while significant progress has been made in identifying genetic risk factors for schizophrenia, the disorder's genetic architecture remains multifaceted and complex. The polygenic nature of schizophrenia, combined with the influence of rare variants, CNVs, and epigenetic mechanisms, suggests that a comprehensive understanding of the disorder will necessitate the continued integration of genomic, epigenomic, and environmental data. As research advances — particularly through large-scale sophisticated computational methods, and the study of both common and rare variants — we are likely to gain further insights into the genetic architecture of schizophrenia. Ultimately, these advancements could potentially inform the development of more targeted and effective therapeutic strategies for managing this complex disorder.

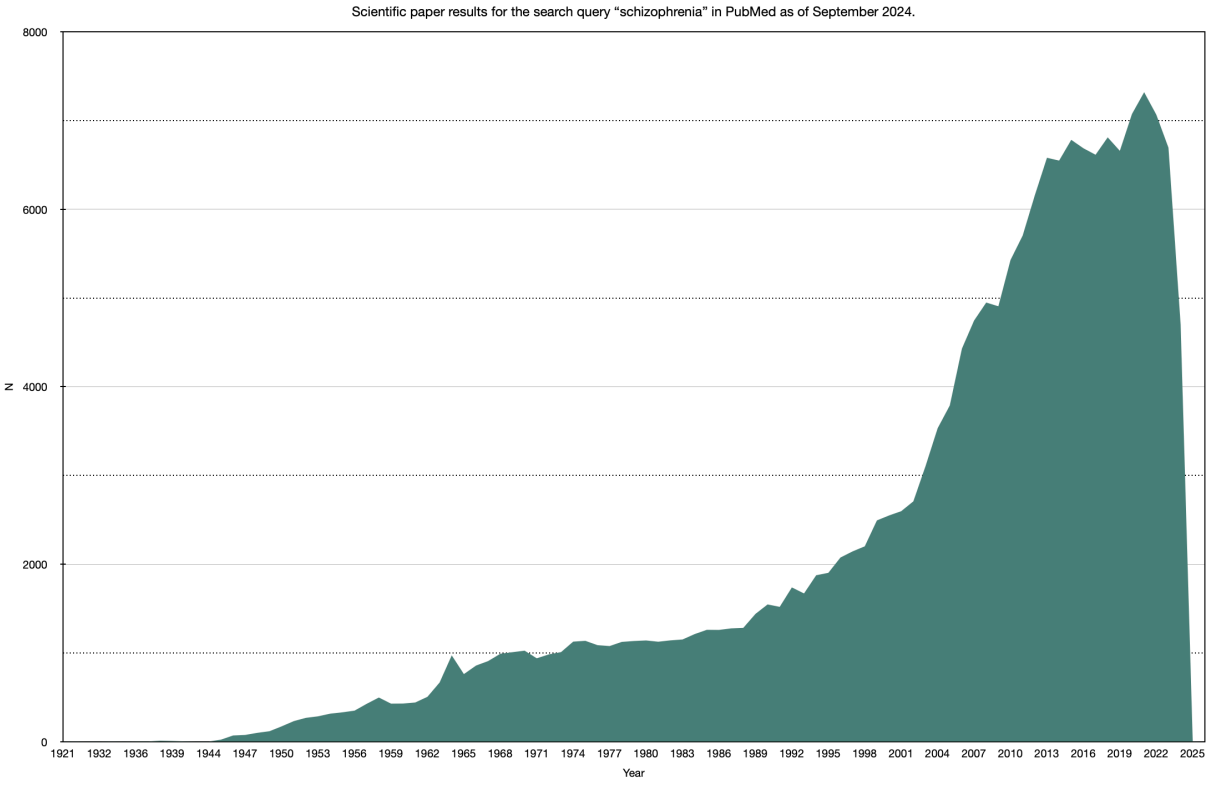

Figure 5. Histogram showing the number of hits for the search query 'schizophrenia' in PubMed as of September 2024. Data from (128)

E. Neurobiological Correlates

Building on this genetic foundation, the exploration of neurobiological correlates through neuroimaging has provided critical insights into the structural and functional abnormalities associated with schizophrenia. Neuroimaging studies, particularly those employing structural MRI, have consistently revealed reductions in gray matter volume across several brain regions, including the prefrontal cortex, temporal lobes, and hippocampus—areas intimately involved in cognition, emotion, and memory (129). These findings suggest that schizophrenia may be linked to neurodevelopmental abnormalities that begin in adolescence or early adulthood, potentially even before the onset of clinical symptoms (130).

Functional MRI (fMRI) studies have further elucidated the neural mechanisms underlying schizophrenia by examining patterns of brain activity and connectivity. A particularly well-replicated finding is the dysregulation of the default mode network

(DMN), a network of brain regions active during rest and involved in self-referential thinking (131). Individuals with schizophrenia frequently exhibit hyperactivity within the DMN and reduced connectivity between the DMN and other brain networks, such as the salience network, which may contribute to the cognitive and perceptual disturbances characteristic of the disorder (132).

In addition to these structural and functional abnormalities, neurochemical dysregulation has long been implicated in the pathophysiology of schizophrenia. The dopamine hypothesis, which posits that hyperactivity of dopamine transmission in the mesolimbic pathway contributes to the positive symptoms of schizophrenia, remains one of the most influential theories in the field (133). However, recent research has expanded this framework to include other neurotransmitter systems, such as glutamate and gamma-aminobutyric acid (GABA), which are thought to play critical roles in the cognitive deficits and negative symptoms observed in schizophrenia (134,135). This integrative approach underscores that schizophrenia is not a disorder of a single neurotransmitter pathway but rather a complex dysregulation of multiple systems that interact to produce the diverse symptoms observed in patients.

Neurodevelopmental models of schizophrenia propose that the disorder originates from disruptions in brain development during critical periods of neural maturation. These disruptions, triggered by genetic and environmental factors, lead to aberrant neural circuit formation and altered neurotransmitter function. Studies using induced pluripotent stem cells have revealed that schizophrenia is associated with common neurodevelopmental pathways affecting brain circuitry and neurotransmitter systems, providing further support for the neurodevelopmental hypothesis of the disorder (136). These findings highlight the importance of early brain development in the etiology of schizophrenia and suggest that the disorder may result from a cascade of neurobiological events initiated long before clinical symptoms emerge.

Further enriching this complex neurobiological landscape, structural MRI has provided critical insights into the early detection and staging of schizophrenia. White matter abnormalities, particularly in tracts such as the superior longitudinal fasciculus, cingulum bundle, and corpus callosum, have been consistently identified in early-onset

and drug-naive patients, suggesting that structural dysconnectivity is present from the initial stages of the disorder (137–139). Furthermore, gray matter reductions in regions such as the prefrontal cortex, hippocampus, and thalamus are evident even during the first episode of psychosis, underscoring the role of structural MRI in identifying early neurobiological disruptions (140). These neuroimaging markers are not only crucial for early diagnosis but also for staging the disease, as progressive changes in gray and white matter have been associated with more advanced stages of schizophrenia (141,142).

Structural MRI has also been explored for its utility in differentiating schizophrenia from other psychiatric disorders, such as bipolar disorder. For instance, patients with schizophrenia tend to exhibit increased ventricular volume and reduced hippocampal volume, which are not typically observed in bipolar disorder. This distinction is particularly valuable in early stages, facilitating early stratification of diagnosis, treatment strategies, and prognostic trajectories (143). The hypothalamic-pituitary-adrenal (HPA) axis, which regulates the body's response to stress, is thought to be involved in the etiopathogenesis of schizophrenia. Dysregulation of the HPA axis has been observed in individuals at high risk for schizophrenia, as well as in those with established psychosis, and is thought to interact with genetic, epigenetic, and environmental factors, contributing to the progression of the disorder (144). The neural diathesis-stress model of schizophrenia integrates these various factors, offering a comprehensive framework for understanding how stress-related neurobiological processes may influence the onset and course of the disorder.

Moreover, recent research has linked neuroimaging abnormalities with molecular and genetic data, offering new insights into the pathophysiology of schizophrenia. For instance, a study combining multimodal neuroimaging with transcriptome analysis found that schizophrenia is associated with specific patterns of brain abnormalities that correlate with disruptions in neurotransmitter systems, particularly those involving dopamine, glutamate, and GABA (145). These findings underscore the importance of integrating neuroimaging and molecular data to better understand the complex neurobiological underpinnings of schizophrenia.

In summary, the neurobiological correlates of schizophrenia encompass a wide range of structural, functional, and molecular abnormalities, reflecting the disorder's complexity. Understanding these neurobiological processes is crucial for developing more effective treatments and advancing our knowledge of how schizophrenia develops and progresses over time. However, while these insights are invaluable, the translation of these findings into clinical practice often encounters challenges, particularly in the context of the generalizability of controlled research settings to the diverse and complex nature of real-world patient populations. This gap between controlled research and everyday clinical practice highlights the importance of real-world evidence (RWE) in bridging this divide, particularly in understanding how treatments perform across different patient populations and settings.

F. Applied Research and Real-World Evidence

I. Real-World Evidence in Schizophrenia Research

Randomized controlled trials (RCTs) have historically been considered the gold standard in evaluating the efficacy of medical interventions, given their methodological rigor and ability to control for confounding variables. These trials are indispensable for establishing the foundational evidence required for the regulatory approval of new treatments. Nevertheless, the strict inclusion and exclusion criteria inherent to RCTs significantly constrain the generalizability of their findings to real-world clinical settings (146). This limitation is particularly pronounced in the context of schizophrenia, where patients with comorbid conditions or treatment-resistant symptoms are frequently excluded from participation. Such exclusions may create a divergence between the outcomes observed in clinical trials and those encountered in everyday practice, complicating the translation of research findings into effective clinical care.

This gap underscores the increasing relevance of real-world evidence (RWE) in elucidating the performance of treatments across diverse patient populations and within routine clinical environments (102). In contrast to the controlled conditions of RCTs, RWE is derived from data collected during regular clinical practice, encompassing

sources such as electronic health records, patient registries, and observational studies. RWE captures the heterogeneity and complexity of patients seen in everyday clinical settings, providing a more nuanced understanding of treatment effectiveness, safety, and long-term outcomes (147). These insights are particularly crucial for populations often underrepresented in clinical trials, thereby offering a more comprehensive view of how treatments function in practice (148).

In recent years, the field of schizophrenia research and treatment has increasingly acknowledged the vital role of RWE as a complement to traditional RCTs. Although RCTs remain essential for regulatory approval, their applicability to real-world clinical settings is often limited due to the controlled environments in which they are conducted. This limitation has spurred a growing interest in RWE, which provides insights into how treatments perform across diverse patient populations beyond the confines of clinical trials (149).

The inclusion of RWE in schizophrenia research addresses some of the key limitations associated with RCTs, particularly concerning external validity. The stringent inclusion and exclusion criteria of RCTs frequently fail to capture the complexity of real-world patient populations, such as those with comorbidities or varying degrees of disease severity. This discrepancy between RCT characteristics and real-world practice has prompted a critical reassessment of how evidence is generated and applied in clinical settings (150). In contrast, RWE studies offer valuable insights into the effectiveness and safety of treatments within broader, more representative populations. Utilizing data from sources like electronic health records, patient registries, or insurance claims, these studies provide a comprehensive perspective on how treatments function in practice. Additionally, RWE can identify gaps in clinical trial evidence and guide decision-making in contexts where RCT data may be limited or unavailable (151).

These findings have profound implications for clinical decision-making, especially in the customization of treatments to address the complex clinical profiles of such patients (103). Moreover, the application of RWE is pivotal in the realm of personalized psychiatry, where treatment strategies are tailored to the individual characteristics of each patient. By integrating genetic, neurobiological, and real-world

data, researchers can devise more personalized treatment approaches that cater to the specific needs of schizophrenia patients. This methodology holds the potential to enhance clinical outcomes by ensuring that patients receive the most suitable and effective treatments for their unique clinical profiles (32).

The inclusion of RWE in schizophrenia research is crucial for comprehending long-term outcomes and the effects of treatments in everyday clinical settings. For example, a meta-analysis comparing the efficacy of antipsychotics in RCTs with their effectiveness in real-world studies using all-cause discontinuation as the primary outcome found that while both study designs generally yield consistent results and RCTs offer vital evidence for regulatory use, real-world studies provide additional insights more relevant to daily clinical practice. This meta-analysis indicates that real-world studies typically support the findings of RCTs but add important nuances essential for routine patient care (150).

Twelve years ago, an NIHM-funded study co-authored by research leaders in the field of schizophrenia treatment aimed to perform a meta-analysis of randomized clinical trials comparing long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia (152). The authors stated that "*while we had anticipated that LAIs (with their intrinsically better adherence) would be more effective than OAPs in preventing relapse, this was not evident in a synthesis of the available RCTs. Notably, these results are in contrast to naturalistic cohort studies showing superiority of LAIs in preventing rehospitalization. (...) In order to evaluate the real-world effectiveness of LAIs compared with OAPs, large and long pragmatic trials are needed, which better resemble common clinical practice (152).*" Five years later, this same group performed a similar study evaluating the effectiveness of LAIs vs oral antipsychotics through a metanalysis of prospective and retrospective cohort studies (i.e. real world studies) (153). Interestingly, in the discussion they recognize that the "*superiority of SGA-LAIs over OAPs is the opposite of the subgroup analyses in our meta-analysis of RCTs where FGA-LAIs, but not SGA-LAIs separated significantly from OAPs. Thus, based on these inconsistencies, more high-quality head-to-head trials in representative patients are needed that compare FGA-LAIs and SGA-LAIs with OAPs (153).*"

Therefore, it would be an understatement to say that the use of RWE is not without its challenges. The quality of data collected in real-world settings can vary significantly, and issues such as missing data, selection bias, and confounding factors must be rigorously addressed. Ensuring the reliability and validity of RWE necessitates robust study designs and advanced analytical techniques to overcome these challenges and generate evidence that can effectively complement RCTs (154,155). Furthermore, as RWE becomes more widely adopted, ongoing debates persist regarding its role in regulatory decision-making. While RCTs remain the cornerstone for demonstrating the efficacy of new treatments, there is a growing acknowledgment that RWE can provide essential insights into treatment effectiveness, safety, and healthcare utilization across broader populations. This recognition has led to calls for a more integrated approach, wherein RWE is utilized alongside RCTs to inform clinical guidelines and policy decisions (156).

Furthermore, integrating real-world data with RCTs is fraught with considerable challenges, particularly due to discrepancies in treatment efficacy and effects, heterogeneity, inconsistency, and the low precision often observed in the data. The harmonization of findings is further complicated by differences in study populations, participant characteristics, and representativeness, alongside variations in eligibility criteria, context-related variables, adherence rates, and outcome definitions. Methodological disparities, the presence of unmeasured confounding factors, limited data availability, and the absence of standardized definitions and criteria exacerbate the complexity of merging these two types of data. Moreover, the exclusion of critical factors such as sex, ethnicity, or specific antipsychotics, coupled with the variability in treatment guidelines, poses significant obstacles to the effective integration of real-world and RCT data.

Looking ahead, the future of schizophrenia research is likely to see an increased emphasis on integrating RWE with traditional clinical trial data to establish a more comprehensive evidence base. This approach has the potential to enhance the applicability of research findings to real-world clinical practice, thereby improving the quality of care for schizophrenia patients. By leveraging the strengths of both RCTs and RWE, researchers and clinicians can achieve a more holistic understanding of the

benefits and risks associated with treatments, ultimately leading to more informed decision-making and better patient outcomes (155).

II. Impact of COVID-19 on Mental Health and Schizophrenia

The COVID-19 pandemic, officially declared from 2020 to 2022, had a profound and far-reaching impact on mental health globally, exacerbating existing conditions and leading to a marked increase in the incidence of anxiety, depression, and stress-related disorders (157,158). Among those most vulnerable were individuals with schizophrenia, a population already burdened by the complexities of their condition. The pandemic intensified their challenges through mechanisms such as social isolation, disruptions to healthcare services, and the economic repercussions of prolonged societal restrictions (159). Research now shows that individuals with schizophrenia could be at an increased risk of contracting COVID-19 and experiencing severe outcomes, including higher mortality rates (160). Several factors contributed to this heightened vulnerability, including underlying health conditions, limited access to healthcare, and the potential immunosuppressive effects of psychotropic medications (161).

Furthermore, the stigma and discrimination associated with mental illness could lead to delayed testing and treatment, further amplifying the virus's impact on this marginalized group (162). The pandemic thus highlighted the critical need for an integrated healthcare approach that addresses both mental and physical health, particularly for individuals with severe mental illnesses like schizophrenia, who require comprehensive and coordinated care strategies (163).

The intersection of COVID-19 and schizophrenia presented unique public health challenges. As the pandemic unfolded, it became increasingly clear that individuals with schizophrenia were disproportionately affected—not only in terms of heightened susceptibility to the virus but also in the broader context of their mental healthcare. The pandemic revealed significant gaps in the healthcare system, including the need for timely and equitable access to testing, treatment, and ongoing care (164). Moreover, the

pandemic underscored the broader societal implications of mental illness, particularly concerning stigma and discrimination.

The parallel between the structural stigmatization experienced by individuals with schizophrenia and other marginalized groups, such as refugees and migrants during the pandemic, is striking. My recent work highlighted these parallels, emphasizing the compounded vulnerabilities faced by those systematically excluded from essential services during crises (165). These observations reinforce the need for public health interventions that are not only responsive to the immediate demands of the pandemic but also address long-standing inequities in healthcare access and delivery (158).

In response to these challenges, there is a pressing need to develop and implement targeted public health interventions that address the specific needs of individuals with schizophrenia during health emergencies. Such interventions must prioritize equitable access to healthcare services, reduce stigma, and provide comprehensive care that integrates both mental and physical health needs (166). Innovative care models, including expanded telemedicine use, have emerged as vital tools in ensuring continuity of care during the pandemic, and their continued development and integration into routine care will be crucial in the post-pandemic landscape (167).

The impact of COVID-19 on individuals with schizophrenia, and mental health in general, underscores the necessity of a rounded approach to healthcare. This approach must prioritize the integration of mental and physical health services, ensuring that vulnerable populations receive comprehensive and equitable care, particularly during health crises.

G. Synthesis of Contributions

I. What Have We Done!? – Synopsis of Our Research Contributions

Throughout my doctoral research program, I have led and co-developed a series of studies aimed at addressing critical gaps in our understanding of schizophrenia and

related psychoses. As a clinician, I have tried to work on questions that bother everyday clinicians when providing care for individuals with schizophrenia. This body of work spans genetic research, clinical treatment efficacy, the integration of real-world data with RCTs, and the exploration of potential neurobiological markers for early diagnosis and treatment. All of these have been aimed to contribute to advancing both theoretical knowledge and clinical practices in the field.

In **Chapter 1**, we explored the associations between PRS, psychosis liability, and clozapine use in individuals with schizophrenia (101). Schizophrenia is highly heritable, yet the clinical utility of genetic data in treatment decision-making remains underexplored. Our study sought to understand whether genetic predisposition could inform treatment decisions, particularly the prescription of clozapine, which is often reserved for refractory cases.

Chapter 2 addressed a longstanding concern among clinicians regarding the applicability of RCTs to real-world clinical settings (104). Given that RCTs often exclude patients with complex symptoms or comorbidities, we aimed to evaluate whether the outcomes of these trials accurately reflect the broader population of schizophrenia patients encountered in everyday practice.

In **Chapter 3**, we critically assessed the alignment of global treatment guidelines with real-world evidence (105). While major treatment guidelines (i.e. APA (168), the National Institute for Health and Care Excellence (169), the Royal Australian and New Zealand College of Psychiatrists (170,171)) predominantly rely on RCT data to recommend second-generation antipsychotics, we hypothesized that real-world outcomes might differ significantly, particularly regarding the effectiveness of LAIs in preventing relapse. However, these guidelines are based on published evidence thus far - that all antipsychotics have equal efficacy, as suggested by RCT meta-analyses (172). Moreover, LAIs are often considered to confer no real advantage beyond improving medication adherence. To challenge these assumptions, we developed a novel methodological framework that integrated both RCT data and real-world evidence (RWE) from large national registries.

Chapter 4 emerged from ongoing debates about the necessity and utility of neuroimaging in first-episode psychosis (106). Clinical guidelines worldwide differ on whether routine neuroimaging should be performed in first-episode psychosis, with some recommending its use only in cases where organic pathology is suspected. In our study, we conducted a controlled investigation of brain MRI scans in youths with early-onset psychosis compared to community controls. We aimed to determine whether routine neuroimaging could uncover clinically apparent alterations in search of a useful, accessible, translatable neurobiological marker indicative of early-onset psychosis. In that sense, we may help provide evidence of routine neuroimaging as potentially distinguishing it as nosologically distinct.

Finally, in **Chapter 5**, early on in the COVID-19 pandemic, we investigated the intersection of psychiatric disorders and public health policy during the COVID-19 pandemic (173). During the early weeks of the pandemic, uncertainty, fear, and lack of evidence were critical challenges when providing care or administering resources (174). Our focus was on how individuals with psychiatric disorders, including schizophrenia, were impacted in terms of access to COVID-19 testing and outcomes, with an emphasis on identifying disparities and vulnerabilities in this population. We hypothesized that people with mental disorders would be tested for COVID-19 less frequently than people without mental disorders and would also test positive more often when compared to people without mental disorders.

As an addition to the present thesis, in a published review in *Translational Psychiatry* we explored the barriers to implementing genetic testing in clinical psychiatry and proposed solutions to overcome them. Despite the rapid advancements in psychiatric genetics, the translation of genetic testing into clinical practice is hampered by various sociocultural, logistical, and ethical barriers (85). This review is part of our broader effort to integrate genetic testing into psychiatric practice to support our lifelong goal of improving access to quality, equitable, effective, personalized healthcare to individuals with schizophrenia around the globe.

II. Integration of Findings

This research is unified by a primary objective: rigorously testing various hypotheses in clinical practice and research on schizophrenia to inform more effective treatment strategies. This thesis aims to showcase the potential of integrating diverse data sources, from lab genetics and clinical neuroimaging to nationwide cohorts and big data, to advance our understanding of the etiology, diagnosis, and treatment of schizophrenia and psychotic disorders. However, it also highlights the challenges and limitations of applying these methodologies in clinical practice, emphasizing the need for further research and innovation to close the gap between basic science and clinical application. In the next section, we outline the key hypotheses and objectives that directed our research, reflecting our overarching aim of improving the lives of individuals with schizophrenia and related psychoses.

Hypotheses

1. Patients with the highest clinical severity will have the highest burden of polygenic risk score (PRS) for schizophrenia, followed by clozapine users, patients who have not required hospitalization or clozapine, their relatives and healthy controls.

2. Most real-world schizophrenia patients would not be eligible to participate in standard randomized clinical trials due to common exclusion criteria, and these excluded patients will have worse outcomes over the course of their illness.

3. Long-acting injectable antipsychotics demonstrate superior effectiveness in preventing relapse in real-world settings compared to oral formulations, despite limited differences observed in randomized controlled trials.

4. The prevalence of neuroimaging alterations in patients with early-onset psychotic disorders (<18 years) is higher than in community controls.

5. People with mental disorders are tested for COVID-19 less frequently than people without mental disorders and would test positive more often when compared to people without mental disorders.

Objectives

1. To examine whether the schizophrenia polygenic risk score (PRS-SCZ) can stratify patients with schizophrenia based on their clinical severity.

2. To describe the characteristics of the real-world schizophrenia population that is not represented in traditional randomized clinical trials due to exclusion criteria and to compare their clinical outcomes to those of RCT-eligible patients.

3. To compare the efficacy and effectiveness of antipsychotics for relapse prevention in schizophrenia by synthesizing data from randomized controlled trials and real-world evidence, with a particular focus on long-acting injectable formulations versus their oral counterparts.

4. To evaluate the prevalence and significance of brain magnetic resonance imaging (MRI) alterations in patients with early-onset psychotic disorders (<18 years) compared to community controls.

5. To describe the association between the frequency of COVID-19 testing and positivity rates in individuals with mental disorders compared to those without.

Materials, Methods, and Results

JAMA Psychiatry | Brief Report

Associations Between Polygenic Risk Score Loading, Psychosis Liability, and Clozapine Use Among Individuals With Schizophrenia

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IMPORTANCE Predictors consistently associated with psychosis liability and course of illness in schizophrenia (SCZ) spectrum disorders (SSD), including the need for clozapine treatment, are lacking. Longitudinally ascertained medication use may empower studies examining associations between polygenic risk scores (PRSs) and pharmacotherapy choices.

OBJECTIVE To examine associations between PRS-SCZ loading and groups with different liabilities to SSD (individuals with SSD taking clozapine, individuals with SSD taking other antipsychotics, their parents and siblings, and unrelated healthy controls) and between PRS-SCZ and the likelihood of receiving a prescription of clozapine relative to other antipsychotics.

DESIGN, SETTING, AND PARTICIPANTS This genetic association study was a multicenter, observational cohort study with 6 years of follow-up. Included were individuals diagnosed with SSD who were taking clozapine or other antipsychotics, their parents and siblings, and unrelated healthy controls. Data were collected from 2004 until 2021 and analyzed between October 2021 and September 2022.

EXPOSURES Polygenic risk scores for SCZ.

MAIN OUTCOMES AND MEASURES Multinomial logistic regression was used to examine possible differences between groups by computing risk ratios (RRs), ie, ratios of the probability of pertaining to a particular group divided by the probability of healthy control status. We also computed PRS-informed odd ratios (ORs) for clozapine use relative to other antipsychotics.

RESULTS Polygenic risk scores for SCZ were generated for 2344 participants (mean [SD] age, 36.95 years [14.38]; 994 female individuals [42.4%]) who remained after quality control screening (557 individuals with SSD taking clozapine, 350 individuals with SSD taking other antipsychotics during the 6-year follow-up, 542 parents and 574 siblings of individuals with SSD, and 321 unrelated healthy controls). All RRs were significantly different from 1; RRs were highest for individuals with SSD taking clozapine (RR, 3.24; 95% CI, 2.76-3.81; $P = 2.47 \times 10^{-46}$), followed by individuals with SSD taking other antipsychotics (RR, 2.30; 95% CI, 1.95-2.72; $P = 3.77 \times 10^{-22}$), parents (RR, 1.44; 95% CI, 1.25-1.68; $P = 1.76 \times 10^{-6}$), and siblings (RR, 1.40; 95% CI, 1.21-1.63; $P = 8.22 \times 10^{-6}$). Polygenic risk scores for SCZ were positively associated with clozapine vs other antipsychotic use (OR, 1.41; 95% CI, 1.22-1.63; $P = 2.98 \times 10^{-6}$), suggesting a higher likelihood of clozapine prescriptions among individuals with higher PRS-SCZ.

CONCLUSIONS AND RELEVANCE In this study, PRS-SCZ loading differed between groups of individuals with SSD, their relatives, and unrelated healthy controls, with patients taking clozapine at the far end of PRS-SCZ loading. Additionally, PRS-SCZ was associated with a higher likelihood of clozapine prescribing. Our findings may inform early intervention and prognostic studies of the value of using PRS-SCZ to personalize antipsychotic treatment.

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Supplemental content

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Group Information: The other members of the Genetic Risk and Outcome of Psychosis (GROUP) and Clozapine International Consortium (CLOZIN) Investigators appear in Supplement 2.

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Genetic factors are estimated to explain 60% to 80% of the liability to schizophrenia (SCZ). To date, 270 common risk loci contributing to SCZ have been identified,[1] highlighting the polygenic nature of SCZ. To summarize the aggregate risk that single-nucleotide polymorphisms (SNPs) may confer, polygenic risk score (PRS) analysis was developed.[2,3]

In bipolar disorder, PRS studies have evinced how polygenic liability is associated with lithium response and symptom severity,[4,5] showing promise for the use of PRSs to stratify patients and stage disorders. However, conflicting PRS findings are reported for disease severity and treatments in SCZ,[6,7] such as clozapine, a medication generally reserved for patients unresponsive to 2 or more trials of antipsychotic drugs.[8]

Here, by ascertaining the use of clozapine and other antipsychotics in relatively sizable, largely longitudinal, and well-characterized cohorts, we aimed to overcome some of the limitations of previous studies examining associations between PRS-SCZ and antipsychotic treatment choices. In addition, to deepen the understanding of possible differences in PRS-SCZ loading across a psychosis liability spectrum, we explored PRS-SCZ loading across individuals with SSD taking clozapine, those taking other antipsychotics during the 6-year follow-up, their relatives, and unrelated healthy controls.

Key Points

Question Are polygenic risk scores for schizophrenia (PRS-SCZ) associated with a psychosis liability spectrum and a clinician's decision to prescribe clozapine?

Findings In this genetic association study with 2344 participants from 2 cohorts, we found that PRS-SCZ loading was highest among individuals with schizophrenia spectrum disorders taking clozapine, followed by those taking other antipsychotics, their relatives, and unrelated healthy controls. In addition, PRS-SCZ was positively associated with a clozapine prescription relative to other antipsychotics.

Meaning While in this study PRS-SCZ loading increased with greater psychosis liability, in individuals with schizophrenia spectrum disorders and a relatively high PRS-SCZ, clozapine is more likely to be prescribed.

Methods

Data were collected from 2004 until 2021 and analyzed between October 2021 and September 2022. Ethical approval for all studies was obtained from the applicable institutional review boards in each country. The study was compliant with the Declaration of Helsinki (2013). All participants provided written informed consent.

Participants from the longitudinal Genetic Risk and Outcome in Psychosis (GROUP) cohort[9] were in 1 of the following 5 groups: individuals with SSD taking clozapine (n = 186, defined as clozapine use at ≥1 of the 3 time points during follow-up; with additional participants from the cross-sectional Clozapine International Consortium [CLOZIN] cohort, n = 687),[10] individuals with SSD for whom only antipsychotics other than clozapine had been recorded at 3 time points during the 6-year follow-up (n = 524), their siblings (n = 731) and parents (n = 695), and unrelated healthy controls (n = 369). GROUP and CLOZIN (3192 participants in total) are observational cohorts conceived to elucidate genetic determinants of SSD (eMethods in Supplement 1).

Genotyping, genotype- and participant-level quality control, genotype imputation, PRS procedures, and computation of explained variances are based on previously described methods (eMethods, eTables 1 and 2, and eFigure 1 in Supplement 1).[9,10] Polygenic risk scores for SCZ were derived from a European-ancestry study[1] and generated by applying a bayesian framework method that uses continuous shrinkage (cs) on SNP effect sizes. PRS-cs-auto is robust to varying genetic architectures, provides substantial computational advantages, and enables multivariate modeling of local linkage disequilibrium patterns (eTable 3 and eMethods in Supplement 1).[11]

We used multinomial logistic regression (using the multinom function in the nnet R package)[12,13] to assess possible differences in mean PRS-SCZ across the 5 groups: individuals with SSD taking clozapine, individuals with SSD taking other antipsychotics, their siblings, their parents, and unrelated healthy controls. Risk ratios (RRs) were defined as ratios of the probability of pertaining to 1 of 4 groups divided by the probability of being an unrelated healthy control.[12]

We then examined associations between PRS-SCZ and clozapine prescribing decisions by using logistic regression models of PRS-SCZ on medication status (clozapine vs other antipsychotics). We also grouped individuals into PRS quintiles and estimated odds ratios (ORs) by logistic regression for SCZ case-control status (unrelated healthy controls vs clozapine users and vs other antipsychotic users), as well as medication status in each quintile relative to the lowest risk quintile. Sensitivity analyses accounting for possible influences of covariates and PRS methodology were conducted to verify the robustness of our findings (eMethods in Supplement 1). Precision estimates are given using 95% CI. The statistical significance threshold was Bonferroni corrected (multinomial regression: $P < .05/12 = .004$; regular logistic regression: $P < .05/3 = .017$).

Results

Polygenic risk scores for SCZ were generated for the 2344 participants (mean [SD] age, 36.95 years [14.38]; 994 female individuals [42.4%]) remaining after quality control (**Figure 1**; eTables 3 and 4 in Supplement 1). All RRs were significantly different from 1 (Figure 1; eTable 5 in Supplement 1). Risk ratios were highest in individuals with SSD taking clozapine (RR, 3.24; 95% CI, 2.76-3.81; $P = 2.47 \times 10^{-46}$), followed by those taking other antipsychotics (RR, 2.30; 95% CI, 1.95-2.72; $P = 3.77 \times 10^{-22}$), parents (RR, 1.44; 95% CI, 1.25-1.68; $P = 1.76 \times 10^{-6}$), and siblings (RR, 1.40; 95% CI, 1.21-1.63; $P = 8.22 \times 10^{-6}$).

In addition, PRS-SCZ was positively associated with clozapine use (OR for clozapine vs other antipsychotic use, 1.41; 95%

CI, 1.22-1.63; $P = 2.98 \times 10^{-6}$) (**Table**). Odds ratios increased with greater numbers of SCZ risk alleles in each group, reaching the maximum OR for the fifth quintile when comparing individuals taking clozapine with unrelated healthy controls (OR, 38.21; 95% CI, 18.96-78.11) (**Figure 2**A and B).

Furthermore, compared with those in the first PRS-SCZ quintile, individuals in the fifth PRS quintile had the highest odds of receiving a clozapine prescription relative to another antipsychotic (OR, 2.50; 95% CI, 1.80-3.93) (Figure 2C). Finally, results of all sensitivity analyses aligned with all aforementioned findings (eResults, eTables 5 and 6, and eFigures 2, 3, 4, and 5 in Supplement 1).

Discussion

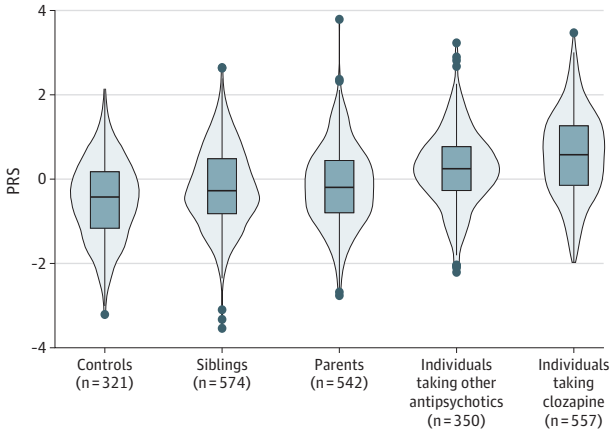
To our knowledge, this is the first study comparing PRS-SCZ across a 5-group psychosis liability spectrum. By applying a range of analyses, we consistently demonstrate that individuals taking clozapine have the highest PRS-SCZ loading, followed by individuals using other antipsychotics, their relatives, and unrelated healthy controls. Moreover, PRS-SCZ was positively associated with the likelihood of receiving a prescription of clozapine vs another antipsychotic.

Clinical psychiatry decision-making is informed by a range of features; for example, episode severity and recurrence rates may guide relapse prevention efforts. Although in our study the variance explained by PRS in medication status (clozapine or other antipsychotics) was modest (2.6%), implications of our findings include the potential of combining clinical features with PRSs to stratify individuals with first-episode psychosis. Thus, estimates of likelihoods to determine individuals' future need of clozapine use could one day become more precise. Future studies may establish how integrating clinical features with PRSs may allow for personalized interventions (eAppendix in Supplement 1).

Strengths and Limitations

Strengths of our study include the 6-year follow-up, the sample size for a genetic study with pharmacotherapeutic data, and the diversity of analyses all pointing to similar strengths and directions of associations. Limitations include the lack of symptom-level data, daily functioning, and relapse data longitudinally, as well as a lack of additional groups of patients (eg, individuals with first-episode psychosis) from multiple ancestries. Future work should include such data to assess whether PRS-SCZ improves prediction models of clozapine prescription probability relative to clinical features alone and to allow for further comparisons between a wider range of SCZ groups. Second, although antipsychotic use in the GROUP cohort was assessed at 3 time points during a 6-year follow-up period, we cannot rule out that these individuals were prescribed clozapine later in life. On a similar note, medication use in the GROUP cohort was verified for the 6 months predating cohort entry. However, because all GROUP participants reported 2 or fewer lifetime psychotic episodes at study entry, and clozapine guidelines stipulating that clozapine be considered after 2 or more failed antipsychotic trials are strictly followed in the Netherlands, it is highly unlikely that individuals had been taking clozapine before cohort entry. Additionally, our approach is conservative as such possible former clozapine users and late-in-life clozapine users were currently classified as using other antipsychotics.

Figure 1. Scaled Distributions of Polygenic Risk Scores for Schizophrenia (PRS-SCZ)



Individuals with schizophrenia spectrum disorders who were taking clozapine had the highest PRS-SCZ, followed by individuals taking other antipsychotics, parents, siblings, and controls. All differences were statistically significant (*t* test $P < .001$), except for the parents-siblings comparison (eTable 7 in Supplement 1). PRS-SCZ was *z* scored in all samples and visualized per group. The mean PRS-SCZ is 0; hence, PRS values for controls are lower than 0. The bar in the middle of the box plot is the median PRS-SCZ for individuals in each group. The box plot rectangle is delimited by the 25th and 75th percentiles. The widths of the violins reflect the data distributions; the dots represent outliers outside the interval (Q1 − 1.5 × IQR; Q3 + 1.5 × IQR, where Q indicates quartile).

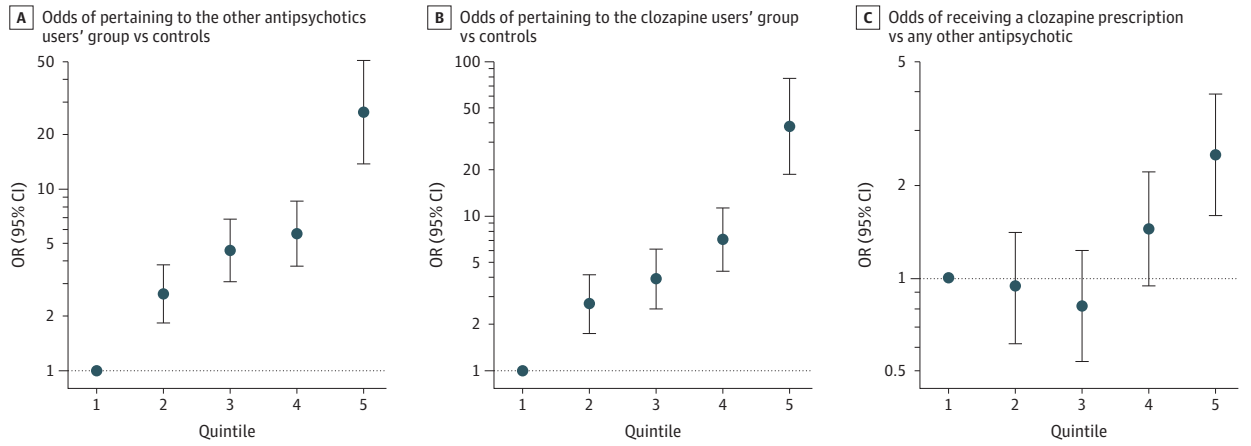
Table. Odds of Antipsychotic Prescriptions and Explained Variances Based on PRS-SCZ in Individuals With SSD

Model	Case (No. of individuals)	Control (No. of individuals)	R^2 observed, 50:50[a]	OR (95% CI)	*P* value of logistic regression OR
1	Clozapine (557)	Other antipsychotics (350)	2.59	1.41 (1.22-1.63)	2.98×10^{-6}
2	Clozapine (557)	Controls (321)	22.05	2.99 (2.51-3.57)	3.57×10^{-34}
3	Other antipsychotics (350)	Controls (321)	13.99	2.45 (2.02-2.98)	1.82×10^{-19}
4	Any antipsychotic (907)	Controls (321)	18.45	2.75 (2.35-3.22)	3.49×10^{-36}

Abbreviations: OR, odds ratio; PRS, polygenic risk score; SCZ, schizophrenia; SSD, schizophrenia spectrum disorders.

[a] Variance explained on the observed scale R^2 with 50:50 ascertainment. When transforming variance explained in SSD-control status (model 4; 18.45%) to the liability scale (with an approximate prevalence of SSD = 0.01), an explained variance of 13.78% is found, which is in line with previous findings.[1] (The eMethods section in Supplement 1 contains details.)

Figure 2. Odds Ratios by Polygenic Risk Profile



Odds ratios (ORs) increased with greater number of schizophrenia risk alleles in each group, with maximums reached in the fifth quintiles for individuals with schizophrenia spectrum disorders who were taking other antipsychotics relative to controls (panel A: OR, 26.41; 95% CI, 13.72-50.84), for clozapine users relative to controls (panel B: OR, 38.21; 95% CI, 18.96-78.11), and for clozapine users relative to users of other antipsychotics (panel C: OR, 2.50; 95% CI, 1.80-3.93). Odds ratios are shown in a log scale on the y-axis by genetic risk score profile; note the change in scale on each y-axis. Polygenic risk scores were divided into quintiles (1 = lowest, 5 = highest), and 4 dummy variables were created to contrast quintiles 2 through 5 to quintile 1 as reference. Odds ratios and 95% CIs were estimated using logistic regression.

Conclusions

In this study, PRS-SCZ loading differed between groups of individuals with SSD, their relatives, and unrelated healthy controls, with patients taking clozapine at the far end of PRS-SCZ loading. In addition, PRS-SCZ was associated with a higher likelihood of clozapine prescribing. Our findings add to a growing body of evidence showing that PRS loading varies across mental illness categories within the same diagnostic spectrum. Moreover, the results described here illustrate how individuals who are prescribed an advanced-step treatment modality may be at the far extreme of PRS-SCZ loading relative to other liability groups. The association between PRS-SCZ and clozapine prescription we uncovered sets the stage for projects probing the utility of PRSs in personalizing treatment for individuals with SSD.

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JAMA Psychiatry | Original Investigation

Representation and Outcomes of Individuals With Schizophrenia Seen in Everyday Practice Who Are Ineligible for Randomized Clinical Trials

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IMPORTANCE Most evidence about efficacy and safety of antipsychotics in schizophrenia spectrum disorders relies on randomized clinical trials (RCTs). However, owing to their strict eligibility criteria, RCTs represent only a part of the real-world population (ie, unselected patients seen in everyday clinical practice), which may result in an efficacy-effectiveness gap.

OBJECTIVE To quantify the proportion of real-world individuals with schizophrenia spectrum disorders who would be ineligible for participation in RCTs, and to explore whether clinical outcomes differ between eligible and ineligible individuals.

DESIGN, SETTING, AND PARTICIPANTS This study applied eligibility criteria typically used in RCTs for relapse prevention in schizophrenia spectrum disorders to real-world populations. Individuals with diagnoses of schizophrenia spectrum disorders recorded in national patient registries in Finland and Sweden were identified. Individuals who had used antipsychotics continuously for 12 weeks in outpatient care were selected. Individuals were followed up for up to 1 year while they were receiving maintenance treatment with any second-generation antipsychotic (excluding clozapine). Follow-up was censored at treatment discontinuation, initiation of add-on antipsychotics, death, and end of database linkage.

MAIN OUTCOMES AND MEASURES Proportions of RCT-ineligible individuals with schizophrenia spectrum disorders owing to any and specific RCT exclusion criteria. The risk of hospitalization due to psychosis within 1-year follow-up in ineligible vs eligible persons were compared using hazard ratios (HR) and corresponding 95% CIs.

RESULTS The mean (SD) age in the Finnish cohort (n = 17 801) was 47.5 (13.8) years and 8972 (50.4%) were women; the mean (SD) age in the Swedish cohort (n = 7458) was 44.8 (12.5) years and 3344 (44.8%) were women. A total of 20 060 individuals (79%) with schizophrenia spectrum disorders would be ineligible for RCTs (Finnish cohort: 14 221 of 17 801 [79.9%]; Swedish cohort: 5839 of 7458 [78.3%]). Most frequent reasons for ineligibility were serious somatic comorbidities and concomitant antidepressant/mood stabilizer use. Risks of hospitalization due to psychosis was higher among ineligible than eligible individuals (Finnish cohort: 18.4% vs 17.2%; HR, 1.14 [95% CI, 1.04-1.24]; Swedish cohort: 20.1% vs 14.8%; HR, 1.47 [95% CI, 1.28-1.92]). The largest risks of hospitalization due to psychosis were observed in individuals ineligible owing to treatment resistance, tardive dyskinesia, and history of suicide attempts. Finally, with more ineligibility criteria met, larger risks of hospitalization due to psychosis were observed in both countries.

CONCLUSIONS AND RELEVANCE RCTs may represent only about a fifth of real-world individuals with schizophrenia spectrum disorders. Underrepresented (ineligible) patients with schizophrenia spectrum disorders have moderately higher risks of admission due to psychosis while receiving maintenance treatment than RCT-eligible patients. These findings set the stage for future studies targeting real-world populations currently not represented by RCTs.

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Supplemental content

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Most evidence about efficacy and safety of medical treatments is based on randomized clinical trials (RCTs), which are highly standardized, systematic studies. RCT outcomes (efficacy) may differ from the utility of interventions in routine clinical practice (effectiveness), in what has been termed the efficacy-effectiveness gap. Efficacy-effectiveness gaps have been identified in several health care areas, including pneumology,[1,2] oncology,[3] infectology,[4] and internal medicine[5]; nonpharmacological interventions in psychology[6]; and antidepressants.[7]

A possible efficacy-effectiveness gap in effectiveness and safety of antipsychotics in individuals with schizophrenia, which, to our knowledge, has not been investigated so far, may stem from the strict exclusion criteria applied in typical RCTs aiming at marketing approval. Therefore, a broad and diverse set of individuals is excluded from these trials, such as those experiencing suicidal ideations, substance use disorders, or somatic and psychiatric comorbidities. Such excluded people may have different courses of illness and possibly also different treatment outcomes.

Here, we aimed to quantify the real-world population (ie, unselected patients seen in everyday clinical practice) not directly represented in RCTs, ie, those who are ineligible owing to any RCT exclusion criteria, as well as the real-world populations ineligible owing to specific exclusion criteria. Moreover, we assessed whether there are differences in key outcomes between individuals who are potentially eligible and those who are not (overall and for specific RCT exclusion criteria). To answer these research questions, we analyzed data from real-world populations in 2 nationwide registries.

Key Points

Question What percentage of patients with schizophrenia in the real world are represented in randomized clinical trials (RCTs) and do their outcomes differ from those not represented in RCTs?

Findings In this study of 25 259 real-world individuals with diagnoses of schizophrenia spectrum disorders recorded in national patient registries in Finland and Sweden, about a fifth were represented in RCTs and their outcomes were better than of those individuals with schizophrenia not meeting RCT inclusion criteria.

Meaning Future research should consider the heterogeneity of individuals with schizophrenia and the patient groups typically ineligible for participation; RCTs may become more inclusive by representing a broader spectrum of individuals with schizophrenia and by targeting specific currently underrepresented groups.

Methods

In this analysis, we simulated the application of typical inclusion and exclusion criteria of RCTs conducted in individuals with schizophrenia (eAppendix 1 in the Supplement) to the national patient registries of Finland and Sweden. The protocol for our analysis was registered on the Open-Science Framework prior to analysis on September 15, 2020,[8] and we complied with the Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) reporting guideline (eAppendix 2 in the Supplement).[9] The Regional Ethics Board of Stockholm approved this research project (decision 2007/762-31). Permissions were also granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission THL/847/5.05.00/2015), the Social Insurance Institution of Finland (65/522/2015), and Statistics Finland (TK53-1042-15). The study was registry based, and no contact was made with the participants of the study; therefore, according to legislation in both countries, obtaining informed consent from participants was not required.

Real-World Databases Used and Follow-up

We had access to the data extracted from the national patient registries in Finland (January 2005-December 2017) and Sweden (January 2006-December 2016) (eAppendix 1A in the Supplement includes details about the cohorts), which here represent real-world individuals with schizophrenia and schizoaffective disorder (referred to from here on as *schizophrenia*). Pseudonymized data were originally extracted by the register maintainers via personal identity codes, which enable data linkage between registries of both countries. Personal identity codes were replaced with research identity codes before data were shared with the researchers. We chose 2 registries to assess similarity in findings across countries and reduce the likelihood of chance findings.

In both registries, we first focused on individuals hospitalized at least once owing to schizophrenia and who used second-generation antipsychotics at the start of follow-up because those are the typical interventions in modern RCTs[10] and also the most used antipsychotics in Finland and Sweden nowadays.[11] We did not consider individuals using clozapine or first-generation antipsychotics because the former is not a first-line treatment but reserved for treatment resistance (here defined as clozapine or electroconvulsive therapy treatment, reported ever before follow-up), and the latter are only rarely used in real-world clinical practice in Finland and Sweden.[11] Continuous medication use was derived using the PRE2DUP method from dispensed prescriptions.[12]

The duration of follow-up was 12 months as this is a typical duration of relapse-prevention RCTs,[10] with time zero defined as when the inclusion criteria were fulfilled, ie, after 12 weeks of continuous antipsychotic use in monotherapy as an outpatient. We chose this 12-week criterion to ensure clinical stability of schizophrenia in maintenance treatment with antipsychotics, which is a starting point for relapse prevention trials. We censored follow-up at discontinuation of antipsychotics, hospitalization (other types than analyzed as outcome event), death, after the defined follow-up time, and end of data linkage. For details about patient involvement and data sharing options, see the eMethods in the Supplement.

Outcomes and Statistical Analyses

By applying to these databases the standard RCT inclusion and exclusion criteria mentioned in the eMethods (eAppendix 1A) in the Supplement, we defined populations consisting of:

1. Individuals potentially eligible for standard RCTs about relapse prevention with antipsychotics (ie, meeting all inclusion criteria but having none of the exclusion criteria);

Table 1. Characteristics of Individuals Included (Individuals Without Any Exclusion Criteria) vs Excluded (After Application Of All Exclusion Criteria) for Randomized Clinical Trials

Characteristic	No. (%)			
	Finnish cohort (n = 17 801)		Swedish cohort (n = 7458)	
	Eligible (n = 3580)	Ineligible (n = 14 221)	Eligible (n = 1619)	Ineligible (n = 5839)
Male	1837 (51.3)	6992 (49.2)	962 (59.4)	3152 (54.0)
Female	1743 (48.7)	7229 (50.8)	657 (40.6)	2687 (46.0)
Age, y				
<18	0	26 (0.2)	0	9 (0.2)
18-30	676 (18.9)	2470 (17.4)	205 (12.7)	770 (13.2)
31-45	1016 (28.4)	3624 (25.5)	627 (38.7)	1892 (32.4)
46-65	1888 (52.7)	6332 (44.5)	787 (48.6)	2774 (47.5)
>65	0	1769 (12.4)	0	394 (6.8)
Age, mean (SD), y	45.6 (12.3)	47.9 (14.1)	44.9 (11.2)	46.5 (12.8)
Schizoaffective disorder	385 (10.8)	3459 (24.3)	232 (14.3)	2045 (35.0)
Disability pension	NA	NA	1320 (81.5)	4985 (85.4)

Abbreviation: NA, not applicable.

2. Individuals ineligible for such an RCT for any reason (ie, meeting all inclusion criteria but having ≥1 exclusion criteria);
3. Individuals ineligible for such an RCT owing to each specific exclusion criterion (ie, forming subpopulations of ineligible individuals owing to age, substance use, risk of suicide, treatment resistance, serious somatic disease, mood stabilizer or antidepressant use, intellectual disability, tardive dyskinesia, or pregnancy/breastfeeding).

We summarized relevant baseline characteristics and report the distribution of the prescribed antipsychotics (for the most commonly used drugs)[11] of the eligible and ineligible populations. Based on previous knowledge,[11] we categorized most commonly prescribed antipsychotics in these cohorts as olanzapine, quetiapine, risperidone, and aripiprazole, while the rest were grouped as either any long-acting injectable (LAI) antipsychotic or other oral antipsychotics.

The primary outcome was hospitalization due to psychosis (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes F20-F29). Secondary outcomes were hospitalization due to any psychiatric reason (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes F00-F99), all-cause hospitalization, the need for add-on antipsychotics, and all-cause discontinuation of antipsychotic use. To verify the robustness of our results for different time points, in addition to the main analyses at 12 months, we conducted analyses for the primary outcome at 6 months and 9 months of follow-up. Additionally, as sensitivity analyses, we applied the same primary outcome analyses to separate cohorts of (1) clozapine users and (2) individuals only treated in outpatient care (eAppendix 1A in the Supplement).

To compare potential differences in the risk of these outcomes between eligible and ineligible individuals, we calculated hazard ratios (HRs) and their 95% CIs using a Cox regression model with eligible individuals as reference. Proportional hazards assumption was tested and complied with by plotting Kaplan-Meier curves and via Schoenfeld residuals. To shed light on the associations of specific exclusion criteria with the primary outcome, we additionally compared individuals with a given exclusion criterion with eligible individuals. We also compared the primary outcome between individuals who met 1, 2, or 3 or more exclusion criteria with those of eligible individuals. We conducted all analyses using SAS statistical software version 9.4 (SAS Institute) between November 2020 and May 2021. We calculated 95% CIs to provide estimates of the accuracy of our population parameters. *P* values are only reported in Tables as additional measures of the magnitude and precision of the differences, but we do not characterize results as statistically significant or according to some arbitrary *P* value threshold.

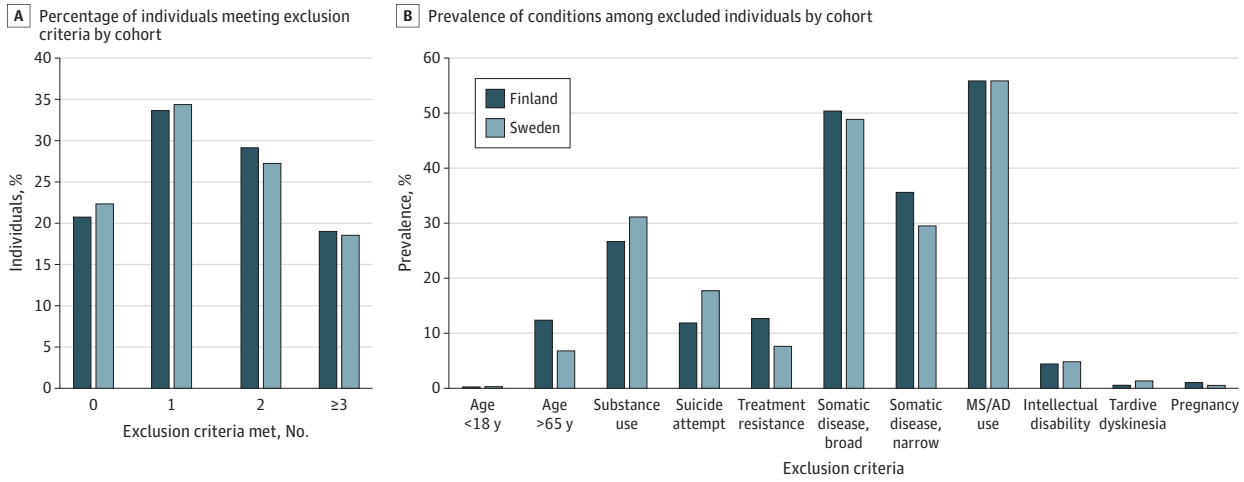
Results

Proportions, Descriptive Statistics, and Antipsychotic Use in Eligible and Ineligible Populations

The mean (SD) age in the Finnish cohort (n = 17 801) was 47.5 (13.8) years, and 8972 (50.4%) were women; the mean (SD) age in the Swedish cohort (n = 7458) was 44.8 (12.5) years, and 3344 (44.8%) were women. In the Finnish cohort, 3580 individuals (20.1%) were eligible for RCT participation; 14 221 (79.9%) met at least 1 exclusion criterion and were thus ineligible. Similarly, in the Swedish cohort, 1619 individuals (21.7%) were eligible for RCTs, and 5839 (78.3%) were ineligible.

There were no major differences in the distribution of age and sex between eligible and ineligible individuals (**Table 1**). Individuals who were ineligible for RCTs were more likely to use oral quetiapine (Finland: 3735 [26.3%] vs 612 [17.1%]; Sweden: 809 [13.9%] vs 110 [6.8%]; eFigure 1 in the Supplement). LAI antipsychotics were prescribed less frequently to ineligible than to eligible individuals (Finland: 1767 [12.4%] vs 753 [21.0%]; Sweden: 1075 [18.4%] vs 390 [24.1%]; eFigure 1 in the Supplement). In the Swedish data set where information on disability pension was available, ineligible individuals were somewhat more likely (4985 [85.4%]) to receive disability pension than eligible ones (1320 [81.5%]), indicating more severe decline in occupational function.

Figure. Distribution of the Number of Exclusion Criteria Met and Prevalence of Specific Conditions Among Persons Ineligible for Randomized Clinical Trials



A, Percentage of individuals in the cohorts who fulfilled none, 1, 2, or ≥3 exclusion criteria in the Finnish and Swedish cohorts. B, Prevalence (%) of specific conditions among individuals ineligible for randomized clinical trials in the Finnish and Swedish cohorts. AD indicates antidepressant; MS, mood stabilizer.

Ineligibility Reasons and Subpopulations

In the Finnish and Swedish cohorts, 5875 (33.0%) and 2514 (33.7%), respectively, fulfilled only 1 exclusion criterion, while 3271 (18.4%) and 1338 (17.9%), respectively, met 3 or more criteria (**Figure**, A). The most frequent reasons for ineligibility were serious somatic comorbidities (broad definition: 7202 [51%] and 2866 [49%]; narrow: 5287 [36%] and 1747 [30%] in Finland and Sweden, respectively) and concomitant use of mood stabilizers or antidepressants (7983 [56%] and 3281 [56%]), followed by a history of substance use (3808 [27%] and 1828 [31%]) and suicide risk (1690 [12%] and 1032 [18%]) (Figure, B).

Subpopulations ineligible owing to specific exclusion criteria had variation in age and sex distributions (eTable 1A and B in the Supplement). The proportion of men was highest in those excluded owing to substance use (2510 men [65.9%] in the Finnish cohort and 1230 [67.3%] in the Swedish cohort), whereas those excluded owing to age (almost entirely owing to age >65 years) were mainly women (687 men [38.3%] in the subgroup of the Finnish cohort excluded owing to age and 143 [36.3%] in the Swedish cohort). There was significant overlap between specific exclusion criteria with each other. Besides obvious overlap between broad and narrow definitions of serious somatic comorbidities, those with a history of suicide attempt often also had substance use (Finnish cohort: 882 [52%]; Swedish cohort: 533 [52%]) and mood stabilizers/antidepressants use (1009 [58%] in the Finnish and 603 [60%] in the Swedish cohorts) and those with tardive dyskinesia had serious somatic conditions (24 [60%] and 47 [63%] in the Finnish and Swedish cohorts, respectively) and mood stabilizers/antidepressants use (24 [60%] and 36 [48%] in the Finnish and Swedish cohorts, respectively).

Olanzapine was the most frequently prescribed antipsychotic across specific subpopulations (eFigures 2 and 3 in the Supplement). Quetiapine replaced olanzapine as the most frequently prescribed antipsychotic among those with a history of suicide attempts and among those with tardive dyskinesia in the Finnish cohort. Risperidone was equally commonly prescribed among pregnant or breastfeeding individuals as olanzapine in the Swedish cohort. In Finland, LAI antipsychotics were used in about 10% of all individuals in most subpopulations (except substance use), while in Sweden the use of LAI antipsychotics was more frequent: almost 20% in all groups (except mood stabilizers/antidepressants users).

Primary and Secondary Outcomes in Eligible and Ineligible Populations

During the 12 months of follow-up, individuals who would be ineligible for RCTs were more likely to be hospitalized owing to psychosis, compared with eligible individuals (Finnish cohort: 2609 [18.4%] vs 615 [17.2%]; HR, 1.14 [95% CI, 1.04-1.24]; Swedish cohort: 1174 [20.1%] vs 240 [14.8%]; HR, 1.47 [95% CI, 1.28-1.92]). Similar risk estimates were observed for 6- and 9-month follow-up times (**Table 2**).

Compared with eligible individuals, individuals who were ineligible for RCTs had increased risks of any psychiatric hospitalization (HR, 1.34 [95% CI, 1.23-1.45]) in the Finnish cohort; HR, 1.74 [95% CI, 1.52-1.99] in the Swedish cohort) and for all-cause hospitalization (HR, 1.55 [95% CI, 1.43-1.68] in the Finnish cohort; HR, 1.77 [95% CI, 1.55-2.03] in the Swedish cohort; **Table 3**). In the Swedish cohort, ineligible persons had a higher risk for needing an additional antipsychotic than eligible persons (HR, 1.31 [95% CI, 1.15-1.48]), which was not observed in the Finnish cohort (HR, 1.06 [95% CI, 0.96-1.17]). The risk of all-cause antipsychotic discontinuation did not differ between ineligible and eligible individuals (Table 3).

Primary Outcome in Subpopulations Ineligible for Specific Reasons

The largest risks of hospitalization due to psychosis were observed in individuals ineligible owing to treatment resistance, tardive dyskinesia, and history of suicide attempts

Table 2. Risk of Hospitalization Due to Psychosis in Individuals Ineligible (After Application of ≥1 Exclusion Criteria) vs Eligible (Persons Without Any Exclusion Criterion)

Eligibility	Finnish cohort					Swedish cohort				
	No. of individuals	No. (%) with event	Time to event/ censoring, mean (SD), d	HR (95% CI)[a]	*P* value	No. of individuals	No. (%) with event	Time to event/ censoring, mean (SD), d	HR (95% CI)[a]	*P* value
Main outcome analyses: hospitalization due to psychosis, 12 mo										
Eligible	3580	615 (17.2)	278 (130)	1.14 (1.04-1.24)	.005	1619	240 (14.8)	273 (127)	1.47 (1.28-1.92)	<.001
Ineligible	14 221	2609 (18.4)	257 (137)			5839	1174 (20.1)	248 (137)		
Alternative time period 1: hospitalization due to psychosis, 6 mo										
Eligible	3580	443 (12.4)	154 (56)	1.15 (1.03-1.27)	.01	1619	166 (10.3)	156 (53)	1.49 (1.26-1.75)	<.001
Ineligible	14 221	1939 (13.6)	147 (60)			5839	835 (14.3)	145 (60)		
Alternative time period 2: hospitalization due to psychosis, 9 mo										
Eligible	3580	537 (15.0)	218 (93)	1.15 (1.05-1.26)	.004	1619	212 (13.1)	218 (89)	1.45 (1.25-1.69)	<.001
Ineligible	14 221	2327 (16.4)	205 (98)			5839	1033 (17.7)	200 (99)		

Abbreviation: HR, hazard ratio.

[a] An HR >1 means higher risk in the ineligible group. Primary analyses were with 12-month follow-up and sensitivity analyses with 6 and 9 months.

Table 3. Risk of Secondary Outcomes in Individuals Ineligible (After Application of ≥1 Exclusion Criteria) vs Eligible (Individuals Without Any Exclusion Criteria) at 12-Month Follow-up

Eligibility	Finnish cohort				Swedish cohort			
	No. (%) with event	Time to event/ censoring, mean (SD)	HR (95% CI)[a]	*P* value	No. (%) with event	Time to event/ censoring, mean (SD)	HR (95% CI)[a]	*P* value
Hospitalization due to any psychiatric reason								
Eligible	643 (18.0)	278 (131)	1.34 (1.23-1.45)	<.001	251 (15.5)	273 (127)	1.74 (1.52-1.99)	<.001
Ineligible	3202 (22.5)	256 (138)			1440 (24.7)	246 (138)		
All-cause hospitalization								
Eligible	694 (19.4)	280 (130)	1.55 (1.43-1.68)	<.001	250 (15.4)	273 (127)	1.77 (1.55-2.03)	<.001
Ineligible	4011 (28.2)	259 (136)			1478 (25.31)	246 (138)		
Need for additional antipsychotic								
Eligible	454 (12.7)	254 (138)	1.06 (0.96-1.17)	.28	286 (17.7)	238 (137)	1.31 (1.15-1.48)	<.001
Ineligible	1783 (12.5)	233 (141)			1221 (20.9)	211 (141)		
All-cause discontinuation of antipsychotic use								
Eligible	570 (15.9)	280 (130)	1.03 (0.94-1.13)	.59	408 (25.2)	275 (126)	1.01 (0.90-1.12)	.91
Ineligible	2191 (15.4)	259 (137)			1370 (23.5)	251 (136)		

Abbreviation: HR, hazard ratio.

[a] An HR >1 means higher risk in the ineligible group.

(**Table 4**). Finally, with more ineligibility criteria met, larger risks of hospitalization due to psychosis were observed in both countries (eResults and eTables 2 and 3 in the Supplement).

Sensitivity analysis in the cohort of clozapine users uncovered similar proportions of individuals being ineligible (5806 [81.6%] in the Finnish cohort and 1346 [80.2%] in the Swedish cohort) for RCTs as in the main analyses (eTable 4 in the Supplement). Results from the second sensitivity analysis were also similar to the primary analysis: of 4727 individuals treated in outpatient care only, 3508 (74.2%) were ineligible for RCT participation (eTable 5 in the Supplement).

Discussion

In this study, we applied typical inclusion and exclusion criteria of RCTs to the real-world populations of individuals with schizophrenia in Finnish and Swedish national registries. We found that almost 80% of individuals with schizophrenia would be ineligible to participate in typical RCTs and are therefore not represented in them. The most frequent reasons for ineligibility observed in the 2 cohorts were serious somatic comorbidities and concomitant use of mood stabilizers or antidepressants, followed by history of substance use and risk of suicide. Furthermore, we found that RCT-ineligible real-world individuals had, on average, a moderately higher risk for rehospitalization due to psychosis while receiving maintenance treatment with antipsychotics. This increased risk was observed in several subpopulations, ie, individuals ineligible for specific reasons such as substance use, risk of suicide, treatment resistance, or tardive dyskinesia. Moreover, ineligible individuals appeared to have a higher burden of psychiatric and somatic comorbidities, as indicated by increased psychiatric and any-reason hospitalization rates.

Table 4. Risk of Hospitalization Due to Psychosis Within 12 Months of Follow-up for the Population of Individuals Remaining After Applying Each Specific Exclusion Criterion Separately Compared With Individuals Who Did Not Meet Any Exclusion Criteria (Eligible Group)

	Finnish cohort					Swedish cohort				
Eligibility	No. of individuals	Relapsed, No. (%)	Time to event/ censoring, mean (SD), d	HR (95% CI)[a]	*P* value	No. of individuals	Relapsed, No. (%)	Time to event/ censoring, mean (SD), d	HR (95% CI)[a]	*P* value
Age <18 and >65 y										
Eligible	3580	615 (17.2)	278 (130)	0.71 (0.61-0.83)	<.001	1619	240 (14.8)	273 (127)	1.04 (0.78-1.38)	.80
Ineligible	1795	212 (11.8)	267 (133)			403	60 (14.9)	264 (131)		
Substance use										
Eligible	3580	615 (17.2)	278 (130)	1.43 (1.29-1.59)	<.001	1619	240 (14.8)	273 (127)	1.88 (1.61-2.21)	<.001
Ineligible	3808	801 (21.0)	228 (143)			1828	430 (23.5)	224 (140)		
Suicide attempt										
Eligible	3580	615 (17.2)	278 (130)	1.61 (1.42-1.83)	<.001	1619	240 (14.8)	273 (127)	2.13 (1.79-2.54)	<.001
Ineligible	1690	395 (23.4)	225 (144)			1032	270 (26.2)	219 (141)		
Treatment resistance										
Eligible	3580	615 (17.2)	278 (130)	1.71 (1.52-1.93)	<.001	1619	240 (14.8)	273 (127)	2.31 (1.87-2.85)	<.001
Ineligible	1805	476 (26.4)	242 (143)			450	134 (29.8)	233 (141)		
Serious somatic disease, broader definition										
Eligible	3580	615 (17.2)	278 (130)	1.09 (0.99-1.20)	.09	1619	240 (14.8)	273 (127)	1.53 (1.31-1.77)	<.001
Ineligible	7202	1247 (17.3)	252 (138)			2866	586 (20.5)	243 (139)		
Serious somatic disease, narrower definition										
Eligible	3580	615 (17.2)	278 (130)	1.10 (0.99-1.22)	.08	1619	240 (14.8)	273 (127)	1.58 (1.34-1.86)	<.001
Ineligible	5087	877 (17.2)	247 (139)			1747	361 (20.7)	236 (138)		
Mood stabilizer/antidepressant concomitant use										
Eligible	3580	615 (17.2)	278 (130)	1.10 (1.01-1.22)	.03	1619	240 (14.8)	273 (127)	1.51 (1.30-1.75)	<.001
Ineligible	7983	1456 (18.2)	262 (135)			3281	682 (20.8)	251 (136)		
Intellectual disability										
Eligible	3580	615 (17.2)	278 (130)	0.98 (0.79-1.21)	.83	1619	240 (14.8)	273 (127)	1.19 (0.87-1.62)	.28
Ineligible	622	102 (16.4)	269 (133)			282	47 (16.7)	257 (133)		
Tardive dyskinesia										
Eligible	3580	615 (17.2)	278 (130)	1.77 (0.95-3.31)	.07	1619	240 (14.8)	273 (127)	2.13 (1.36-3.32)	<.001
Ineligible	40	10 (25.0)	211 (137)			75	21 (28.0)	235 (129)		
Pregnant or breastfeeding women										
Eligible	3580	615 (17.2)	278 (130)	0.87 (0.55-1.37)	.55	1619	240 (14.8)	273 (127)	1.29 (0.53-3.13)	.57
Ineligible	143	19 (13.3)	240 (145)			30	5 (16.7)	237 (148)		

Abbreviation: HR, hazard ratio.

[a] An HR >1 means higher risk in the ineligible group.

We envision the following implications of our findings. Because we showed that the majority of individuals with schizophrenia are not represented by typical RCTs and that clinical outcomes can differ between eligible and ineligible individuals, targeted RCTs, subgroup analyses of RCTs with broader inclusion criteria, and observational cohorts focusing on underrepresented subpopulations are warranted. To date, only a few RCTs have been conducted in specific patient groups.[13-15] Additionally, because approximately 50% of ineligible individuals met somatic comorbidities exclusion criteria in our study, risks of adverse effects and their potential serious consequences as well as the risk of clinically significant pharmacological interactions could be higher in real-world populations than in RCTs. This may require clinical attention and further research after pivotal RCTs and drug market approval.[16] The latter could exploit the potential offered by electronic health records for screening and recruiting trial participants and therefore enrich their real-world representativeness. It also underlines the importance of aftermarket/postapproval studies (ie, phase 4 studies) requested by regulators and conducted by pharmaceutical companies to particularly investigate the safety of new treatments in broader populations. Furthermore, we found that choices of antipsychotics were somewhat different between ineligible vs eligible individuals. In previous real-world studies using within-individual designs minimizing selection bias, LAI antipsychotics were associated with lowered risk of rehospitalization whereas quetiapine often was not, compared with no use of antipsychotics.[17,18] Ineligible individuals were less likely to use LAI antipsychotics and more likely to use quetiapine than eligible individuals. Reasons for these differ-

ences are not fully clear from our data; however, it is possible that LAI antipsychotics are avoided as those are slower to taper, eg, in persons with high risk of extrapyramidal symptoms, or active substance use, which increases the risk of interactive effects leading possibly to respiratory depression or seizures. Quetiapine may be prescribed more often for subgroups presenting more affective symptoms (eg, with suicidal ideation) or for tardive dyskinesia.[19] This also describes a fundamental difference between real-world studies (such as the present study) and RCTs: in the real world, treatments are chosen by clinicians by their best judgment and following clinical care guidelines, while in RCTs the treatment is preset by the design. Therefore, to further elucidate antipsychotic use and effectiveness in practice, in addition to typical RCTs, which are important to examine whether a drug works in principle in selection bias-free conditions (efficacy), pragmatic trials (such as STAR*D[20] and CATIE[21]) and observational studies (such as the SOHO study[22,23]) may in future be of benefit.[24] These are performed on less selected populations and resemble clinical practice more closely than typical RCTs. Finally, our results provide estimates for risks of rehospitalization for schizophrenia in different patient populations, which could be used to inform individuals and clinicians about the expected outcome on antipsychotics within 1 year. Of note, individuals with a previous history of substance use, suicide attempt, or clozapine use (as a proxy for treatment resistance) had only a moderately higher risk of rehospitalization for acute psychosis. In this context, it needs to be considered that these estimates only apply to individuals with schizophrenia already stable taking medication for 12 weeks before the start of the 1-year observation period. For some individuals in these subpopulations, it might be difficult to reach this level of stability. Nevertheless, the observed differences in rehospitalization rates between subpopulations call for more specific epidemiological studies on expected absolute risks and predictors of relapse and rehospitalization.

Limitations

Our analysis is somewhat limited because our selection of individuals eligible for RCTs matches the population in actual RCTs only to a certain extent for different reasons. (1) Participation in a trial requires participants not only to meet eligibility criteria but also to be willing to participate in a trial; the latter might be an important driver of outcomes, which we cannot disentangle in the real-world population. This, in addition to other factors such as dropouts, might explain the difference in rehospitalization rates on antipsychotic maintenance therapy between RCTs (4% at 7-12 [median, 9] months)[10] and the real world (here 14% at 9 months in eligible individuals). (2) The selection criteria used for our analysis are typical for a specific, relatively common type of RCTs (ie, relapse prevention of schizophrenia with antipsychotics) and specific real-world samples (Finland and Sweden). Therefore, our results may not be directly generalizable to other types of RCTs or to countries with different health care systems or resources. Although the main results represent only individuals previously treated in inpatient care due to schizophrenia spectrum disorders, additional analyses in the Swedish outpatient cohort showed similar results, allaying concerns about bias resulting from cohort and statistical method selections. (3) Furthermore, inclusion and exclusion criteria vary between RCTs (eAppendix 1B in the Supplement). Some RCTs apply more relaxed criteria than the ones we used, eg, by allowing the participation of individuals with psychiatric or somatic comorbidities, with stable concomitant antidepressant or mood-stabilizing medications, history of suicide attempts (without active suicidal thoughts or behaviors), or substance use (when inactive at the time or when criteria for dependence are not met). Of note, the data from real-world cohorts do not allow one to apply all eligibility criteria exactly as in RCTs because only diagnoses and not clinical ratings are available, and some symptoms are often underreported in diagnostic data (eg, suicidality and substance use). However, previous research has shown that register-based inpatient diagnoses of schizophrenia are valid.[25] Consequently, while our estimates refer to standard RCT with rather strict criteria, possibly other RCTs represent more than the 20% of real-world patients. Nonetheless, our results highlight that there is considerable heterogeneity in real-world individuals, which is not addressed by most standard RCTs.

Conclusions

In conclusion, based on comprehensive main and sensitivity analyses leveraging sizeable nationwide cohorts and in line with hypotheses put forward before but backed with less solid evidence,[26-31] only a minority (about one-fifth) of real-world individuals with schizophrenia may be eligible for typical RCTs and their clinical outcomes were estimated to differ from ineligible individuals. However, because we did not investigate relative treatment effects (eAppendix 1A in the Supplement) and because the observed differences in absolute risks for clinical outcomes were not extreme, we emphasize that there are no major indications from our research that overall RCT results on efficacy and safety of antipsychotics would not apply to ineligible individuals. Nevertheless, our results indicate that specific subgroups among the majority of real-world individuals ineligible for RCTs can have a different course of illness, which also means they might experience differential treatment benefits. Therefore, in line with previous literature,[28,30,32-36] future studies focusing on specific subpopulations, pragmatic trials to investigate treatment strategies, and well-designed observational studies are needed to investigate and improve the outcomes of the many individuals afflicted by schizophrenia and currently underrepresented in research settings.

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Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data

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See Comment page 82

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Summary

Background There is debate about the generalisability of results from randomised clinical trials (RCTs) to real-world settings. Studying outcomes of treatments for schizophrenia can shed light on this issue and inform treatment guidelines. We therefore compared the efficacy and effectiveness of antipsychotics for relapse prevention in schizophrenia and estimated overall treatment effects using all available RCT and real-world evidence.

Methods We conducted network meta-analyses using individual participant data from Swedish and Finnish national registries and aggregate data from RCTs. The target population was adults (age >18 and <65 years) with schizophrenia and schizoaffective disorder with stabilised symptoms. We analysed each registry separately to obtain hazard ratios (HRs) and 95% CIs for relapse within 6 months post-antipsychotic initiation as our main outcome. Interventions studied were antipsychotics, no antipsychotic use, and placebo. We compared HRs versus a reference drug (oral haloperidol) between registries, and between registry individuals who would be eligible and ineligible for RCTs, using the ratio of HRs. We synthesised evidence using network meta-analysis and compared results from our network meta-analysis of real-world data with our network meta-analysis of RCT data, including oral versus long-acting injectable (LAI) formulations. Finally, we conducted a joint real-world and RCT network meta-analysis.

Findings We included 90 469 individuals from the Swedish and Finnish registries (mean age 45·9 [SD 14·6] years; 43 025 [47·5%] women and 47 467 [52·5%] men, ethnicity data unavailable) and 10 091 individuals from 30 RCTs (mean age 39·6 years [SD 11·7]; 3724 [36·9%] women and 6367 [63·1%] men, 6022 White [59·7%]). We found good agreement in effectiveness of antipsychotics between Swedish and Finnish registries (HR ratio 0·97, 95% CI 0·88–1·08). Drug effectiveness versus no antipsychotic was larger in RCT-eligible than RCT-ineligible individuals (HR ratio 1·40 [1·24–1·59]). Efficacy versus placebo in RCTs was larger than effectiveness versus no antipsychotic in real-world (HR ratio 2·58 [2·02–3·30]). We found no evidence of differences between effectiveness and efficacy for between-drug comparisons (HR ratio *vs* oral haloperidol 1·17 [0·83–1·65], where HR ratio >1 means superior effectiveness in real-world to RCTs), except for LAI versus oral comparisons (HR ratio 0·73 [0·53–0·99], indicating superior effectiveness in real-world data relative to RCTs). The real-world network meta-analysis showed clozapine was most effective, followed by olanzapine LAI. The RCT network meta-analysis exhibited heterogeneity and inconsistency. The joint real-world and RCT network meta-analysis identified olanzapine as the most efficacious antipsychotic amongst those present in both RCTs and the real world registries.

Interpretation LAI antipsychotics perform slightly better in the real world than according to RCTs. Otherwise, RCT evidence was in line with real-world evidence for most between-drug comparisons, but RCTs might overestimate effectiveness of antipsychotics observed in routine care settings. Our results further the understanding of the generalisability of RCT findings to clinical practice and can inform preferential prescribing guidelines.

Funding None.

Introduction

Randomised controlled trials (RCTs) are the best source of evidence to estimate relative treatment effects.[1] For some interventions, eg, statins, effects estimated in RCTs are largely consistent across settings.[2] Such agreement occurs when factors that interact with treatment are minimal. However, this scenario might not apply to some interventions, especially in mental health, where multiple context-related variables can vary between RCTs and real-world practice, leading to different estimates of clinical outcomes and thus giving rise to an efficacy–effectiveness gap.[3] In the mental health field, a factor that can further increase such an efficacy–effectiveness gap is our recent finding that up to 80% of individuals with

Research in context

Evidence before this study

There is an ongoing debate about the generalisability of results from randomised clinical trials (RCTs) to real-world clinical settings. We have previously found that 80% of real-world patients with schizophrenia spectrum disorders are ineligible to participate in relapse-prevention antipsychotics RCTs, and that ineligible patients overall have worse outcomes than eligible patients with schizophrenia. We searched PubMed on July 5, 2023, from database inception, with no language restrictions, for studies integrating RCT and real-world evidence about antipsychotics. The search "real-world AND RCT AND antipsychotic AND network meta-analysis" did not yield any results. The search "real-world AND RCT AND antipsychotic" yielded no applicable studies to our study design, only either RCTs or real-world studies. We therefore set out to integrate RCT and real-world evidence and used individual patient data from national registries from Finland and Sweden and study-level information from 30 RCTs (as published by Schneider-Thoma and colleagues [2021, updated to March, 2022]) to compare antipsychotic drugs for individuals with schizophrenia and schizoaffective disorder, using relapse as the main outcome.

Added value of this study

We included over 100 000 individuals with schizophrenia and schizoaffective disorder from Swedish and Finnish national registries and RCTs. By using two national registries and study-level information from the most comprehensive and up-to-date systematic review of RCTs, our work constitutes the largest meta-analysis of antipsychotic treatment effects and the first study synthesising large-scale evidence from real-world and RCT settings in psychiatry. We found that the advantage of long-acting injectable (LAI) antipsychotics compared with their oral counterparts is larger in real-world than RCT settings, which was another ongoing debate in psychiatry. Furthermore, RCT evidence was in line with real-world evidence for most between-drug comparisons. Finally, we found evidence that relative effects of antipsychotics versus placebo estimated in RCTs might overestimate effects versus no antipsychotic use in routine care settings.

Implications of all the available evidence

Our results could inform clinical treatment guidelines for schizophrenia and schizoaffective disorder with regards to preferred treatment options for relapse prevention when considering the combination of efficacy and effectiveness as one measure. For example, based on our findings of superior effectiveness of olanzapine to haloperidol, patients might decide to try olanzapine if haloperidol insufficiently reduces their symptoms. In addition, LAI formulations of antipsychotics should be considered as earlier use options in updated clinical guidelines, as we showed they perform better in real-world clinical settings to avoid relapse in schizophrenia than previously shown in RCTs. Our methodology and work lay the groundwork for future analyses integrating RCT and real-world efficacy and effectiveness measures for other psychiatric disorders.

schizophrenia are ineligible to participate in RCTs, meaning that populations in RCTs are not representative of real-world populations.[4]

Network meta-analysis constitutes a powerful method to synthesise comparative evidence when multiple treatment options are available for the same condition,[5] as is the case for schizophrenia.[6] Furthermore, we chose a network meta-analysis approach since pharmaceutical companies do not prioritise studies on the comparative efficacy between treatments.[7] For instance, esketamine was approved for treatment-resistant depression in 2019 by the US Food and Drug Administration based on placebo-controlled trials, despite the availability of another approved treatment option for this indication.[8] Another example from the field of mental health is brexpiprazole, which was approved for schizophrenia by the European Medicines Agency (EMA) based on four RCTs, three of which were placebo-controlled. The only active-comparator RCT used quetiapine as control, although, according to the EMA, aripiprazole would have been a more appropriate comparator.[9] Industry-sponsored studies are not of lower methodological rigor.[10] However, they might sometimes favour the sponsored intervention when comparators with inferior benefit or harm profile are selected.[11]

Some observational studies have provided conflicting results about the effects of antipsychotics for maintenance treatment in schizophrenia.[12–14] In the last decade, however, the improved quality and increased availability of real-world and RCT data have facilitated large-scale use of such data in research.[15] A combined analysis of RCT and real-world data could thus increase statistical power to detect differences between active treatments and help identify best-performing drugs for relapse prevention across real-world and RCT settings.[16] Moreover, network meta-analysis could overcome the limitation of the aforementioned scarcity of active drug comparators in RCTs done for schizophrenia to date. Although some researchers have combined RCTs and observational studies on long-acting injectable (LAI) antipsychotics in schizophrenia,[17] we are unaware of network meta-analysis pooling RCT and real-world evidence of antipsychotic treatment effects for relapse prevention. We therefore synthesised RCT and real-world evidence of relapse prevention effects of oral and LAI antipsychotics by applying network meta-analysis. Our goal was to inform clinical guidelines and routine care about relative effects of antipsychotics and the generalisability of RCT data to routine care of patients with schizophrenia.

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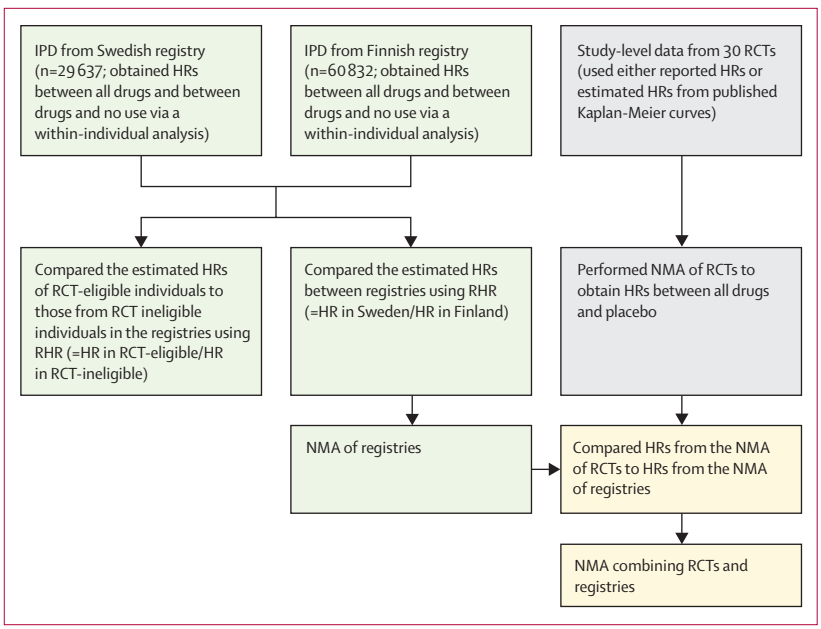

Figure 1: **Overview of study design and methods**
HR=hazard ratio. IPD=individual patient data. NMA=network meta-analysis. RCT=randomised clinical trial. RHR=HR ratio. Green correspond to the analyses of registries; grey to those of RCTs; yellow to those of real-world-RCT combined analyses.

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See Online for appendix

For the **protocol** see https://osf.io/q9prm/

Methods

Study design

In our network meta-analyses, in line with expert recommendations,[18] we made the inclusion, treatment, and time zero criteria as similar as possible across the real-world and RCT datasets (figure 1). First, we analysed two national registries separately and compared treatment effects between them. We also compared effects in registry individuals eligible for RCTs versus those ineligible (as defined in our previous work and also described in this paper).[4] Then, we conducted network meta-analysis of registry data. Second, we estimated relative efficacies in a network meta-analysis of RCTs. Third, we compared both sources, thus examining a possible efficacy–effectiveness gap. Fourth, we performed a joint network meta-analysis of all evidence. Finally, we performed several sensitivity analyses. Following recommendations,[19,20] we provide estimates and corresponding confidence intervals, avoiding the use of statistical significance to characterise results. PRISMA-network meta-analysis checklist is provided in the appendix (pp 81–92). The protocol of this study was published before analysis (no amendments to the protocol were made; the only add-on includes two post-hoc analyses (described here). The Finnish registry was approved by the Finnish National Institute for Health and Welfare. Further permissions were granted by pertinent institutional authorities at this Institute, the Social Insurance Institution of Finland, and Statistics Finland. Regarding the Swedish registry, the project was approved by the regional ethical review board in Sweden (decisions 2007/762-31 and 2016-1533-32). The current real-world study was registry-based, and no contact was made with the participants of the study; therefore, informed consent from patients was not required. For RCT data, ethical approval and patient consent were obtained within the context of original studies.

Study population

The real-world study population consisted of individuals diagnosed with schizophrenia or schizoaffective disorder in nationwide Swedish and Finnish registries, which included patients identified from inpatient, specialised outpatient care, sickness absence, and disability pension data. We included individuals whose symptoms were likely to be stable while on maintenance treatment with antipsychotics, in line with the design of RCTs on relapse prevention and similar to previous research.[4] Real-world participants needed to fulfil three inclusion criteria: (1) a diagnosis of schizophrenia (ICD-10 F20) or schizoaffective disorder (F25),[40] (2) currently on second-generation antipsychotic or haloperidol monotherapy, and (3) stability of 12 weeks on antipsychotic monotherapy. Similar stability criteria were applied to antipsychotic non-use periods by people who had also been on monotherapy (as described above) since non-use was employed as reference exposure. The use of other first-generation antipsychotics as monotherapy has been reported to be negligible in the Finnish and Swedish populations.[21] Each patient could have multiple treatment periods of the same or different antipsychotics and non-use. Follow-up started after a 12-week stabilisation period and ended at an outcome event (see below), a change in exposure status, death, or hospitalisation due to other reasons than relapse, at the predefined follow-up period (6 and 12 months) or at the end of data linkage. Follow-up extended until Dec 31, 2017, in the Finnish cohort and until Dec 31, 2018, in the Swedish cohort (appendix pp 4–6).[13,22]

Regarding RCTs, we included the relapse-prevention studies from Schneider-Thoma and colleagues[23] comparing second-generation antipsychotics to each other, haloperidol, or placebo after an updated search of this review on March 6, 2022 (appendix p 7). Participants had schizophrenia or schizoaffective disorder, with very few having related disorders (appendix p 8). All were stabilised on antipsychotics (according to the authors' definitions).

Outcomes

The main outcome was relapse during 6 months. In real-world data, we defined relapse as hospital admission due to acute psychosis. In RCTs, we used the outcome "relapse" as defined by the authors of the RCTs as no substantial differences in treatment effects due to differences in relapse definitions were observed in the original systematic review (see section on sensitivity analyses for an analysis using psychiatric rehospitalisation as an outcome in RCTs).[23]

We used two alternative outcomes to assess the robustness of our findings. First, we analysed all-cause discontinuation (until study endpoint in RCTs). Second, we repeated analyses using 12 months of follow-up.

Data analysis

In real-world analyses, we analysed all periods of second-generation antipsychotics and haloperidol in monotherapy use and non-use periods of antipsychotics. Analyses were conducted with stratified, within-individual Cox models to obtain hazard ratios (HRs). This method was chosen to minimise chances of confounding. We estimated HRs between all antipsychotics, and between antipsychotics and non-use of antipsychotics, separately in the two registries. Analyses were adjusted for time since cohort entry and for use of other psychotropic medications (appendix pp 4–6). Analyses were conducted in SAS 9.4. The end-product of this stage was one set of estimates per registry (HRs between all drugs, between drugs and non-use, and corresponding standard errors of logHRs). Subsequently, we inspected the agreement between the registries in a scatterplot, plotting the estimated HRs and 95% CIs versus oral haloperidol (where HR>1 favours haloperidol). To quantify agreement, we estimated the ratio of HRs (HR ratio) for each drug (ie, HR from real-world over HR from RCTs, where HR ratio of 1 refers to perfect agreement between registries for the effects *vs* haloperidol; HR ratio >1 means $HR_{real\text{-}world}>HR_{RCT}$). Then, we synthesized the drug-specific HR ratios in a random-effects meta-analysis, using meta package[24] in R.[25] We estimated the weighted Spearman rank correlation coefficient (ρ) for the two sets of HRs using wcorr package,[26] with weights equal to the inverse of the variances of the HR ratios, where ρ=1 corresponds to identical ranking (according to the point estimates) in the two registries. To obtain a p value against the null hypothesis of no correlation, we performed a permutation test (appendix p 44).

Next, we synthesised the results from the registries in a random-effects network meta-analysis.[27] We assumed a common heterogeneity parameter (τ) for all comparisons in the network, and ranked treatments using p scores.[28] The main assumption of network meta-analysis is transitivity; we assessed this by looking at the distribution of possible effect modifiers across the registries. Consistency refers to the agreement between direct and indirect evidence, and we assessed it via a global (design-by-treatment test)[29] and a local method (back-calculation method).[30] We used the netmeta package.[31]

We explored differences between RCT-eligible and RCT-ineligible individuals, as defined in our previous publication.[4] In brief, we applied the following exclusion criteria commonly used in modern RCTs of second-generation antipsychotics to real-world individuals, to obtain RCT-eligible and ineligible individuals:[4] age (>18 and <65 years); current or past diagnosis of substance use disorder; history of suicide attempt; treatment resistance; serious somatic disease; mood stabiliser or antidepressant use; intellectual disability or mental retardation; tardive dyskinesia; and pregnancy or breastfeeding (further details are provided in the appendix p 4). Then, we repeated the real-world analyses outlined in the previous paragraph for RCT-eligible and RCT-ineligible individuals separately and compared estimates of effectiveness. Of note, eligibility criteria are known to vary across RCTs. Due to the necessary operationalisation of exclusion criteria by documented diagnoses in the registries, our RCT-eligibility criteria

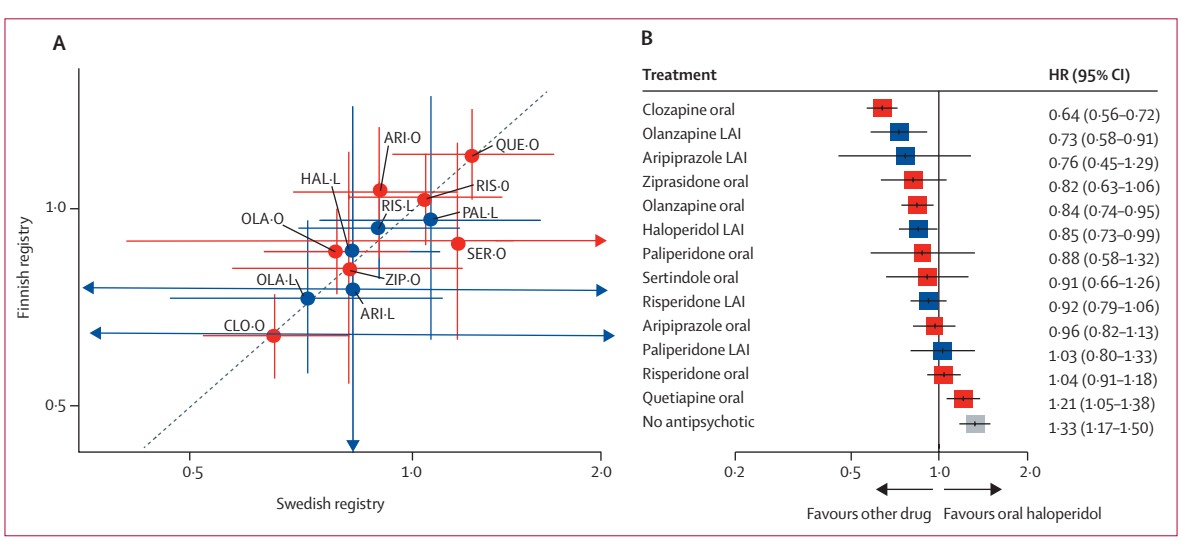

Figure 2: **Results from analyses of registry data**
(A) Relapse HRs versus oral haloperidol and 95% CI estimated separately from the two registries. (B) Results from a network meta-analysis of the two registries. Drugs are ordered by decreasing effectiveness. Red indicates oral formulation, blue LAI. For each drug, x·L denotes LAI and x·O the oral formulation. ARI=aripiprazole. CLO=clozapine. HAL=haloperidol. HR=hazard ratio. LAI=long-acting injectable. OLA=olanzapine. PAL=paliperidone. RIS=risperidone. SER=sertindole. QUE=quetiapine. ZIP=ziprasidone.

might be more restrictive than the eligibility criteria used in some RCTs (appendix pp 5, 18–42).[4] The eligibility criteria we used likely reflect the practice of an explanatory, rather than a pragmatic trial.

In a first post-hoc analysis, we explored differences between LAI and oral formulations of antipsychotics, to quantify differences in effectiveness between formulations. Our hypothesis was that real-world evidence shows larger benefit of LAI over counterpart oral formulations compared to RCTs,[13] since individuals with poor adherence might be excluded from RCTs. From each registry we obtained HRs between LAI versus oral counterparts; then, we synthesised these HRs in a random-effects meta-analysis to compare the average treatment effects between the two formulations across all drugs available as LAI and oral formulations. Following suggestions of peer reviewers, we performed two additional post-hoc analyses: first, we excluded from the registries individuals diagnosed with schizoaffective disorder; second, we excluded from the registries individuals using clozapine at baseline. We then repeated the main analysis of the registry data to verify the robustness of our conclusions when excluding these patients.

In RCT analysis, we used HRs to obtain similar effect measures for real-world and RCTs. If original publications of RCTs provided HRs for relapse at 6-month follow-up (or 12-month follow-up for sensitivity analyses), we used those. Otherwise, we used published survival curves to estimate HRs according to established methodology[32] used in several meta-analyses[33,34] (appendix p 45). Transitivity was already assessed in the original network meta-analysis.[23] For the RCT network meta-analysis, we used the same methods as for the real-world network meta-analysis described above.

To compare real-world and RCT findings, we created scatterplots with one axis showing relative efficacy (HR) of drugs versus oral haloperidol in RCTs and the other effectiveness in the real world, including 95% CIs. To quantify real-world to RCT agreement, we used HRs versus oral haloperidol to obtain HR ratios (ie, HR obtained from real-world data over HR from RCTs), and estimated the weighted Spearman rank correlation.

If results were deemed comparable between the real world and RCTs, we synthesised all evidence in network meta-analysis, using the same methods as for the distinct network meta-analysis of real-world and RCT data. We used placebo (in RCTs) and non-use (in real-world data) as different nodes in the network. To present results, we chose oral haloperidol as reference treatment given its widespread and long-standing use.

We performed a series of prespecified sensitivity analyses. First, we ran a sensitivity analysis by starting the follow-up for real-world non-users the moment they discontinued their previous antipsychotic use (mimicking situations wherein non-users are first stabilised on antipsychotic monotherapy). Second, we excluded RCTs of individuals with first-episode psychosis. Third, we excluded open-label RCTs. Fourth, we repeated analyses using rehospitalisation (until study endpoint) instead of study-defined relapse as the RCT outcome.

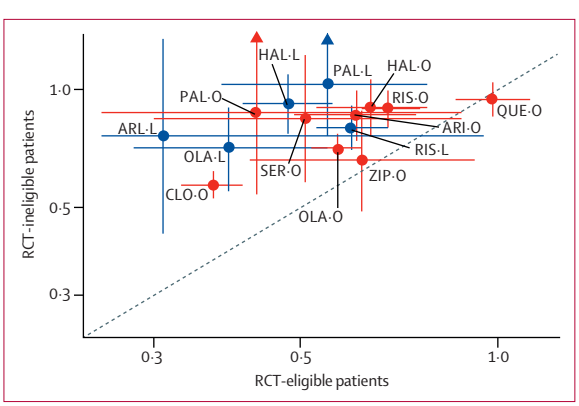

Figure 3: **HRs of all drugs versus no antipsychotic use, for real world individuals who would be eligible for a standard RCT and RCT-ineligible individuals**

Effectiveness was estimated via a network meta-analysis of the Swedish and Finnish registries. Red indicates oral formulation, blue LAI. For each drug, x·L denotes LAI and x·O the oral formulation. ARI=aripiprazole. CLO=clozapine. HAL=haloperidol. HR=hazard ratio. LAI=long-acting injectable. OLA=olanzapine. PAL=paliperidone. RIS=risperidone. SER=sertindole. QUE=quetiapine. ZIP=ziprasidone.

Role of the funding source

There was no funding source for this study.

Results

We included 29 637 individuals, with a total of 18 713 person-years, from the Swedish registry and 60 832 individuals, with a total of 64 583 person-years, from the Finnish registry. Mean age at cohort entry was 44·9 years (SD 12·0) in the Swedish and 46·4 years (15·9) in the Finnish registry. In the Swedish registry 12 741 (43·0%) patients were female and 16 896 (57·0%) were male; in the Finnish registry 30 284 (49·8%) patients were female and 30 548 (51·2%) were male. For the entire real-world population (n=90 469), the mean age was 45·9 years (SD 14·6) and 43 025 (47·5%) were women and 47 467 (52·5%) were men. Ethnicity data were unavailable in the registries.

Figure 2A shows estimated effects from the two registries for all drugs versus oral haloperidol. The weighted Spearman's rank correlation for the HRs was 0·93 (p=0·0004). The HR ratio for Swedish over Finnish registry was 0·97 (95% CI 0·88–1·08); additional statistics and graphical displays are in the appendix (pp 47–51). We deemed that the registries had comparable populations, transitivity was plausible, and we therefore conducted network meta-analysis. We found no evidence of network heterogeneity or inconsistency (appendix p 51). Clozapine was most effective, followed by olanzapine LAI (figure 2B).

Figure 3 shows the comparison of real-world effects between RCT-eligible and RCT-ineligible individuals, for drugs versus no antipsychotic use. We observed that drug

effectiveness for all drugs was larger in RCT-eligible individuals. The pooled HR ratio was 1·40 (95% CI 1·24–1·59; appendix pp 68–80), ie, drugs' effectiveness was 40% larger in RCT-eligible individuals. When comparing LAI versus oral formulations of drugs for which both were present in the real-world dataset, we found evidence of superior effectiveness of LAI. The average HR across the registries for LAI versus oral was 0·88 (0·81–0·95; appendix pp 47–51).

From 51 studies fulfilling the inclusion criteria in terms of population and interventions, 30 RCTs (10 091 participants) analysed relapse with survival analysis and were thus usable for the main outcome analysis (one additional study did not provide censoring information on the survival curve and therefore was not usable). The mean age across those 30 RCTs was 39·6 years (SD 11·7), the median of mean age was 39·0 years (range 21·5 to 49·7). The mean percentage of women was 36·9% (n=3724) and of men 63·1% (n=6367). The majority of participants was White (59·7%); the proportion of other ethnicities in the study populations was not reported consistently and outcomes were never provided separately for distinct ethnicities. Therefore, ethnicity information was not included in the analysis. A flow chart of the selection process, descriptives of the included studies, and a risk of bias assessment are in the appendix (pp 7–43). For three trials, we obtained relapse HRs from published data. For the remaining 27 RCTs, we extracted HRs from published Kaplan-Meier curves. Results of individual studies, pairwise meta-analyses of each comparison, and a meta-analysis of five studies comparing LAI versus oral formulations of the same drug are shown in the appendix (pp 52–56). In the meta-analysis of those five studies, opposite to the finding in registries, the pooled effect favoured oral administrations, albeit with statistical uncertainty. The network meta-analysis of RCTs indicated heterogeneity (τ=0·45) and inconsistency (design-by-treatment test p=0·004; local method found that three of 11 detachable comparisons showed evidence of inconsistency; appendix pp 56–59) and the certainty in the estimates was generally low (appendix pp 57–59). In figure 4, we show the network graph and the estimated effects versus oral haloperidol.

We then compared real-world and RCT effect estimates and found differences between RCTs and real-world: the average ratio of HR of drug versus no antipsychotic (real-world data) over HR of drug versus placebo (RCT data) was 2·58 ([95% CI 2·02–3·30]; p<0·0001), that is, treatment efficacy in RCTs was on average 2·58 times larger than the corresponding drug's effectiveness in the real world. However, the weighted Spearman's rank correlation was 0·59 (p=0·06), indicating that treatment ranking in RCTs reflected, to some extent, ranking in the real world. When comparing HRs of drugs versus haloperidol, we found the HR ratio to be 1·17 ([0·83–1·65]; p=0·36), that is, almost no evidence of disagreement. Spearman's weighted correlation was 0·64 (p=0·04). For most drugs, point estimates were in good agreement between RCTs and the real world (figure 5). However, for olanzapine we found discrepancies of the estimated effects, although with large statistical uncertainty. RCTs showed weak evidence favouring oral versus equivalent LAIs (HR 1·21 [0·89–1·63]). The HR ratio for the oral-LAI comparison in the real world versus in RCTs was 0·73 ([0·53–0·99]; p=0·04), that is, LAIs had superior effects in the real world compare with RCTs.

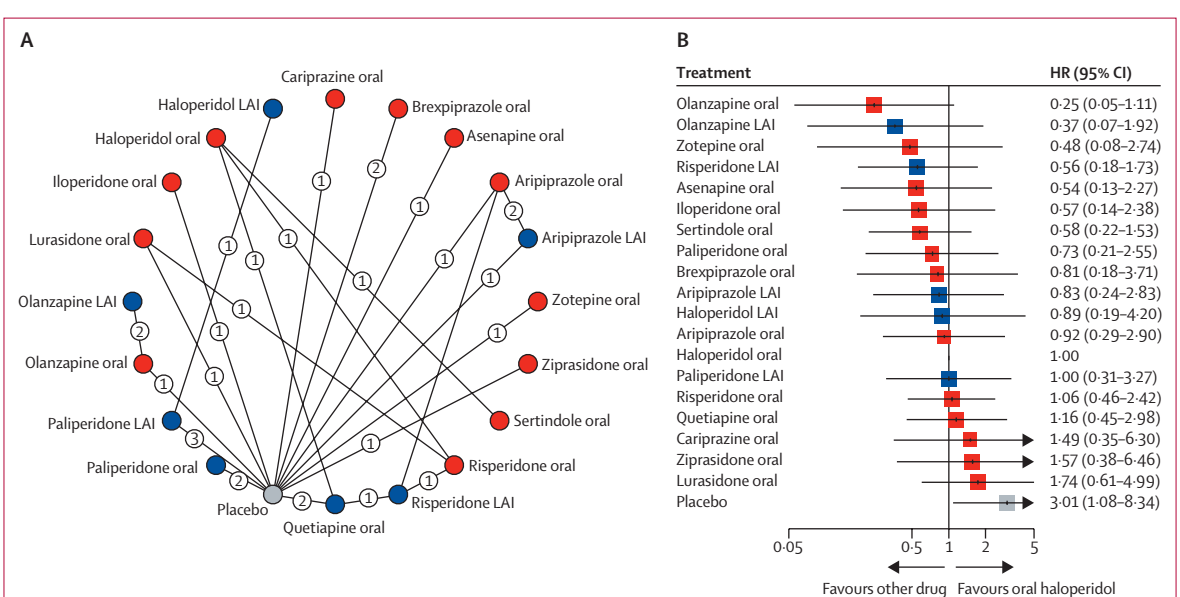

Figure 4: **Results from analyses of randomised data**
(A) The network of available RCTs. Numbers indicate the number of studies performing each comparison. (B) Estimated HRs for all drugs versus placebo via a network meta-analysis; red indicates oral, blue LAI. HR=hazard ratio. LAI=long-acting injectable. RCT=randomised controlled trial.

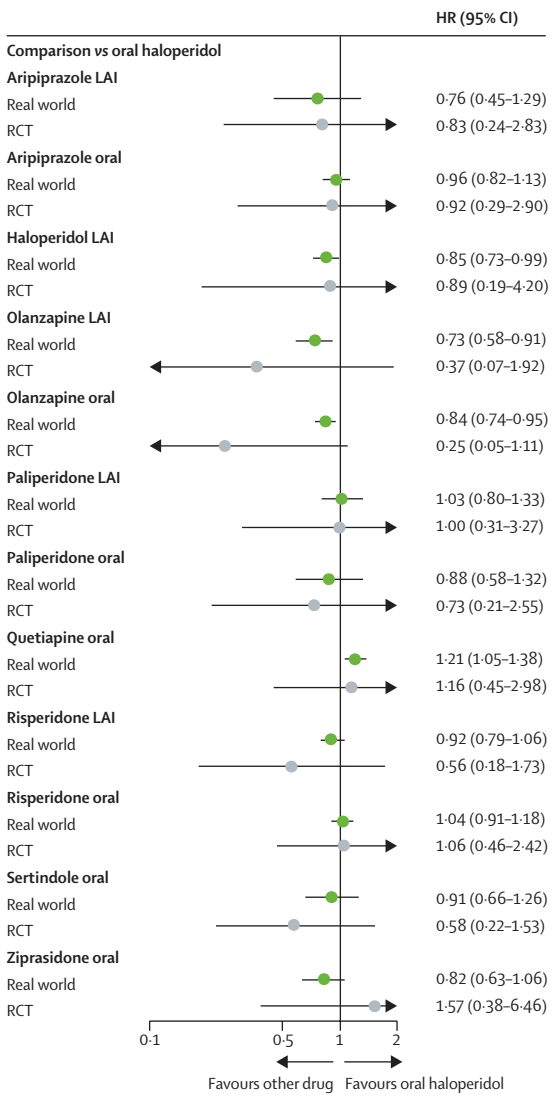

Figure 5: **Comparison HRs of all drugs versus oral haloperidol in the registries versus RCTs**

Only drugs found in both datasets (real-world and RCTs) are shown. Grey indicates estimates from RCTs, green from registry data. HR=hazard ratio. LAI=long-acting injectable. RCT=randomised controlled trial.

We then performed a joint network meta-analysis of RCT and registry data. This network meta-analysis showed little evidence of heterogeneity (τ=0·14) and inconsistency (design-by-treatment test p=0·40). Precision was low for the top-ranked drugs (asenapine, iloperidone, and zotepine) and these drugs were only available in RCTs (one trial *vs* placebo each; figure 6). Clozapine (available only in the real world) ranked second according to p scores (HR 0·61 [95% CI 0·48–0·77], p<0·0001), combining a large effect size with high precision. Olanzapine oral (HR 0·71 [0·57–0·88], p=0·002) was present in both RCTs and the real world and ranked high in the joint network meta-analysis, the RCT network meta-analysis, and real-world network

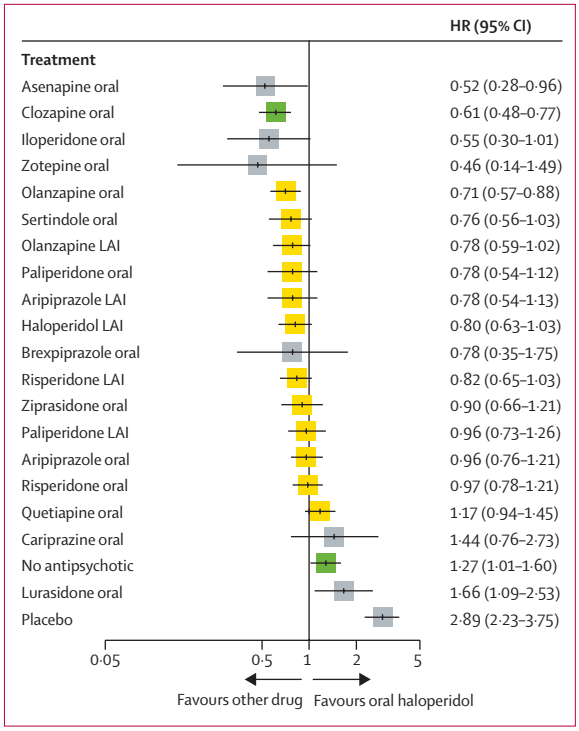

Figure 6: **HRs of drugs versus oral haloperidol from a network meta-analysis combining RCT and registry evidence**

Grey indicates drugs that were only available in RCTs, green drugs that were only available in registry data, and orange drugs present in both RCT and registry data. Drugs are ranked according to their p scores. HR=hazard ratio. LAI=long-acting injectable. RCT=randomised controlled trial.

meta-analysis; however, the two sources disagreed on the magnitude of the effect (figure 5). Drugs with the least benefit compared with placebo or no antipsychotics (cariprazine and lurasidone) only had RCT evidence. Drugs with evidence from both registries and RCTs generally yielded more precise but less pronounced effects.

Finally, results from secondary outcomes and most sensitivity analyses (appendix pp 93–118) either agreed with the main analyses or did not provide further insights, because of low precision estimates. The sensitivity analysis of using rehospitalisation as an outcome showed differences with the main analysis; however, this analysis had poor data quality (appendix pp 115–118).

Discussion

We used individual patient data from two national registries and study-level information from 30 RCTs (totalling >100 000 individuals) to compare antipsychotic drugs for individuals with schizophrenia and schizoaffective disorder, using relapse as the main outcome. To the best of our knowledge, our work constitutes the largest meta-analysis of antipsychotic treatment effects and the first study synthesising large-scale evidence from real-world and RCT settings in the field of mental health.

Our real-world results indicate that antipsychotic beneficial effects versus no drug use are larger in individuals eligible for RCTs (ie, those meeting stringent inclusion criteria) than in ineligible individuals (ie, those who are not usually represented in RCTs). Similarly, drug effects versus placebo in RCTs were higher than effects versus no drug use in the real world. We thus triangulated a difference between RCT and real-world effects. However, RCT estimates of relative effects for relapse prevention between drugs were generally in good agreement with those from registries. We therefore conclude that, although efficacy versus placebo in RCTs might not be directly portable to real-world effectiveness versus no antipsychotic use, we find no evidence of an efficacy–effectiveness gap[3] in head-to-head antipsychotic drug comparisons.

In the registry data, we found LAIs to be more effective than oral formulations, in line with previous analyses of real-world data using a different outcome;[36,37] conversely, in RCTs we found weak evidence favouring oral drugs. This discrepancy might be due to less severely ill and more adherent individuals being included in RCTs compared with the individuals in registries, frequent follow-up visits in RCTs or low doses of olanzapine LAI in two of the five RCTs, or both (appendix pp 52–56).[38] Nonetheless, in a meta-analysis with broader inclusion criteria across comparisons, LAI was superior to oral compounds also in RCTs.[17]

We believe that our work might inspire other areas of medicine to attempt similar integrative real-world-RCT approaches, as well as serve as a basis for updating and revisiting current treatment guidelines for schizophrenia. For example, except for the indication of clozapine in treatment-resistant schizophrenia, most guidelines do not list specific antipsychotics in any preferential order. We found that in the real world, clozapine and LAIs performed well for relapse prevention (with olanzapine LAI outperforming other LAI formulations); in the RCT network meta-analysis and joint RCT and real-world network meta-analysis olanzapine LAI also ranked very high. We thus recommend to consider LAIs (eg, olanzapine) not only in the event of patient preference and non-adherence (as currently suggested in the American Psychiatric Association [APA] schizophrenia treatment guideline),[39] but also in patients with schizophrenia in general. Additionally, we fill a knowledge gap in superiority of antipsychotics by substantiating evidence of superior effectiveness of certain antipsychotics (eg, of olanzapine to haloperidol). Finally, as the APA and other schizophrenia guidelines are partly based on expert opinions,[39] we suggest the joint assessment of real-world evidence with RCTs for further development of schizophrenia treatment guidelines.

A strength of our study is the methodology used to integrate data from real-world and RCT settings. Additionally, our analyses were based on a larger study population with a more extended follow-up period than any previous studies in these registries. Moreover, the large number of individuals and the long follow-up allowed us to run within-person analysis, where each patient acted as their own control, reducing the risk of confounding. Nonetheless, limitations should be borne in mind when interpreting the results. First, there could still be unmeasured confounding in our within-individual analysis, such as due to severity or instability of symptoms (eg, if patients in the real world start or stop medication when they feel either more or less ill). Second, participation in RCTs could be driven not only by eligibility, but also by the individuals' willingness to participate, for example, the presence of paranoid delusions can curtail an individual's predisposition to participate in a trial. Third, inclusion of patients with schizoaffective disorder can theoretically pose a problem, as RCTs, in contrast to the real world setting, usually include only few such patients. Fourth, owing to data availability limitations, we were unable to conduct some specific analyses. For example, we restricted our analyses to 6 months and 12 months because this was the duration of follow-up for most RCTs; however, schizophrenia affects patients for much longer durations. Similarly, we limited analyses to HRs, and thus data of 17 RCTs only reporting numbers of patients with relapses but not HRs or survival curves could not be used. Using other effect measures (eg, risk ratios) would lead to great loss of information from the registries, due to frequent censoring before 6 months. Furthermore, we did not do a formal appraisal of the evidence of the joint real-world and RCT network meta-analysis, for example, using the CINeMA approach[41] as this does not currently accommodate observational studies. In addition, we were unable to conduct analyses stratified by sex, ethnicity, or gender or include amisulpride in any of our analyses. Nor were we able to fully harmonise definitions of the outcome and eligibility criteria so as to match RCT definitions (that also vary substantially between RCTs). Consequently, our definition of RCT eligibility applied to the individuals in the real world is even more explanatory and less pragmatic than in RCTs (particularly because we excluded patients who had ever had a diagnosis of substance use disorder or suicide attempt). Fifth, one of the sensitivity analyses we performed, that is, using rehospitalisation as an outcome in RCTs, gave results incongruent with the main analysis, but data quality was poor (appendix pp 115–118). Finally, although a network meta-analysis of RCTs was not our main focus, the RCT network was thinly connected, heterogeneous, and inconsistent and thus the certainty in the estimates of this specific analysis was relatively low.

We suggest all future RCTs make individual patient data available, to enable individual patient data meta-analyses. To optimise interpretability and utility of RCT findings, superiority trials over active comparators should be favoured, keeping placebo-controlled trials as pivotal registration studies.[42] Furthermore, dose-specific comparative analyses between RCTs and the real world

should be conducted. Also, it would be interesting to apply similar approaches to different real-world health-care settings. Another research avenue is to explore the comparative tolerability of antipsychotics across real-world and RCT settings, although this will probably be challenging.

In summary, except for effect differences between oral and LAI antipsychotics, we found that antipsychotic between-drug comparison findings for the outcome of relapse prevention might be portable from RCTs to the real world. Effects of antipsychotic drugs versus placebo reported in RCTs might overestimate effects as compared with no antipsychotic use observed in routine practice.

Contributors

All authors conceived the study. OE, HT, and JS-T curated the data. OE, HT, JR, JS-T, JPE, MO, JT, and JL made the statistical analysis plan. OE, HT, JR, JS-T, and MO carried out the data analysis. AC, EV, SL, JT, and JL supervised the project. OE, HT, JR, JS-T, JPE, MO, JT, and JL wrote the first draft. Project management was done by JL. All coauthors were involved in the critical review and writing of the final draft that was submitted, as well as the submitted revision. HT and AT verified and had full access to all the real world data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JS-T, SL, MO, and JR verified and had full access to the RCT data and take responsibility for the integrity of the data. OE and HT take responsibility for data analysis. JL had the final responsibility for the decision to submit for publication.

Declaration of interests

OE has received honoraria and consulting fees from Biogen to his institution, all unrelated to the current work. JPE has received Continuing Medical Education (CME) speaker fees and other non-financial honoraria from Otsuka, Lundbeck, Casen Recordati, Rovi, Angelini Pharma, Neuraxpharm, and Janssen, outside the submitted work; and has participated in research projects coordinated by IQVIA. EV has received grants and served as consultant, advisor, or CME speaker for AB-Biotics, Abbvie, Aimentia, Angelini, Boehringer Ingelheim, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Idorsia, Janssen, Lundbeck, Organon, Otsuka, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. JT, EMR, HT, and ATa have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. HT reports personal fees from Gedeon Richter, Janssen-Cilag, Lundbeck, and Otsuka. JT has participated in research projects funded by grants from Janssen to his employing institution. JT has served as a consultant for HLS Therapeutics, Janssen, Orion, and WebMed Global and has received honoraria from Janssen and Otsuka. PFP has received research funds or personal fees from Lundbeck, Angelini, Menarini, Sunovion, Boehringer Ingelheim, and Proxymm Science, outside the current study. AC has received research, educational, and consultancy fees from the Italian Network for Paediatric Trials, CARIPLO Foundation, Lundbeck, and Angelini Pharma, outside the submitted work. He is the Clinical Lead and Principal Investigator of a trial of seltorexant in adolescent depression, sponsored by Janssen. SL has received honoraria as an advisor or for lectures or educational material from Alkermes, Angelini, Apsen, Eisai, Gedeon Richter, Janssen, Karuna, Kynexis, Lundbeck, Medichem, Medscape, Merck Sharpp and Dome, Mitshubishi, Neurotorium, NovoNordisk, Otsuka, Recordati, Roche, Rovi, Sanofi Aventis, and TEVA. NC has received grants and acted as a CME consultant, advisor, or speaker for Angelini, Esteve, Exeltis, Janssen, Lundbeck, Novartis, Pfizer, and Servier, outside the submitted work. All other authors declare no competing interest.

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Radiological findings in brain MRI scans in youth with early-onset psychosis: A controlled study

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ABSTRACT

There is a lack of consensus on whether routine brain magnetic resonance imaging (MRI) should be recommended as part of the initial assessment in patients with psychosis. No study so far has qualitatively assessed brain MRI in patients with early-onset psychosis (EOP), in whom neurodevelopmental factors may play a stronger role. We aimed to determine the prevalence of brain MRI findings in patients with EOP compared to healthy controls, and assess whether these findings were clinically relevant. Retrospective clinical chart review of all patients with EOP in whom a brain MRI scan was acquired during admission to an inpatient child and adolescent psychiatry unit during January 2013–December 2017, compared to age and biologically assigned gender matched healthy controls. Between group analyses tested differences in rates of qualitatively abnormal MRI scans and changes in clinical management as a result of radiological findings. A total of 256 individuals were included (128 patients with EOP and 128 healthy controls). Patients with EOP presented with a significantly higher rate of abnormal MRI scans relative to healthy controls (21.9% vs 11.7%, p = .030; OR = 2.11, [95% CI:1.06–4.17]). Radiological findings in the EOP group triggered clinical referral for further evaluation or management more often than in the healthy control group (7.0% vs 1.6%, p = .030; OR = 4.76, [95% CI:1.01–22.50]). MRI scans in youth with EOP may be characterized by an increased number of radiological abnormalities than in controls. The rates of MRI findings requiring clinical referral suggests that routine MRI acquisition may need to be considered in patients with EOP.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; CT, computerized tomography; EOP, early-onset psychosis; FLAIR, fluid-attenuated inversion recovery; HC, healthy controls; K-SADS-PL, schedule for affective disorders and schizophrenia for school-age children–present and lifetime version; MDD, major depressive disorder; MRI, magnetic resonance imaging; NOS, not otherwise specified; OR, odds ratio; SD, standard deviation.

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1. Introduction

It has been estimated that in 6% of patients presenting with a first episode of schizophrenia, symptoms may be attributable to a medical condition rather than a primary psychiatric disorder (Johnstone et al., 1987). Identifying comorbid or etiological medical conditions underlying psychotic symptoms is crucial in order to provide appropriate treatment. Brain imaging techniques such as magnetic resonance imaging (MRI) are usually performed as part of a medical assessment in patients presenting with psychotic symptoms to identify potential non-psychiatric pathology, since the differentiation between primary and secondary psychosis on the basis of phenomenology alone is extremely difficult (Johnstone et al., 1988).

However, there is a lack of consensus on the need to include routine MRI screening in the assessment of patients with psychotic disorders (Forbes et al., 2019; Morris et al., 2009), and international clinical guidelines have provided inconsistent recommendations on this topic (CIBERSAM, 2015; Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016; Keepers et al., 2020; National Institute for Health and Care Excellence, 2008). A recent review including 16 studies assessing the clinical utility of acquiring a structural brain imaging sequence in first-episode psychosis, most of which had used computerized tomography (CT) scans, concluded that there was insufficient evidence to confirm whether brain imaging should be routinely ordered in patients presenting with a first episode of psychosis without associated neurological or cognitive impairment (Forbes et al., 2019). However, CT scans lack the spatial resolution of MRI, and therefore subtle grey and white matter abnormalities may have not been detected in these studies.

So far, a number of MRI studies have reported increased rates of radiological findings in patients with psychosis (22.2–40.0%) when compared to control samples (5.5–26.6%) (Borgwardt et al., 2006; Falkenberg et al., 2017; Lubman et al., 2002; Sommer et al., 2013). While most findings have not been causally related to psychosis nor have led to changes in clinical management, some radiological findings have been suggested to play a significant role in the neuropathology of the disease (Landin-Romero et al., 2016). The largest study to date found similar rates of clinically relevant imaging findings in brain MRI between patients with psychosis and controls (Sommer et al., 2013). Nonetheless, in this study patients were recruited in a research setting, and it has been suggested that radiological abnormalities may be underestimated in research samples due to exclusion of participants with suspicion of organic abnormalities or comorbidities (Falkenberg et al., 2017).

Some authors have suggested that psychotic disorders with an onset prior to age 18 may be associated with more salient biological features, linked with greater genetic load and neurodevelopmental antecedents (Arango et al., 2014; Rapoport et al., 2001; Solé-Padullés et al., 2017; Vourdas et al., 2003). However, evidence regarding the utility of brain imaging techniques when assessing early-onset psychosis (EOP) –defined as onset of psychosis prior to age 18 –is extremely limited, since most reports have focused on adult patients (Forbes et al., 2019). The only previous study in youth aged 13 to 19 years-old with psychosis revealed 11% of "positive" tests, none of which was deemed to be clinically relevant (Adams et al., 1996). However, these conclusions were drawn from a non-controlled review of brain CT scans.

The rationale for the current study is based on the lack and inconsistency of information on the clinical utility of performing brain MRI scans in children and adolescents with EOP so far, focusing on cases of psychosis of unknown origin. We aimed (1) to assess the prevalence of abnormal radiological findings in adolescents with EOP without neurological symptoms in comparison to a sample of healthy controls and (2) to determine whether abnormal radiological findings changed any established clinical behavior. We hypothesized that patients with EOP would show a higher rate of radiological abnormalities than controls, and that these would lead to more frequent clinical consultation in patients with EOP. As exploratory analyses, we examined whether, within patients with EOP, radiological findings were associated with other clinical and developmental variables.

2. Material and methods

This study was approved by the Clinical Research Ethical Committee of the Hospital Clínic of Barcelona and was carried out in accordance with the latest version of the Declaration of Helsinki (2013). A retrospective, single-center, controlled study was undertaken, which consisted of a chart review of patients admitted to the Inpatient Unit of the Department of Child and Adolescent Psychiatry and Psychology of the Hospital Clinic of Barcelona, from January 2013 to December 2017, relative to an age and biologically assigned gender matched control group.

2.1. Participants

Patients with EOP aged 10 to 17 were included if they fulfilled DSM-IV-TR criteria for a psychotic disorder with an onset within the previous 5 years, and had undergone a brain MRI scan during admission. In Spain, MRI scanning is recommended in all patients presenting with symptoms of a first episode of psychosis by local guidelines (https://www.ciberisciii.es/ficheros/SAM/Gu%C3%ADaPEPinfanciaAdolescencia_v5.0.pdf) (CIBERSAM, 2015). Patients were evaluated and diagnosed by experienced child and adolescent psychiatrists during hospitalization. All patients underwent a general medical screening at intake, which included a blood and urine sample. Diagnoses included psychosis not otherwise specified, schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder with psychotic symptoms and major depressive episode with psychotic symptoms. Given that they may be associated with a known cause of psychotic symptoms, patients with EOP presenting with neurological symptoms during physical examination at intake, or with clinical suspicion of an underlying neurological condition, such as epilepsy or encephalitis, were excluded from the analyses. Likewise, patients with drug-induced psychoses were excluded from the analyses, as were cases with substance dependence (given the difficulty to rule drug-induced psychosis in these cases).

The healthy control group consisted of individuals matched by age and gender, recruited in the context of previous research studies in the Department, through advertisements in primary care and community centers, and were from the same geographical area as patients. Specific exclusion criteria for control participants were any personal history of psychotic symptoms and the presence of any other current psychiatric disorder or substance dependence.

Exclusion criteria for the whole sample were: intellectual disability, history of head trauma with loss of consciousness or previously known neurological conditions, given that they may either increase likelihood of abnormal MRI scans and/or are known causes of psychosis.

2.2. Socio-demographic and clinical variables

In EOP patients, sociodemographic and clinical variables were recorded from their clinical charts. This information was obtained by the attending clinicians at intake and during hospitalization, from interviews with the patient, their caregivers and third parties, when necessary, in addition to clinical data registered by the patients' mental health team. The data included main and comorbid psychiatric diagnoses, age at onset of psychosis, illness duration, pharmacological treatment and comorbid substance use. Given the association of neuroradiological findings with perinatal complications and developmental delay or deviation, these data were also recorded and classified dichotomously. Perinatal complications included any alteration during pregnancy (e.g., first, second or third trimester abnormal bleeding, threatened premature labor, preterm membrane rupture, preeclampsia or eclampsia, gestational diabetes or viral infections) or during labor (e.

g., fetal macrosomia, protraction or arrest disorders, instrumented delivery, or emergency caesarean section). Developmental delays or deviations included any abnormality in the acquisition of developmental feats requiring evaluation or support by a specialist (such as specific learning disabilities; language, psychomotor or social difficulties, among others).

Control participants were assessed by child and adolescent psychiatrists or psychologists in the outpatient department of the same hospital, and information was obtained from both the participants and their caregivers. Socio-demographic information was collected, and a mental health evaluation was performed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL) (Geller et al., 2001); perinatal complications and developmental delays were not systematically recorded in this group.

2.3. Structural brain MRI scanning: acquisition and assessment

All individuals were scanned on a 1.5 T (General Electric) or 3 T (Siemens Trio) scanner systems at the Hospital Clínic of Barcelona. T1-weighted MP-RAGE images from the brain were acquired for every participant. Additionally, T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences were acquired in all cases. All brain MRI scans were evaluated systematically by a certified senior neuroradiologist from the Imaging Diagnosis Center of the Hospital Clinic of Barcelona, who then proceeded to elaborate a clinical report describing qualitative structural findings and suggestions concerning need for radiological follow-up and/or clinical referral.

MRI findings were classified as congenital malformations, cysts, vascular anomalies, white matter abnormalities, grey matter abnormalities, neoplasms, normal variations and other findings, according to an adapted classification of that proposed by Jansen and colleagues (Jansen et al., 2017). Extra-cranial findings, such as sinus abnormalities, were excluded.

2.4. Statistical analyses

IBM SPSS version 23 software (https://www.ibm.com/es-es/products/spss-statistics) was used to perform statistical analysis. T-tests and chi-square were used to assess socio-demographic and clinical variables. Chi-square tests were used for analyzing the main outcome variables and for exploratory analyses, one-sided Fisher's exact test was used when applicable to test the a priori hypotheses. Odds ratios (OR) were calculated for the main outcome analyses, and the 95% confidence interval (CI) was used to estimate the precision of the OR.

3. Results

One hundred twenty-eight patients with EOP and 128 age and sex matched controls were included. Clinical and demographic characteristics of the sample are summarized in Table 1. Thirty-two patients with EOP with an available brain MRI scan were excluded from the analyses due to the following reasons: drug-induced psychosis and/or substance dependence (n = 10), intellectual disability (n = 10), epilepsy diagnosis (n = 7), and other neurological conditions (n = 5), Among patients with EOP, 46.1% (n = 59) presented psychiatric comorbidities. The most common diagnoses were depressive (17.2%, n = 22) and eating disorders (10.9%, n = 14), followed by behavioral disorders -which included oppositional defiant and conduct disorders- (7.8%, n = 10), attention deficit and hyperactivity disorder (7.8%, n = 10), autism spectrum disorders (7.0%, n = 9), anxiety disorders (2.3%, n = 3), obsessive-compulsive disorder (2.3%, n = 3) and post-traumatic stress disorder (2.3%, n = 3).

3.1. Brain MRI findings

Patients with EOP presented a higher prevalence of abnormal MRI scans in comparison to controls (21.9%, n = 28 vs 11.7%, n = 15, χ^2 = 4.72, p = .030; OR = 2.11, [95% CI: 1.06, 4.17]). For a detailed account of type of neuroradiological finding, specialist referral and management according to radiological reports, see Table 2. Among cases with an abnormal MRI scan, 42.9% (n = 12) of patients with EOP presented more than one radiological finding, while this was the case in 20.0% (n = 3) of controls. Patients with EOP (n = 32) who had been excluded from the analyses had a 37.5% rate of abnormal MRI scans.

Within the EOP group, patients with perinatal complications had a higher proportion of abnormal MRI scans than those who did not, at trend level significance (34.5%, n = 10 vs 18.1%, n = 15, χ^2 = 3.34, p = .068; OR = 2.39, [95% CI: 0.92, 6.16]). There were no significant differences in terms of proportion of radiological findings within patients with EOP when divided by sex, age at MRI, age of onset of disease, illness duration, diagnosis, neurodevelopmental delay/deviations, psychiatric

Table 1
Socio-demographic and clinical characteristics of individuals with Early-Onset Psychosis and Healthy Controls.

	EOP (n = 128)	HC (n = 128)	*Test, p-value*
Sex (%females)	56.3% (n = 72)	53.9% (n = 69)	$\chi^2 = 0.14$, $p = .706$
Age (years, SD)	14.9 ± 1.7 [10–17]	14.9 ± 1.7 [10–17]	$t = 0.04$, $p = .957$
Abnormal MRI findings	21.9% (n = 28)	11.7% (n = 15)	$\chi^2 = 4.72$, $p = .030$
Duration of illness (weeks, SD)	19.2 ± 47.0	–	–
Perinatal complications (N = 112)	25.9% (n = 29)	–	–
Developmental delay and/or alteration (N = 120)	30.8% (n = 37)	–	–
Psychosis diagnosis			
Psychosis NOS	68.8% (n = 88)	–	–
MDD with psychosis	10.2% (n = 13)	–	–
BD with psychosis	7.8% (n = 10)	–	–
Schizoaffective disorder	4.7% (n = 6)	–	–
Schizophreniform disorder	4.7% (n = 6)	–	–
Schizophrenia	3.9% (n = 5)	–	–
Psychiatric comorbidity			
ADHD	4.5% (n = 10)	–	–
ASD	4.1% (n = 9)	–	–
Conduct disorder	4.5% (n = 10)	–	–
Depressive disorder	15.9% (n = 35)	–	–
Eating disorder	6.4% (n = 14)	–	–
Treatment			
Antipsychotics	100.0% (n = 128)	–	–
Mood stabilizers	18.0% (n = 23)	–	–
Antidepressants	35.9% (n = 46)	–	–
Stimulants	1.6% (n = 2)	–	–
Substance use			
Total	31.3% (n = 40)	–	–
Cannabis	28.1% (n = 36)	–	–
Alcohol	18.0% (n = 23)	–	–
Other substances	2.4% (n = 3)	–	–

EOP = Early Onset Psychosis; HC= Healthy Controls; SD = standard deviation; MRI = magnetic resonance imaging; NOS = Not otherwise specified; MDD = Major depressive disorder; BD = Bipolar disorder; ADHD = Attention-deficit/hyperactivity disorder; ASD = Autism spectrum disorder.

Table 2
Neuroradiological findings in patients with Early-Onset Psychosis and healthy controls.

Neuroradiological Findings			EOP (n = 28)	HC (n = 15)	Clinical Referral		Clinical Management
					EOP	HC	
Variants	Mega cisterna magna		5	1	–	–	
	Prominent temporal horns		1	–	–	–	
	Transverse sinus hypoplasia		1	–	–	–	
	Ventricular asymmetry		4	–	–	–	
Congenital malformations	Chiari I malformation		2	–	2	–	Neurology referral; one case was associated with clivus lipoma, the other was associated with periventricular gliosis, posterior corpus callosum hypoplasia and augmented hypophysis size
	Hypoplasia/Partial agenesis of the corpus callosum		2	–	[a]	–	
	Cerebellar hypoplasia (Joubert Syndrome)		1	–	–	–	
	Hypoplasia of brainstem		1	–	[a]	–	
Cysts	Arachnoid cyst	<3 cm	5	5	–	–	
		≥3 cm	–	1	–	–	
	Rathke's cleft cyst		2	–	2	–	Endocrinology and Neurology referral. Hypophyseal MRI follow-up. One case was associated with *megacisterna magna*, an arachnoid cyst and perivascular dilated spaces.
	Germinolytic cyst		–	1	–	–	
	Pineal cyst		–	1	–	–	
	Choroidal fissure cyst		1	1	–	–	
	Neuroepithelial cyst		1	–	–	–	
Vascular anomalies	Developmental venous anomaly		2	1	–	–	
Ventricular system	Ventricular dilation		3	–	–	–	
White matter abnormalities	Gliosis		1	2	–	–	
	Focal hyperintensity	Single	1	–	–	–	
		Multiple, <20	3	2	–	–	
		≥20	1	–	1	–	Neurology referral; associated with partial agenesis of the corpus callosum and brainstem hypoplasia.
Grey matter abnormalities	Amygdala alteration		1	–	1	–	Neurology referral and MRI follow up. Hamartoma vs ganglioma. Associated with mesial sclerosis
	Mesial sclerosis		1	–	[a]	–	
	Focal grey-matter lesion		–	1	–	1	Neurology referral
Neoplasms	Low-grade glioma		–	1	–	1	Neurosurgery referral and nuclear medicine follow-up.
	Pituitary adenoma		1	–	1	–	Endocrinology referral and MRI follow-up
	Cystic Adenoma Sella Turcica		–	1	–	–	
Other	Clivus lipoma		1	–	[a]	–	
	Paramagnetic material deposit		1	–	1	–	Hepatology and Ophthalmology referral to discard Wilson's disease. Hepatic ultrasonogram and blood and urine analysis.
	Augmented hypophysis		2	–	[a]	–	
	Hemosiderin focus in caudate nucleus		1	–	1	–	Neurology referral and electroencephalogram testing; associated with ventricular system dilation and asymmetry.
	Perivascular dilated spaces		2	–	–	–	
Total			47	18	9	2	

Adapted from Jansen et al. *(2017)*.
EOP = Early Onset Psychosis; HC= Healthy Controls.
[a] Patient referral or follow-up already accounted for in another row due to multiple findings in the same subject.

comorbidity or drug use (Fig. 1).

3.2. Clinical management and follow-up

Overall, patients with EOP required clinical referral to another specialist due to the results of their brain MRI scan more often than controls (7.0% vs 1.6%, Fisher's exact test, p = .030; OR = 4.76, [95% CI: 1.01, 22.50]) (Table 2). Among those presenting with an abnormal MRI scan, 32.1% (n = 9) of patients with EOP were referred to a medical specialist for further assessments and/or follow-up, in contrast with 13.3% (n = 2) of controls. The most frequent referral among the EOP group was to a specialist in neurology (66.7%, n = 6), followed by endocrinology (22.2%, n = 2). Among the control group, one participant was referred to a specialist in neurology and the other to a neurosurgical consultation. Within the EOP group, clinical referral was not significantly associated with either sex, diagnosis, history of perinatal complications, neurodevelopmental delays/deviations, psychiatric comorbidity, or drug use.

4. Discussion

To the best of our knowledge, this is the first study to specifically assess radiological abnormalities in adolescent patients with EOP with an unknown cause of psychosis in comparison to healthy controls. The main results of the study were that patients with EOP presented higher rates of qualitatively abnormal brain MRI scans, and these were linked to significantly more changes in clinical management, in relation to controls.

In agreement with our first aim and hypothesis, in our sample, patients with EOP had greater odds of qualitative findings in their brain MRI scan than controls. This contrasts with results from the largest study so far assessing radiological abnormalities in psychosis (Sommer et al.,

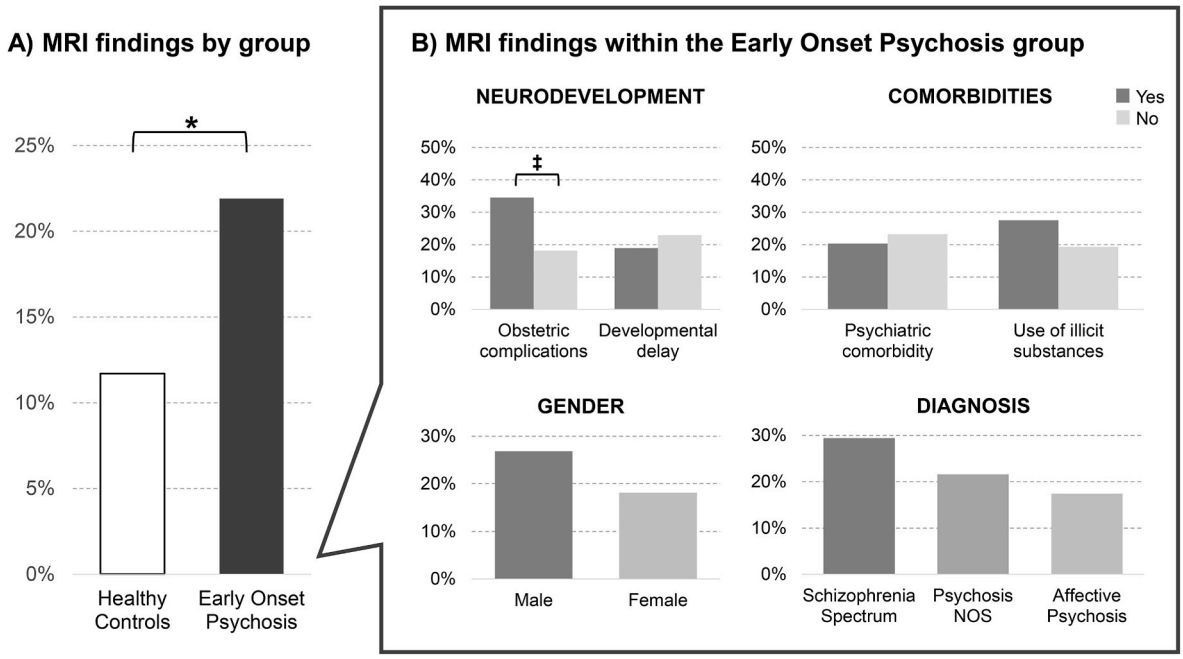

Fig. 1. Percentage of radiological findings in brain magnetic resonance imaging scans in adolescents with early onset psychosis compared to healthy controls (A) and divided according to the presence (yes; in dark grey) or absence (no; in light grey) of clinical characteristics within the case group (B).
MRI = Magnetic Resonance Imaging; Psychosis NOS = Psychotic disorder Not Otherwise Specified; ‡$p < .1$; *$p < .05$.

2013), in which Sommer et al. assessed 656 scans of patients obtained for research purposes in relation to healthy controls, and found no differences in rates of radiological findings between groups. Nevertheless, in a more recent report, Falkenberg and colleagues demonstrated that radiological abnormalities in patients with psychosis may be underestimated within research settings, possibly due to a priori exclusion of participants with suspicion of organic abnormalities or comorbidities (Falkenberg et al., 2017). Our study has the advantage of being performed in a setting where MRI scans are included in current clinical guidelines for patients with a first episode of psychosis. In this study, patients were assessed in a clinical environment, and were only excluded when a neurological condition was diagnosed or suspected clinically, and when they presented other conditions that have either been associated with higher percentages of brain MRI abnormalities, and/or are known causes for psychosis.

We have only identified one study so far providing information on brain radiological findings in youth with EOP (Adams et al., 1996). Adams and colleagues documented 11% of abnormal brain CT scans in a sample of 98 adolescents (aged 13–19 years). However, this study lacked a control group, and CT has poor spatial resolution in soft tissue, which limits its sensitivity and specificity when compared to MRI, and may lead to an underestimation of most common radiological abnormalities (Chalela et al., 2007; Falkenberg et al., 2017). Overall, the rates of radiological findings in our sample fall in the lower range of rates reported in most studies using MRI to assess radiological findings in adult patients with psychosis, which vary between 22.2 and 40.0% (Borgwardt et al., 2006; Falkenberg et al., 2017; Lubman et al., 2002; Sommer et al., 2013). This may be related to the substantially younger mean age of our sample, since some brain MRI findings, such as cortical atrophy, enlarged ventricles or white matter lesions, tend to increase with age (Falkenberg et al., 2017), and possibly with illness duration (Kubota et al., 2015). In our sample we found no association between illness duration and rates of MRI findings, which is likely due to the short overall duration of the disease, and supports the notion that some of the findings observed in patients with EOP may be associated with processes occurring early on in the biological course of the illness. A study qualitatively assessing MRI scans in individuals at clinical high risk for psychosis also found an increased number of radiological abnormalities in these subjects, suggesting that some macroscopic brain abnormalities are likely to emerge before clinical onset of the disease (Borgwardt et al., 2006). In our study, the most frequent findings were those classified as variants, cysts and congenital anomalies (which included Chiari I malformation, abnormalities of the corpus callosum, and cerebellar or brain stem hypoplasia) and cysts, while in the sample by Sommer et al.[11], which consisted of adult patients, nearly half of whom were multiepisode, the most prevalent, clinically relevant findings, were white matter abnormalities and atrophy.

Patients with EOP represent a subset of patients which have been associated with higher rates of negative and cognitive symptoms, poorer long-term outcomes (Arango et al., 2014; Rapoport et al., 2001; Vourdas et al., 2003), and greater genetic susceptibility for the disease (Ahn et al., 2016) than when onset of psychosis occurs during adulthood. They have also been associated with higher rates of perinatal antecedents (Scherr et al., 2012) and pre-morbid neurodevelopmental deviations (Biswas et al., 2007; Petruzzelli et al., 2015). In addition, obstetrical complications have been shown to elevate the risk of psychosis and to increase the odds of brain abnormalities detected by CT or MRI (Costas-Carrera et al., 2020; Mezquida et al., 2018). This may have contributed to the different number and type of radiological findings in our sample relative to studies focusing on adult-onset psychosis. This is further supported by our finding of a more frequent history of perinatal complications in patients with EOP with MRI abnormalities, albeit at trend-level significance.

The second outcome of the study concerned whether radiological findings led to changes in clinical management. A recent review including 16 studies assessing abnormal radiological findings in first episode psychosis concluded that there was insufficient evidence to suggest that brain imaging should be routinely ordered in these patients, since findings rarely required clinical intervention and were very rarely the cause of the psychotic symptoms (Forbes et al., 2019). This conclusion was similar for patients with EOP assessed with a CT scan (Adams et al., 1996). In our study we found that the findings in MRI scans in patients triggered further clinical consultation in a small number of cases, yet this was significantly more common than in

controls: 7% of all EOP participants included in the sample were referred to another medical specialist for further testing or follow-up due to an abnormal MRI scan (32.1% of EOP patients with any radiological finding), and this was unrelated to diagnosis, perinatal antecedents or any other clinical or demographic characteristic in our sample. Whether this data would justify performing routine MRI scans in all patients with emerging psychosis is dependent on several factors. In terms of cost-effectiveness, the only health economic analysis that we are aware of so far, calculated on the basis of adult patients, concluded that MR and CT imaging were only justifiable if the prevalence of findings underlying organic psychosis, and leading to changes in treatment, was 1%, and the time between presentation and assessment was less than 3 months. However, other authors have stressed that the consequences of failing to identify organic conditions underlying psychosis in young adults (Borgwardt et al., 2006; Falkenberg et al., 2017; Schmidt and Borgwardt, 2020) may be so serious that it is worth assessing all patients at disease onset. This may be even more relevant when considering child and adolescent population (CIBERSAM, 2015).

Although no radiological finding was considered to be the direct cause of psychotic symptoms in our sample, many of the findings documented in the EOP group have been associated with vulnerability to psychosis (Novak et al., 2018). For instance, various reports have established a relationship between Arnold-Chiari malformation and psychotic symptoms, due to the compression of the locus coeruleus, epileptiform activity, or recurrent ventricular-peritoneal-shunt obstruction and episodes of hydrocephalus (Hoederath et al., 2014; Ilanković et al., 2006). Abnormal corpus callosum and abnormalities of white matter more generally have also been shown to be evident early in the course of psychosis (Prendergast et al., 2018; Di Biase et al., 2017). Pituitary adenomas may be the cause of a potentially treatable psychotic disorder when associated with Cushing's syndrome (Fujii et al., 2018). Furthermore, rupture of Rathke's cleft cyst has also been deemed as a potential cause of hypophysitis, an inflammatory response that has been implicated in a handful of case reports of secondary psychotic symptoms (Schittenhelm et al., 2008). Posterior fossa lesions, such as mega-cisterna magna, present in 5 EOP patients in our sample, have also been hypothesized to affect dopamine, serotonin, and noradrenergic networks in the brain through the disruption of cerebellar connectivity to mesial dopaminergic areas, locus coeruleus, raphe nuclei, or thalamo-limbic circuits (Pollak et al., 1996). Mesial sclerosis and associated temporal lobe epilepsy have been reported as a potential cause of psychosis (Gayubo Moreo et al., 2004; Puppala et al., 2009), and the role of structural abnormalities of the temporal lobe in psychosis has been widely documented (Roalf et al., 2017; Sumich et al., 2002; Thom et al., 2014). Finally, systemic illnesses such as Wilson's disease may also be the cause of psychotic symptoms due to the deposit of copper in brain, and the excess serum copper is thought to affect dopamine and serotonin systems (Zimbrean and Seniów, 2017). Whether these findings are associated with other brain changes which may be identifiable more generally in patients with psychosis is a question that will need to be assessed with quantitative imaging methods, the use of which is currently limited to the research domain. Future research is also needed to investigate the association between these MRI abnormalities and symptom and illness trajectories.

This study has several limitations. First, the fact that in EOP patients' data was obtained from the historical review of clinical charts, accounts for limited quality of data concerning perinatal complications and neurodevelopmental milestones, which were not recorded using a standardised tool. Second, the control group was recruited through research protocols, which some authors have suggested may underestimate the presence of brain radiological findings (Falkenberg et al., 2017). However, in our study inclusion criteria were broad, and all participants recruited for the study were included regardless of the results of their brain scan, unlike what often happens in quantitative research studies, where such cases are frequently excluded. Furthermore, patients with EOP who had co-occurring conditions associated with higher rates of brain abnormalities were excluded, since the aim of the study was to assess the utility of brain scans in patients with EOP without clinical suspicion of neurological abnormalities. Although the sample size is substantial, especially considering many of the previous studies on this topic, it does not allow to stratify the sample according to the nature and location of the MRI findings. This is important given that different findings are likely to have different clinical implications and pathophysiological correlates. Another shortcoming is that this study was not limited to patients with a first episode of psychosis. However, all patients were within the first five years of onset of the disease, and we observed no relationship between rates of radiological findings and illness duration. In addition, different field strengths (1.5T versus 3T) present small differences in sensitivity for detecting discrete brain lesions (Neema et al., 2009), although the rest of the evaluation was identical between scanners, and we expect this to have had negligible effects on our findings. It is also noteworthy that all EOP individuals were included during hospitalization in an acute psychiatric unit, and therefore all had severe forms of psychosis. Furthermore, the results regarding clinical referrals must be interpreted in the context of the study: differences between countries and clinical settings may influence decisions on referrals and follow-ups. Finally, the design of the study also prevented us from obtaining longitudinal clinical information: while we can establish the clinical relevance of the MRI findings, we are not able to determine whether the findings significantly changed the long-term clinical or functional outcome of the patients.

In conclusion, this study provides new insights on the rates of neuroradiological findings and clinical utility of routine MRI imaging in adolescents with EOP. We suggest that this be taken into account when assessing the decision to routinely perform brain MRI scans at illness onset in patients with EOP, given potential implications in terms of clinical management.

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Declaration of competing interest

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Associations between psychiatric disorders, COVID-19 testing probability and COVID-19 testing results: findings from a population-based study

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Background

Many psychiatrists are worried their patients, at increased risk for COVID-19 complications, are precluded from receiving appropriate testing. There is a lack of epidemiological data on the associations between psychiatric disorders and COVID-19 testing rates and testing outcomes.

Aims

To compare COVID-19 testing probability and results among individuals with psychiatric disorders with those without such diagnoses, and to examine the associations between testing probability and results and psychiatric diagnoses.

Method

This is a population-based study to perform association analyses of psychiatric disorder diagnoses with COVID-19 testing probability and such test results, by using two-sided Fisher exact tests and logistic regression. The population were UK Biobank participants who had undergone COVID-19 testing. The main outcomes were COVID-19 testing probability and COVID-19 test results.

Results

Individuals with psychiatric disorders were overrepresented among the 1474 UK Biobank participants with test data: 23% of the COVID-19 test sample had a psychiatric diagnosis compared with 10% in the full cohort ($P < 0.0001$). This overrepresentation persisted for each of the specific psychiatric disorders tested. Furthermore, individuals with a psychiatric disorder ($P = 0.01$), particularly substance use disorder ($P < 0.005$), had negative test results significantly more often than individuals without psychiatric disorders. Sensitivity analyses confirmed our results.

Conclusions

In contrast with our hypotheses, UK Biobank participants with psychiatric disorders have been tested for COVID-19 more frequently than individuals without a psychiatric history. Among those tested, test outcomes were more frequently negative for registry participants with psychiatric disorders than in others, countering arguments that people with psychiatric disorders are particularly prone to contract the virus.

Keywords

Epidemiology; service users; stigma and discrimination; outcome studies; COVID-19.

Background

Coronavirus disease 2019 (COVID-19) caused by the novel SARS-CoV-2 virus strain emerged in Wuhan, China in late 2019 and has since been declared a pandemic.[1] As of 21 April 2020, there have been over 2.4 million people with COVID-19 and 163 thousand deaths because of COVID-19 worldwide, with about half in the European region. The UK, the fifth most affected country, has reported over 124 000 people with COVID-19 and over 16 500 deaths.[2] The challenges of this pandemic to health systems, such as the National Health Service in the UK, include workforce scarcity, insufficient infrastructure and limited testing capacity.[3]

During epidemics, people with psychiatric disorders may be more susceptible to infections, experience complications and have more difficulties accessing health services.[4] Individuals with psychiatric disorders have been shown to have impaired access to somatic healthcare and physical health screening[5,6] because of a mismatch between patient needs and health systems[7,8] and stigma;[9] therefore, many psychiatrists are worried that patients with psychiatric and substance use disorders may be precluded from receiving timely and appropriate testing.[10]

In addition, individuals with a psychiatric disorder may be at increased risk for COVID-19 complications because of comorbid conditions (cardiovascular, respiratory and metabolic conditions, such as obesity)[11–14] and potential reduced adherence with government measures. However, these issues have remained debatable given the current lack of epidemiological data on associations between psychiatric disorders and COVID-19 testing rates and testing outcomes. More research has therefore been called for to address these questions during and after the COVID-19 pandemic.[15]

Aims

To address the questions of whether psychiatric disorders have any association with frequencies of testing and the results of such tests, we have targeted a large population-based study (the UK Biobank)[16,17] to perform association analyses of psychiatric disorder diagnoses with COVID-19 testing probability and such test results. We hypothesised that people with psychiatric disorders are tested for COVID-19 less frequently than people without a psychiatric disorder and that people with psychiatric disorders more frequently test positive than people without psychiatric disorders.

Method

The full UK Biobank cohort consists of 502 505 individuals recruited between 2006 and 2010, out of which 157 366 participants

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have information on a mental health questionnaire.[18] The composition, set-up and data gathering protocols of the UK Biobank have been extensively described elsewhere.[19,20] We made use of data from UK Biobank participants whose COVID-19 test results were released on 21 April 2020 under application access code 55392.[21] COVID-19 test results in the UK Biobank, reported in data field 40 100, are mostly derived from samples from nose/throat swabs (or a lower respiratory tract sample in intensive care settings), on which polymerase chain reaction is performed. The UK Biobank data field 40 100 is accompanied by the following statement: 'We are releasing COVID-19 test results from 16 March 2020 onwards, as after this date UK testing was largely restricted to those with symptoms in hospital. Detection of SARS-CoV-2 from samples taken from hospitalized patients after this date can, at least for now, be viewed as a surrogate for severe disease.'[22] The first data wave released comprises results from 16 March to 16 April, 2020.[22] Before analyses, duplicate entries of test results were removed from the COVID-19 testing results by selecting the latest test results for each participant.

UK Biobank has received ethics approval from the National Health Service National Research Ethics Service (ref 11/NW/0382). We used the STROBE cross-sectional reporting guidelines to assess research quality.[23]

For our main analyses we selected ICD-10 diagnoses from UK Biobank data field 41270.[24] We compared testing frequency and testing outcome in individuals with and without a diagnosis of a psychiatric disorder (F codes). To check whether testing frequency and test results resemble other health conditions, we then included several additional ICD-10 diagnoses in the analyses: (a) individuals with respiratory or cardiovascular diseases as these are particularly at risk for admission to hospital following infection with COVID-19 (ICD-10 codes Jxx and I0x–I7x); (b) people with metabolic diseases as these are highly prevalent among people with psychiatric disorders and may contribute to much of their generally poor health (codes E0x–E1x and E4x–E7x); and (c) those with central nervous system neurological disorders, as a comparison category of diseases resembling psychiatric disorders with regards to symptomatology and hypothesised neurobiological underpinnings (G0x–G4x). A more detailed description on conditions included is available in the supplementary Table 1 (available at https://doi.org/10.1192/bjo.2020.75).

Subsequently, we investigated each of the major psychiatric disorder categories with a prevalence above a threshold of 5% ($n = 74$) among individuals within the subsample that had test results available. We therefore included substance use disorders (F1x), mood disorders (F3x), and anxiety disorders (F40–F41) in the analyses.

All data was analysed in R v3.6.1.[25] We applied two statistical tests to answer the following primary research questions.

(a) Are people with a psychiatric disorder more or less likely to undergo COVID-19 testing than people without such a diagnosis? To answer this first question, we used two-sided Fisher's exact tests to examine distributions of individuals tested compared with the full UK Biobank cohort.
(b) Are people with a psychiatric disorder more or less likely to test positive for COVID-19 compared with those without such a diagnosis? To answer this second question, we ran logistic regression models, using the COVID-19 test results as a dichotomous outcome (negative/positive), with the ICD-10 diagnoses or mental health categories as predictors. We report the change in log odds (β) from these models.

Age, gender, body mass index and assessment centre were used as covariates in the logistic regression models as the first three have been associated with both psychiatric disorders and COVID-19, and assessment centre was added to these models to prevent regional differences having an impact on the results. To assess the robustness of our findings, we further ran a sensitivity analysis additionally covarying for socioeconomic status, as measured through the Townsend Deprivation Index, which has previously been used in the UK Biobank,[26,27] and pre-existing cardiovascular, respiratory and metabolic conditions as these are commonly observed in people with psychiatric disorders.

Secondary analyses included population-level information on mental health based on mental health questionnaire items asking participants whether they had ever experienced a core symptom of the major mental health categories (data category 136). For example, the two questions on depression were 'Have you ever had prolonged feelings of sadness or depression?' and 'Have you ever had prolonged loss of interest in normal activities?', tapping into the two core symptoms of major depressive disorder of depressed mood and anhedonia.[28] If participants had an affirmative response to either of these items, we scored the depression mental health category as present, otherwise as absent. This way, we aimed to examine relationships of the presence versus absence of mental health symptoms (depressive, manic, anxiety, addiction, psychotic experiences, self-harm and happiness items) with both testing probability and testing results in this general population cohort. To test this, we used identical analysis approaches as for the primary analyses, i.e. Fisher's exact tests and logistic regression with the same covariates as mentioned above. We also ran a sensitivity analysis for this secondary analysis by including the above-mentioned additional covariates, similar to the primary analyses. We ran these analyses with and without including individuals with a diagnosis of psychiatric disorder to disentangle whether people with any such diagnosis are driving results, and to what extent continuous measures of mental health are associated with COVID-19 testing probability and outcome. Please see the supplementary Tables 2 and 3 for an overview of all mental health items and more information on these analyses.

Results

The UK Biobank subsample with COVID-19 test results available consisted of 1474 unique individuals. Of these, 842 tested negative (57.1%) and 632 tested positive (42.9%) for the virus. Individuals tested were significantly older than those not tested in the UK Biobank (58.2 years (s.d. = 8.8) *v.* 57.0 years (s.d. = 8.1); $P = 2.2 \times 10^{-7}$), there were more men among those tested (54.4%) than among those not tested (46.6%), $P = 2.1 \times 10^{-9}$, and the average Townsend Deprivation Index was lower among those tested than among those not tested (−0.16 (s.d. = 3.53) *v.* −1.30 (s.d. = 3.09), $P < 10^{-16}$). There were no significant differences in age ($P = 0.51$), gender ($P = 0.14$) or socioeconomic status ($P = 0.13$) between those testing positive versus negative.

COVID-19 testing and ICD-10 diagnoses

Individuals with a psychiatric disorder were overrepresented among those tested, making up 23% of this sample compared with 10% in the full UK Biobank cohort ($P < 0.0001$; Table 1). This overrepresentation was similar to, or even higher than, that of people with diagnoses of cardiovascular, respiratory, metabolic, or neurological conditions (Table 1). Furthermore, this overrepresentation was also present for each of the specific psychiatric disorder categories investigated (Table 1).

In Table 1, the numbers of the individual categories add up to more than the total number of tested individuals. This is because of comorbidity i.e. the majority of individuals in the UK Biobank

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Table 1 Comparison of number of individuals present in the full UK Biobank cohort with those among the COVID-19 tested subset, per diagnostic group, ordered by decreasing ratio[a]

Diagnosis	Individuals in UK Biobank, *n* (%)	Individuals tested, *n* (%)	Ratio tested/in UK Biobank	*P*
Psychiatric disorder	50 506 (10.1)	344 (23.3)	2.32	1.1×10^{-49}
Neurological	27 950 (5.6)	187 (12.7)	2.28	4.9×10^{-25}
Metabolic	109 179 (21.7)	580 (39.3)	1.81	8.3×10^{-53}
Respiratory	88 095 (17.5)	465 (31.5)	1.80	3.8×10^{-39}
Cardiovascular	178 873 (35.6)	808 (54.8)	1.54	5.1×10^{-51}
Psychiatric disorder subcategories				
Depression	20 043 (4.0)	156 (10.6)	2.65	1.7×10^{-27}
Substance use	23 911 (4.8)	173 (11.7)	2.47	9.8×10^{-27}
Anxiety	11 536 (2.3)	80 (5.4)	2.36	5.5×10^{-12}

a. The columns indicate the number of individuals with a specific diagnosis in either the full UK Biobank cohort or in the tested subset, and the resulting ratio. The numbers in brackets indicate the corresponding percentage of individuals. The *P*-value is determined by Fisher's exact test.

have more than one ICD-10 diagnosis, and particularly individuals with psychiatric disorders have high rates of comorbidity. We have provided an overview of this comorbidity in Supplementary Table 2.

Among those tested, individuals with a diagnosis of a psychiatric disorder significantly less frequently tested positive for COVID-19 compared with those without such a diagnosis ($P = 0.01$, $\beta = -0.35$; Fig. 1a). When looking into specific psychiatric disorders, we found that particularly individuals with substance use disorders were significantly less likely to test positive ($P = 0.0002$; $\beta = -0.70$; Fig. 1b). Although people with anxiety and depressive disorders were also less likely to test positive than those without such a diagnosis, these results were non-significant.

The pattern of results did not change in our sensitivity analysis where we additionally covaried for pre-existing cardiovascular, respiratory and metabolic conditions, as well as socioeconomic status; both general psychiatric disorder and substance use specifically remained significantly associated with test outcome (Supplementary Fig. 1).

COVID-19 testing and mental health

Please see Table 2 for the prevalence of affirmative responses to mental health items among the full UK Biobank cohort versus those among individuals tested for COVID-19. As shown in the

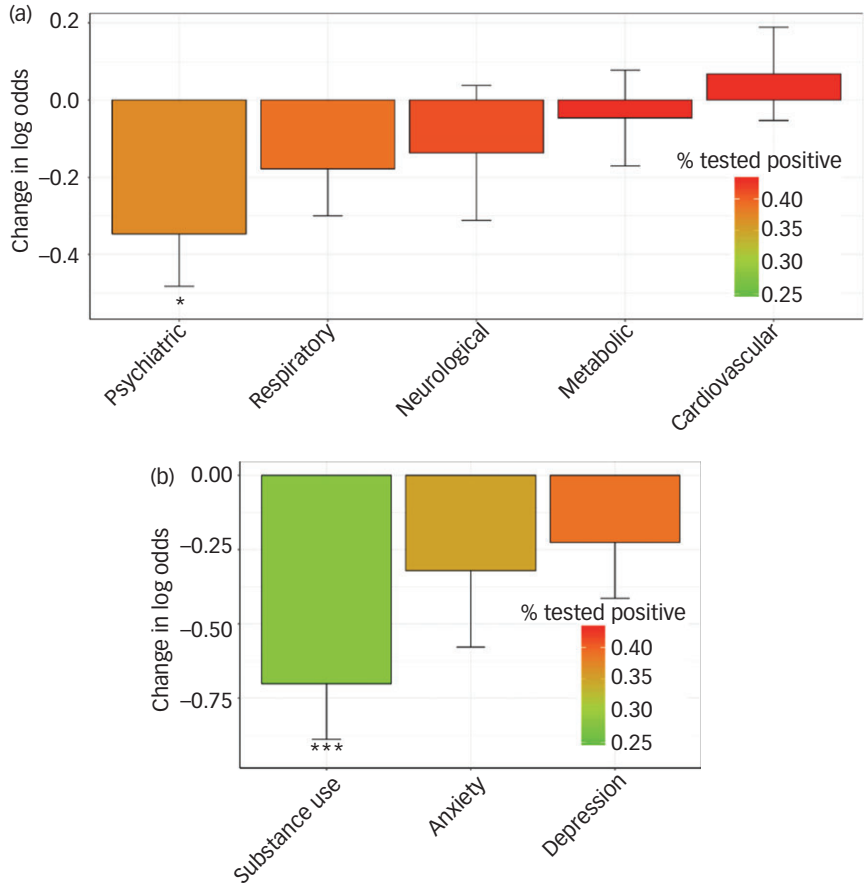

Fig. 1 Bar plot of change in log odds for testing positive, by ICD-10 diagnosis.

(a) The results for the main ICD-10 diagnoses, (b) results for the psychiatric disorders subcategories. Change in log odds is shown on the *y*-axis, with diagnosis on the *x*-axis. Colours indicate per cent that tested positive. *$P < 0.05$, ***$P < 0.0005$.

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Table 2 Comparison of number of individuals in the full UK Biobank cohort and those among the COVID-19 tested subset, per mental health questionnaire category[a]

Diagnosis	Individuals in UK Biobank, *n* (%)	Individuals tested, *n* (%)	Ratio tested/in UK Biobank	*P*
Happiness	86 010 (54.7)	177 (49.6)	0.91	0.04
Depression	89 034 (56.6)	225 (63)	1.11	0.01
Mania	42 499 (27.0)	109 (30.5)	1.13	0.14
Anxiety	55 199 (35.1)	142 (39.8)	1.13	0.07
Self-harm	30 418 (19.3)	87 (24.4)	1.26	0.02
Addiction	9 382 (6.0)	30 (8.4)	1.41	0.06
Psychotic experiences	7 803 (5.0)	29 (8.1)	1.64	0.01
Excluded individuals with a psychiatric disorder				
Happiness	86 010 (54.7)	149 (49.2)	0.90	0.06
Anxiety	55 199 (35.1)	111 (36.6)	1.04	0.59
Mania	42 499 (27)	87 (28.7)	1.06	0.52
Depression	89 034 (56.6)	185 (61.1)	1.08	0.12
Psychotic experiences	7 803 (5.0)	17 (5.6)	1.13	0.59
Addiction	9 382 (6.0)	22 (7.3)	1.22	0.33
Self-harm	30 418 (19.3)	73 (24.1)	1.25	0.06

a. The columns indicate the number of individuals with an affirmative response to a specific category in either the full UK Biobank cohort, or among the tested subset, and the resulting ratio. The numbers in brackets indicate the corresponding percentage of individuals. The *P*-value is determined by Fisher's exact test. The top half of the table indicates numbers across all participants, the bottom half the numbers after excluding individuals with a psychiatric disorder diagnosis.

top half of Table 2, there were significant differences in responses between those in the full cohort compared with those in the tested subsample. However, these differences were much smaller than those found for diagnostic categories, and they were no longer significant after excluding individuals with a psychiatric disorder (bottom half).

We further found no statistically significant associations between responses to the mental health items and test results, as shown in Fig. 2. These results stayed the same after correcting for the additional covariates (see supplementary Figures 2 and 3 for the full results).

Discussion

Main findings

Contrary to our hypotheses, we found that individuals with psychiatric disorders have been more frequently tested for COVID-19 compared with those without a diagnosis. Furthermore, among those tested, individuals with psychiatric disorders, substance use disorders in particular, had lower odds of testing positive than individuals without such a diagnosis. We believe these are important findings as they carry the potential to reduce stigma: while people in the general population may be concerned that individuals with psychiatric disorders do not comply with containment measures and are thus susceptible to contract COVID-19 our findings may help counter such concerns. Our findings also may help diminish concerns over limited healthcare access preventing people with psychiatric disorders from undergoing testing.

Interpretation of our findings

Before we elaborate on explanations for our findings, it is important to contextualise the high rate of positive tests relative to the total test number in the UK Biobank total study population (42.9%). The UK Biobank data provided testing results gathered from 16 March to 16 April 2020, when it was not part of any routine visit or protocol; as per the UK Biobank data-release information provided to researchers, only people showing severe symptoms were tested. Our data-set reflects the beginning of the pandemic in the UK, when testing was largely restricted to those with symptoms in hospital, i.e. people with severe cases, and when testing capacity was low. In this regard, the UK Biobank states that SARS-CoV-2 testing can be viewed as a surrogate for presentation of severe COVID-19 symptoms.[22]

Possibly, people with psychiatric disorders are being tested more frequently because of comorbid conditions, higher levels of anxiety about contracting COVID-19 or perhaps a combination of both. Furthermore, referring physicians' concerns about COVID-19 in people with psychiatric disorders may contribute to relatively high testing rates. Such reasoning may also, at least in part, explain higher rates of negative COVID-19 test results in people with psychiatric disorders.

Frequently observed negative test results could also be related to their higher chances of somatic illness relative to individuals without such a diagnosis or even with other pre-existing conditions. For example, patients with psychiatric disorders may present to hospitals with COVID-19-like symptoms but could be presenting an exacerbation of chronic pulmonary disease related to high rates of smoking, metabolic syndrome and sedentary lifestyle, further aggravated by late presentation to healthcare services because of poor living conditions or lack of social support. Such situations in patients with a history of psychiatric illness may lead to higher likelihoods of presentations of acute somatic illness requiring admission to hospital and thus, from March 2020 onwards, COVID-19 testing.

A final underlying reason for the low chances of positive COVID-19 testing in patients with a psychiatric history may be that they live relatively more socially isolated than people without such diagnoses. A non-controlled study has shown people with psychosis and mood disorders have about 1.7 social contacts in a week outside home, workplace or healthcare settings, and moderate feelings of loneliness.[29] Furthermore, a study on the relationship between living alone and psychiatric disorders using the 1993, 2000, and 2007 National Psychiatric Morbidity Surveys in the UK found a positive association between both variables that was up to 84% explained by loneliness.[30] Among young adults in modern Britain, relatively lonely individuals have been shown to be more likely to have depressive, anxiety, and alcohol use disorders.[31] Thus, lonelier, more socially isolated people such as those with psychiatric disorders may normally, and now even more so, be in confinement and have less social contact than people without psychiatric disorders, reducing the likelihood of testing positive for COVID-19.

Our results also show the frequency of individuals with a neurological condition undergoing testing being high, comparable with psychiatric disorders in the UK Biobank sample. This could be

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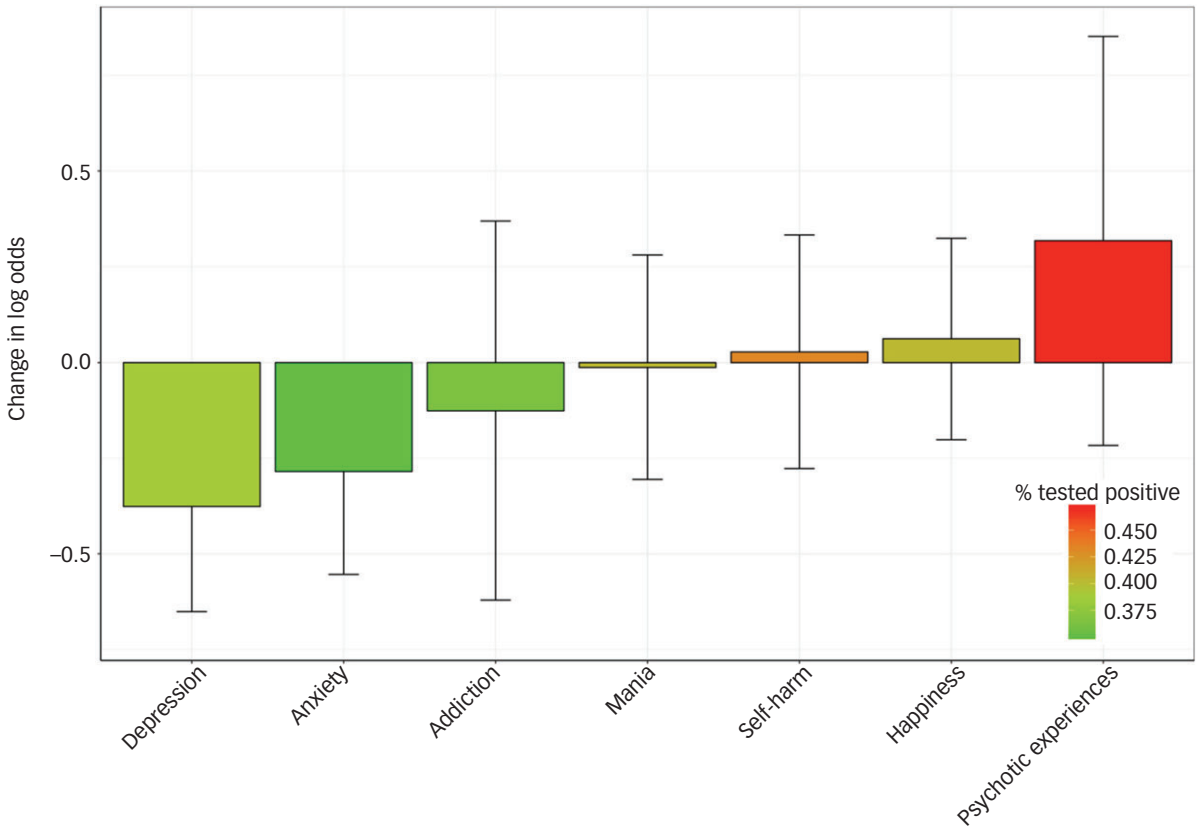

Fig. 2 Bar plots of odds ratios for testing positive, per mental health category based on affirmative responses to mental health questions in the mental health questionnaire in the UK Biobank, after excluding individuals with a psychiatric disorder diagnosis.

Odds ratios are shown on the *y*-axis, with the categories on the *x*-axis, colours indicate per cent that tested positive.

explained from a symptom-level perspective: psychiatric disorders show the most substantial overlap with neurological disorders regarding symptom domains such as cognitive function, behavioral alterations and mood. One example would be the high rates of depressive symptoms in Parkinson's disease[32] and multiple sclerosis.[33] Furthermore, dementias and other types of brain disorders causing behavioral symptoms are grouped within psychiatric disorders in ICD-10;[24] these show high degrees of symptom overlap with neurodegenerative disorders, especially regarding mood and cognitive functioning.[34,35] Therefore, people with neurological conditions, either comorbid with psychiatric conditions or presenting symptomatology overlapping with psychiatric symptoms, being both within the realm of brain functioning, would be expected to be affected similarly in the context of COVID-19.

Furthermore, when looking at the symptom level in the UK Biobank sample (mental health questionnaire items), no relationship was found between testing likelihood or outcome and continuous measures of depressive, manic, anxiety, addiction, psychotic experiences, self-harm or happiness items in those without a past or current diagnosis of psychiatric disorder. Therefore, people with clinical cases of psychiatric disorders, and not subsyndromic individuals, appear to drive our primary findings. Statistical power may currently hamper these analyses.

Limitations

Limitations of this study include the relatively small sample size, the fact that the UK Biobank is not fully representative of the general population,[36–38] absence of replication in other cohorts and lack of information on indications for testing at the level of the individual. The small sample size precluded individuals with diagnoses of some less prevalent psychiatric disorders, such as schizophrenia, schizoaffective disorder and bipolar disorders, to be represented in the analyses. Furthermore, assessment centre was used as a proxy for geographical location, and this variable was set at the start of recruitment, for example if individuals moved after the initial assessment this was not possible to take this into consideration.

Finally, detailed clinical information on indications for testing are unavailable for each individual, precluding us from running subgroup analyses per clinical indication. Nonetheless, the UK Biobank data gathered testing results from 16 March 2020 onwards when it was not part of any routine visit or protocol; as per the UK Biobank data-release information provided to researchers, only people showing severe symptoms were tested. This makes it relatively likely that patients were not tested routinely prior to admission for psychiatric reasons. Furthermore, although we believe having testing rates of other complementary exams would have been helpful to compare the COVID-19 testing with routine testing, we do not have information on other diagnostic procedures during admission, such as urine toxicology.

Implications

Despite the aforementioned limitations, two preliminary conclusions can be drawn based on the current data-set given the convergence of findings for a range of psychiatric disorders and similarities between testing probabilities. First, individuals with a psychiatric disorder are not less likely to undergo testing for COVID-19 than those without psychiatric disorders. Second, patients with

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psychiatric disorders do not test positive more frequently than people undergoing testing without such conditions. We encourage other researchers to perform similar analyses in other cohorts, as well as further research when more data from the UK Biobank become available, for example into associations between extended psychiatric symptom-level data, COVID-19 symptom severity and mortality.

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Supplementary material

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Data availability

UK Biobank data are available through a procedure described at http://www.ukbiobank.ac.uk/using-the-resource/.

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Author contributions

All authors conceived the study and interpreted the results. D.v.d.M. analysed the data. J.P.-E., D.v.d.M. and J.J.L. wrote the manuscript, which was revised by B.D.L., J.K.T., C.H.V. and S.G. J.P.-E. and D.v.d.M. are the guarantors.

Declaration of interest

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; J.P.-E. declares he has served as a CME speaker for Lundbeck, unrelated to this work, while the rest of the authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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REVIEW ARTICLE OPEN

Check for updates

Barriers to genetic testing in clinical psychiatry and ways to overcome them: from clinicians' attitudes to sociocultural differences between patients across the globe

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Genetic testing has evolved rapidly over recent years and new developments have the potential to provide insights that could improve the ability to diagnose, treat, and prevent diseases. Information obtained through genetic testing has proven useful in other specialties, such as cardiology and oncology. Nonetheless, a range of barriers impedes techniques, such as whole-exome or whole-genome sequencing, pharmacogenomics, and polygenic risk scoring, from being implemented in psychiatric practice. These barriers may be procedural (e.g., limitations in extrapolating results to the individual level), economic (e.g., perceived relatively elevated costs precluding insurance coverage), or related to clinicians' knowledge, attitudes, and practices (e.g., perceived unfavorable cost-effectiveness, insufficient understanding of probability statistics, and concerns regarding genetic counseling). Additionally, several ethical concerns may arise (e.g., increased stigma and discrimination through exclusion from health insurance). Here, we provide an overview of potential barriers for the implementation of genetic testing in psychiatry, as well as an in-depth discussion of strategies to address these challenges.

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INTRODUCTION

Genetic testing has evolved rapidly over recent years [1]. New technologies in genetic testing provide important new information about the diagnosis, treatment, and prevention of diseases and are of great value for precision medicine [2–4]. Nonetheless, at the time of writing, a range of barriers impedes such tests from being implemented in clinical psychiatry [5–7]. This review addresses the current state of genetic testing in psychiatry and lists recommendations on how to overcome such barriers. We first address general aspects of genetic testing, mainly its potential clinical yield. We then briefly discuss methods and applications of genetic testing in psychiatry, followed by a review on barriers to genetic testing as well as proposed ways to overcome them.

Indications for genetic testing vary by disorder. Given the current evidence and its widespread professional support we highlight examples of clinical testing indications for autism spectrum disorders (ASD). However, evidence to support direct-to-consumer testing will require further investigation for all psychiatric disorders. Regarding polygenic risk scoring (PRS) and pharmacogenetics, evidence is increasing rapidly, with high potential for future clinical translation of both, such as for diagnostic purposes and pharmacological interventions [8, 9].

POTENTIAL OF GENETIC TESTING IN CLINICAL SETTINGS

To date, genetic testing has been implemented most extensively in oncology and cardiology. For example, multigene panel testing for hereditary cancer predisposition, including breast, ovarian, and colorectal cancer, has been readily incorporated into clinical practice [10–12]. Due to the extensive overlap in cancer phenotypes and genetic heterogeneity, the use of panels containing a broad variety of hereditary cancer genes can have high clinical validity and improve risk assessment, early detection, and prevention of cancer [13, 14]. For already diagnosed patients,

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genetic panel testing can provide useful information for treatment decision-making [15]. Therefore, recommendations have been made to extend the use of genetic testing in oncology and include it as standard of care [15].

In cardiology, DNA-sequencing is widely used for the diagnosis and clinical management of heritable heart diseases, such as hypertrophic cardiomyopathy and long QT syndrome, with a diagnostic yield of genetic testing in the range of 30–50% and 60–70%, respectively [16]. Recent studies have also reported a potential role for PRS in cardiology. For example, in predicting coronary artery disease, it has outperformed any single traditional risk factor [17]. How psychiatry may benefit from the experience with clinical translation of PRS gained in other fields of medicine was recently reviewed elsewhere [18].

Oncology and cardiology are leading fields in the implementation of pharmacogenetic testing. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has produced prescribing guidelines for various drugs according to *CYP2D6*, *DPYD*, and *TPMT* genotypes in oncology [19–21], and *CYP2C19*, *CYP2C9*, *SLCO1B1*, and *VKORC1* genotypes in cardiology [22–24].

In psychiatry, genetic testing can be used to diagnose underlying genetic syndromes (e.g., 22q11.2 deletion syndrome) and—in research settings—to provide insight into prognosis and treatment response, particularly for disorders with high heritability estimates, such as ASD, attention deficit and hyperactivity disorder, schizophrenia, and bipolar disorder [25, 26]. The underlying causes of these disorders are often elusive, resulting in a range of diagnostic and prognostic uncertainties for patients and families. Identifying a genetic condition underlying the diagnosis can help clarify medical risks associated with the diagnosis, test family members at risk for the condition, and avoid unnecessary testing, particularly in ASD [27–31]. Additionally, genetic testing may provide information to identify, classify, and discriminate between different stages of disease or patient subtypes, thereby contributing to the objective of personalized patient care [32–34]. In research settings, genetics has also been shown to help identify prognostic factors, although their clinical applicability has remained unresolved so far [35]. Furthermore, genetic variation in drug response (pharmacogenomics) has been widely investigated: while evidence supports lower chances of drug-gene interactions for patients undergoing pharmacogenetic testing, effects of such genetic testing on remission rates have remained unclear [36]. In line with such findings, the CPIC has issued guidelines on the dosing of antidepressants according to *CYP2C19* and *CYP2D6* genotypes [37, 38]. However, with the advance of technology and new methodologies, focus has shifted from targeted *CYP* genotyping to genome-wide association studies (GWASs) as an important source of pharmacogenetics data. GWASs have proven successful in identifying complex pharmacogenomic traits in medicine, including psychiatry [39]. The largest GWAS of antidepressant response to date found that SNP-based heritability is significantly different from zero, although currently the power to predict such a response in other cohorts using whole-genome data seems limited [40]. Finally, genetic testing may also be a valuable part of multi-omics approaches, including neuroimaging, digital phenotyping, and computational models, when aiming to perform multimodal analyses of predictions for diagnosis, prognosis, and treatment response in psychiatry [41–43].

Should we move from targeted genetic testing to broad genetic testing?

Targeted genetic testing may be done to confirm a suspected diagnosis based on phenotypical or clinical features, family or personal medical history, such as in Duchenne muscular dystrophy and Fragile X syndrome [44, 45]. Using targeted genetic testing, a clinician aims to uncover whether an a priori hypothesized genetic etiology of a specified disease entity is present. In broad genetic testing, the disease entity is not pre-specified, but the clinician still suspects a genetic etiology of the clinical presentation. An example of broad genetic testing is whole-genome sequencing (WGS, sequencing of the entire genome) to examine a possible underlying genetic etiology in ASD (the current yield being around 10% in ASD) [46].

While targeted genetic testing answers a defined hypothesis ("*this* genetic etiology"), broad genetic testing addresses the question of genetic causation more broadly ("*a* genetic etiology") [47]. Broad testing has an increased probability of revealing incidental findings—which is the subject of ongoing debate about the consequences for patients and their families, interpretation of results, usefulness for research, and ethical, financial, and political concerns [48].

As next-generation sequencing gradually becomes less expensive, WGS and whole-exome sequencing (WES; sequencing the ~1% coding part of the genome) are becoming more and more feasible options in clinical practice [49]. However, cost-effectiveness has not yet been fully established and is likely to vary according to the clinical setting; [49, 50] for example, genetic testing is likely to be more cost-effective in neonatology than in family medicine settings.

Readiness—what is an appropriate test?

With ever-evolving technologies, it is essential to monitor and continuously evaluate whether tests meet the requirements to be considered sufficient to be implemented in clinical practice [51]. In general, genetic tests are assessed on the basis of four main topics: (1) analytical validity: the ability to accurately and reliably measure the genotype of interest—this is usually done by testing the sensitivity and specificity of the test; (2) clinical validity: the ability to accurately and reliably detect or predict a clinical condition—in addition to sensitivity and specificity, the positive and negative predictive values (PPVs and NPVs, respectively) of a test are examined; (3) clinical utility: the comparison of risks and benefits, and the assessment of clinical usefulness—this involves consideration of efficacy, effectiveness, and safety; and (4) ethical, legal, and social implications [48, 51–56].

ASD and intellectual disability (ID), collectively referred to as neurodevelopmental disorders (NDD), at present qualify as the only psychiatric disorders with enough evidence supporting genetic testing as part of standard clinical practice. Chromosomal microarray analysis (CMA) has been offered as a diagnostic tool for developmental delay as well as ASD for some years (for an example of a description with clinical indications, see cited references) [57, 58]. Nowadays, WES is recommended as first-tier clinical genetic diagnostic tool for NDD [59], with discussions ongoing for the incorporation of WGS as the first-choice genetic test in NDD [60]. Nonetheless, studies suggest low adoption rates of such tests in clinical practice [61]. For pharmacogenomics, important initiatives were recently launched in Europe with the funding of a large pharmacogenomics project for psychotropic medications by the EU Horizon 2020 program [62, 63].

Furthermore, when evaluating the clinical utility of genetic tests, special consideration must be given to risk. The effect size of risk (or resilience) on a group level, traditionally represented as the odds ratio (OR), must be translated to measures of individual risk, such as PPVs and NPVs. Although group- or population-level effect sizes may appear substantial, their clinical translation requires the application on an individual level, i.e., a translation that represents the individual risk of the patient, rather than the complete at-risk population [64].

METHODS AND APPLICATIONS FOR GENOMIC TESTING IN PSYCHIATRY

The field of psychiatric genetics has advanced tremendously over the past 20 years, with high potential for diagnostics, prognosis,

and treatment [1, 25, 65]. Several types of genetic approaches have been developed, including copy number variant (CNV) analysis, (targeted) next generation sequencing (NGS), and PRS. Below, we present a brief overview of genetic methodologies with the highest yield and utility within clinical settings in psychiatry.

Diagnosis and prognosis

With the advent of GWASs, hundreds of new genetic *loci* have been discovered to be associated with various diseases, including psychopathological traits [66] and psychiatric disorders such as anxiety and mood disorders [67, 68], and schizophrenia [69–71]. While genome-wide association analysis itself cannot be used as a test for diagnostic or prognostic purposes at an individual level, it does provide scientific support for individual calculations of PRS.

PRS can be considered as a measure of the cumulative impact of hundreds to thousands of individually weakly associated common genetic variants [72, 73]. As such, PRS is commonly defined as a single value estimate of an individual's propensity to a phenotype. It is calculated as a sum of their genome-wide genotypes weighted by the corresponding genotype effect sizes from summary statistics GWAS data [72, 73]. While common genetic variants usually only confer a subtle increase in risk for complex phenotypes when examined individually, their cumulative impact expressed in PRS confers a more substantial risk for the disease [8, 74, 75]. Findings from recent studies suggest that PRS may become a useful tool in psychiatry for both diagnostic and prognostic purposes. For example, patients with psychotic symptoms, as well as their relatives, have been found to present significantly higher PRS for schizophrenia and bipolar disorder than healthy controls [34, 76, 77]. PRS has also been shown to be useful in identifying a subset of individuals more likely to relapse and develop schizophrenia among individuals with first-episode psychosis [78–80], patients with schizophrenia likely to be treatment-resistant [81], as well as to be a predictor of antipsychotic effectiveness in individuals with first-episode psychosis [82]. However, several barriers, including low clinical significance, still need to be overcome before PRS can be clinically useful (see section "Barriers to genomic testing in clinical psychiatry settings") [9, 83].

While the risk for most psychiatric disorders has been shown to be influenced by many common, low-risk variants (as outlined above), rare and highly penetrant variants can also play a role. Even though each rare variant explains only a fraction of disease vulnerability in the population, on an individual level, they confer a much greater risk of developing a certain disorder than the risk predicted by PRS. For example, the risk for ASD in individuals with a 3q29 deletion or a 7q11.23 duplication is estimated to be 38% [84, 85] and 33% [86], respectively. Moreover, when comparing European individuals with ASD to matched controls, cases have been shown to carry a 1.19-fold higher global burden of rare CNVs, rising to a 1.69-fold higher prevalence for *loci* previously implicated in either ASD and/or ID [31]. Finally, the proposed clinical implementations of genetic testing in ASD include the development of new therapeutic strategies and the identification of treatable somatic comorbidities [30, 87, 88].

Treatment response prediction

Genetic variants, such as single-nucleotide variants (SNVs), have been associated with a higher risk of adverse drug reactions to psychotropic medications, such as antipsychotics and antidepressants [89]. For example, this is the case with clozapine, a second-generation antipsychotic drug indicated for treatment-resistant schizophrenia and useful in other psychotic and mood disorders [90]. Clozapine may induce agranulocytosis, a life-threatening condition that is associated with genetic variation in several genes, including *HLA-DQB1*, *HLA-B*, and *SLCO1B3/SLCO1B7* [91–95]. The subset of patients carrying any of these variants present a risk up to 1175% higher than the overall clozapine-treated population; therefore, performing genetic testing for this variant may be clinically useful in certain situations, e.g., when patients are prescribed clozapine but do not undergo regular blood checks [92, 96–98]. Another scenario where such testing may be of use is in patients diagnosed with 22q11 deletion syndrome. Although this group shows similar clinical improvement after clozapine therapy, seizures and other rare serious side effects are more commonly reported compared to clozapine-treated patients without 22q11 deletion syndrome (OR= 6.5 and OR=22.1, respectively) [99].

Moreover, investigating the clinical usefulness of genetic testing for indications is also relevant for lithium, given the high variability in response, the narrow therapeutic window, the potential severity of side effects, and the associated current underuse of this drug. In the largest lithium response GWAS to date by The International Consortium of Lithium Genetics (ConLiGen), a single locus of four linked SNPs on chromosome 21 was significantly associated with lithium response (all p values$<5.0\times10^{-8}$) [100]. The same study showed that patients treated with lithium who carried these associated alleles had a significantly lower rate of relapse compared to carriers of the alternate alleles (p value=0.03, hazard ratio=3.8) [100]. Another study (using largely the same dataset, based on 14 different sites) evaluated the extent to which lithium response could be predicted based on almost 48,000 genotyped SNPs using machine learning and found that lithium response could be predicted to above-chance levels in two sites of the dataset and in a subset with only those patients that were followed prospectively [101]. However, response could not be predicted in the overall dataset and it was suggested that this was due to heterogeneity arising from multisite data pooling [101].

Furthermore, over 50 cytochrome P450 enzymes are key for the metabolism of several medications, with 90% of all medications being metabolized by six of them, especially *CYP3A4* and *CYP2D6* [102]. *CYP3A4* is implicated in the metabolism of over 50% of commonly prescribed psychotropic drugs, including antipsychotics, antidepressants, anxiolytics, and mood stabilizers [89], and *CYP2D6* enzymes mediate the oxidative metabolism of at least 30 psychotropic medications [103, 104]. Additionally, polymorphisms of their encoding genes have been shown to influence patients' responses to risperidone and aripiprazole [105, 106], while recent evidence on clozapine hints that not genotype-predicted enzyme activity but rather phenoconversion-predicted enzyme activity (i.e., considering inducers and inhibitors) influences clozapine levels and symptom severity [98].

Finally, clinical guidelines have been developed by the CPIC on the prescription of selective serotonin reuptake inhibitors and tricyclic antidepressants by *CYP2D6* and *CYP2C19* genotypes [37, 38]; atomoxetine by *CYPD26* genotypes [107]; opioid therapy by *CYPD26*, *OPRM1*, and *COMT* genotypes [108]; and carbamazepine and oxcarbazepine by *HLA-A* and *HLA-B* genotypes [109].

BARRIERS TO GENOMIC TESTING IN CLINICAL PSYCHIATRY SETTINGS

Although promising, many of the abovementioned techniques and methodologies are not yet ready for direct implementation in the clinic. Below we elaborate on and analyze several barriers to the implementation of genetic testing in clinical psychiatry (Fig. 1), so that they may be more easily overcome, enabling safe and informed genetic testing and potentially setting the stage for precision medicine in psychiatry.

Methodological

Several methodological challenges currently stand in the way of the applicability of genetic testing at a patient level in psychiatry. First, the effect sizes and the explained variances of PRS at this moment are small, hampering their utility for individual risk prediction [53]. This individual risk prediction is expected to

Barriers	Recommendations
Methodological	
• Applicability and generalization across populations • Inequities in health provision	• Translation of group level findings to individual risk prediction metrics • Fostering of international, cross-population collaborations • Making summary statistics publicly available
Implementational	
• Perceived lack of cost-effectiveness • Coverage of costs • Facilities needed for implantation	• Informing policy makers and insurers about genetic research findings • Implementation of projects and genetic testing/counseling clinics • Large-scale international collaborations and sharing resources between institutions
Clinicians' knowledge, attitudes, and practices	
• Perceived lack of utility • Lack of knowledge, experience, and education • Lack of incorporation of genetic etiology into most psychiatric diagnostic systems	• Improved and intensified training programs • Interdisciplinary collaborations • Adding genetic etiology as specifier to our diagnostic systems and inclusion of genetic testing in diagnostic work-up
Potential harms of genetic testing	
• Psychological distress for patients and family members • Possible negative impact on self-perception, perceived control, stigmatization, and discrimination	• More research focused on genetic testing and counseling outcomes, including quality of life
Ethical concerns of clinicians, patients, and families	
• Ethical, social, and cultural issues • Inequalities between low-, middle-, and high-income countries • Possible mental incompetence	• Development of guidelines with special considerations for psychiatric disorders • Implementation of moral case deliberation sessions in clinical guidelines
Access to genetic counseling and understand of risk by patients	
• Low uptake of genetic counseling services • Limited availability of genetic counseling services • Possible misunderstanding of findings	• Increased involvement of patients and families in the development, implementation, and evaluation of genetic testing • Broad access to genetic counseling

Fig. 1 Barriers to genetic testing in clinical psychiatry settings and recommendations on how to overcome them. The first panel lists barriers as grouped in six different categories according to the nature of the barriers (i.e, methodological, implementational, etc.). In the same regard, recommendations are provided for each of the barrier categories.

improve by increasing GWAS sample size. However, even (relatively) large effect sizes found to date do not guarantee that PRS will be useful for individual risk prediction. It has recently been shown that PRS for schizophrenia did not improve individual outcome prediction compared with information from a routine psychiatric examination [110]. Thus, to achieve clinical utility, PRS must not only have predictive power, but also provide information that cannot be obtained by conventional means.

Second, there is still uncertainty about whether findings from studies can be extrapolated to people of different ancestries as risk differences attributable to ancestry may differ up to 10-fold [111]. So far, results remain conflicting, e.g., regarding the use of PRS for prognosis prediction in patients with first-episode psychosis. Similar discriminatory power for predicting case-control status and disease course was found in people of European and Brazilian ancestry, while this discriminatory power was considerably lower in people of African ancestry [79, 112]. At the policy level, these issues may raise concerns regarding health inequities as people of non-European ancestry may be at a disadvantage if they cannot also benefit from research, largely derived from European subjects [113, 114]. In addition, some authors even argue that PRS may be a "public health hazard," criticizing the lack of interpretation of genome-wide association signals at a cellular and physical level [115].

Implementational

Pharmacoeconomic research has shown conflicting evidence regarding cost-effectiveness of genetic testing [116]. Early studies in major depressive disorder seemed to suggest single gene testing was cost-ineffective [117]; however, more recent, multi-gene, commercially available pharmacogenomic testing has been reported to be cost-effective [118]. Without unequivocal evidence of its cost efficiency, the integration of pharmacogenomic testing in clinical practice will be impeded, as policy makers and other key stakeholders will refuse to provide funding.

In the United States of America (USA), physicians have historically considered funding a considerable barrier to the use of pharmacogenomic testing in clinical practice [119], and for successful implementation, at least genotyping costs must have public or private insurance coverage [5, 120]. Currently, some insurance providers in the USA (such as Managed Medicare and Medicaid) have introduced coverage determinations that enable reimbursement of pharmacogenetic testing, and while the number of claims for coverage of pharmacogenetic testing remains low, it has more than doubled in recent years [121].

Apart from implementation costs, some studies have also identified perceived pragmatic barriers to the implementation of genetic testing, such as infrastructure, human resources, and sustainability [6, 120, 122, 123]. The former would include the

required availability of testing facilities that may be accessible to all, as well as the availability of genetic counseling. Genetic testing should be accompanied by the provision of appropriate services ready to explain the implications of testing, perform the testing itself, and provide guidance regarding the test results [124, 125].

Clinicians' knowledge, attitudes, and understanding

Studies show that clinicians see the potential benefits of using genetic testing, such as guidance in therapeutic decision-making and a positive impact on patients' motivation and adherence, but they also mention several barriers [126, 127]. These include a lack of knowledge (not knowing which test to order or not feeling comfortable with interpreting test results), a perceived lack of utility (the results do not alter clinical decision-making), and even potential harmful implications to patients (concerns about the impact on the patients' employability or insurability) [128]. It would be hard to make a case for genetic testing on an already underserved, stigmatized population such as those with mental illness, when such a procedure would result in a loss of health insurance or employment [129].

Another significant barrier to the adoption of genetic testing is the lack of general understanding of genetics, probability and risk prediction by patients, families, and clinicians themselves [130].

Genetic knowledge is also seen as advancing at an accelerating pace. What is standard practice at the start of a clinician's residency may already be outdated by the end of it. This rapid change and advancement may cause clinicians, including psychiatrists, to feel uncomfortable making decisions about which tests to order, interpreting the results, and most importantly, communicating such results to patients and families [131].

Finally, genetic etiology has not been incorporated into most psychiatric diagnostic systems, e.g., the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Classification of most psychiatric disorders, such as schizophrenia, still relies solely on clinical signs and symptoms. Of note, the identification of a 'medical' cause is explicitly formulated as an exclusion criterion for most diagnoses, such as schizophrenia. This implies that people who meet the schizophrenia inclusion criteria and have an identified genetic etiology (e.g., 22q11 deletion syndrome) formally cannot be diagnosed with schizophrenia [88].

Psychological consequences and potential harms

Obtaining genetic risk information may also carry negative consequences for patients and their family members. First, there is the risk that patients and relatives may misinterpret complex genetic information. For example, when it is stated that "addiction is 50% genetic in origin", this can be understood in several ways. Families may understand that relatives have a 1 in 2 chance of developing a similar disorder or that a lack of positive family history somehow confers immunity [132]. Clearly, both conclusions are false; but the impact of such (common) misconceptions can be dramatic. As the positive perception of genetic testing increases with better understanding, it is essential to provide a clear explanation and confirm that the information has been correctly understood.

Psychological side effects of genetic testing include anticipatory fear and anxiety, particularly when a positive test result is expected and its implications are feared [133, 134]. After receiving a positive genetic test result, patients have been shown to feel as a burden on their families and experience feelings of blame and guilt. This psychological distress affects not only the patient but also family members, who themselves are confronted with a possible increased genetic risk of disease [134]. Self-perception can change negatively after realizing that one is at increased risk for a certain disease, something one may have been previously unconcerned about. Furthermore, given the common perception that genetic risks are immutable, perceived control over the disease, and motivation to change health-related behavior can decrease, secondary to a diminished belief that changing behavior will reduce risks [135, 136].

Lastly, commonly reported concerns with genetic testing include stigmatization and discrimination. Patients with psychiatric disorders are already among the most stigmatized groups in society, which can impair help-seeking and quality of treatment, and can lead to feelings of exclusion [137, 138]. Fear that genetic information will be used for discriminatory purposes by employers and insurance companies also constitutes an important barrier [129].

Access to genetic counseling

Adequate care after genetic testing, including support groups or psychological follow-up, is pivotal for both patients and relatives to cope with results [139, 140]. This can be achieved by embedding genetic testing in genetic counseling. However, at this point, genetic counselors receive relatively few referrals from psychiatrists, despite the reportedly high demand for psychiatric genetic counseling among people with mental illness [141]. Genetic counselors often do not provide this service to patients with mental illness and while most believe psychiatric genetic counseling may be valuable for both patients and family members, they also doubt the utility [141]. This is mainly due to the perception of genetic counselors that they do not have sufficient psychiatric genetic data, resources and time [141]. These issues are even more pressing in low- and middle-income countries (LMIC), where medical genetics training is even less implemented. Moreover, social and cultural determinants also play a key role in the uptake and understanding of genetic services. It has been argued that religious principles and cultural beliefs can pose barriers to the acceptability and use of genetic services [134]. However, we believe the opposite may also hold: religious traditions and thinking may provide valuable insights when discussing ethical aspects of genetic testing, e.g., regarding coping strategies when dealing with the setback of receiving a genetic diagnosis.

RECOMMENDATIONS TO OVERCOME BARRIERS TO GENOMIC TESTING

Below we outline recommendations to overcome the barriers discussed in the previous section. This is not meant as an extensive list and as new insights develop, undoubtedly new avenues to address such challenges will ensue.

Education

From medical school to medical specialty training, the acquisition of appropriate genetics knowledge, skills, and attitudes should be encouraged. This is of paramount importance given the role of psychiatrists in providing support and management to patients and families with, or at risk of, highly heritable psychiatric conditions [142]. Such education helps prepare for future clinical advances and should include empowering clinicians to identify patients who could benefit from genetic testing and counseling, to correctly interpret and apply results in clinical practice, and finally, to communicate genetic information in an understandable and nondirective manner [143].

Psychiatrists should always be aware of and assess the emotional, ethical, legal, and social impact of genetic information on patients and their families [128]. This can be further facilitated by interdisciplinary collaboration between general practitioners, medical geneticists, genetic counselors, and psychiatrists, which in turn may increase clinicians' knowledge and adherence to genetic testing recommendations and improve patient satisfaction [144, 145].

Furthermore, the International Society of Psychiatric Genetics formed a Residency Education Committee to identify key genetic knowledge to be taught in psychiatry training programs [142, 143]. Following this educational guideline may help empower future generations of psychiatrics and ensure adequate implementation of psychiatric genetic testing in clinical settings [4, 146].

On a similar note, training residents in the genetic aspects of mental health would encompass a wide range of clinical benefits.

For example, specific training may raise residents' awareness of genetic risk, allow for community support to patients and families, and facilitate reproductive counseling and family planning to parents with affected children. In addition, training programs may enable residents to make better informed medication choices to reduce the risk of severe medication side effects [142–144].

Implementation of genetic counseling

Initiatives such as PDGENE [147], an ongoing project aimed at offering both genetic testing and genetic counseling at no cost for people with Parkinson's disease in North America, are considered potentially useful in increasing not only patients' access to genetic counseling, but also clinicians' knowledge about the clinical relevance of test results [148]. Similar initiatives can be implemented in the field of psychiatry, to give patients and clinicians better access to genetic counseling, both on-site and remotely. In 2012, the first specialist psychiatric genetic counseling clinic opened in Canada, which was successful in fulfilling unmet needs of patients and family members with questions about the etiology and recurrence risks of disease and has been shown to enhance empowerment and self-efficacy [149].

It is important to make psychiatric genetic counseling services culturally appropriate, socially and financially accessible, and ethically coherent in order not to further alienate already underserved populations [150]. Especially for LMIC, resources for implementing genetic testing and counseling are currently limited. This could be enhanced by large-scale international collaboration [65, 151–153] and sharing resources between institutions, for example, through university-based exchange programs or government-level collaborations. An example of the latter is Genetic Testing in Emerging Economies (GenTEE), a European Union initiative aimed to inform policy decisions in LMIC on the challenges of delivering equitable access to genetic testing services [154].

Dissemination

We believe there is also a pressing need to help shape public mental health policies and clinical guidelines, by informing both public health systems and private insurance companies about tests that have shown beneficial clinical applicability, such as pharmacogenomic testing in cases of repeated nonresponse or high susceptibility to side effects. Factors considered by insurers when formulating medical coverage policies for pharmacogenomic testing include availability of clinical guidelines, use by physicians in current clinical practice, cost-effectiveness, and patient interest [5]. Moreover, the most determining factor in coverage is conclusive evidence of positive pharmacogenomic testing for health outcomes [146, 155, 156]. Whenever these conditions are met, insurers and public health systems should consider funding genetic testing. In the past few years, inroads have been made in the US, where pharmacogenetic testing, now covered by several insurance providers, has seen an increasing trend in its uptake [121]. In the Netherlands, the Dutch Pharmacogenetics Working Group [157] has already integrated pharmacogenetic testing into the prescription systems.

Overcoming implementation barriers

Commercially available pharmacogenetic tests are becoming increasingly accessible due to reduced pricing and simplified implementation procedures [158]. For example, a proposed "evidence-based" genetic testing panel includes a minimum gene and allele set for pharmacogenetic testing in psychiatry that includes 16 variant alleles within five genes (i.e., *CYP2C9*, *CYP2C19*, *CYP2D6*, *HLA-A, HLA-B*) [159]. Such a panel would allow the standardization of protocols to serve as an accompanying tool for clinicians in selecting psychotropic medications and dosing, including antidepressants and mood stabilizers [40, 160, 161].

In addition, some commercially available pharmacogenetic test panels may be well equipped to facilitate the implementation of most pharmacogenomic dosing guidelines relevant to psychiatry, including those associated with *CYP2D6* and *CYP2C19* [159, 161, 162]. However, one should be aware that currently commercially available gene panels show dramatic variability [163]. A standardized, transparent, and systematic evaluation of available evidence is needed to establish this evidence and reduce heterogeneity [159, 163, 164].

Regarding the current lack of integration of genetic etiology in the DSM-5, one way to close this gap is by adding genetic etiology as a specifier to the diagnosis, in addition to the symptom-based diagnostic criteria, as has been suggested for ASD [88]. By including known specifiers in classification systems whilst omitting exclusion criteria such as "attributable to a known medical condition," clinicians will be encouraged to assess and document genetic and nongenetic etiologies for improved diagnostics [88].

Bridging the gap between bench and bedside

We also signal a need to leverage the potential of genetic findings for diverse patient populations. The past years have indeed witnessed an increase in GWASs of mixed populations by the Psychiatric Genomics Consortium, as well as the coming into existence of genetic studies in currently underrepresented populations, as exemplified by the Latin America Genomics Consortium. Further advancing such diversity will facilitate greater PRS accuracy in populations of non-European ancestry [112, 113]. By addressing these research (and consequently health) inequities, the full and equitable potential of PRS will also be realized in individuals already underserved by health services [124, 125, 134].

Additionally, it is necessary to translate group level findings to individual risk prediction metrics to increase the clinical relevance of PRS [8, 53, 75, 165]. This can be done by using PPVs as these allow for stratification of individuals into groups with different outcome probabilities and because they depend on both the strength of association and the baseline prevalence [85]. Furthermore, before stratifying the entire population into risk groups, a more feasible goal may be to identify a subset of individuals already at risk for a certain disease, based on genetic factors in combination with clinical risk factors [53]. This may allow for better risk prediction at an individual level, as modest effect sizes conferred by PRS will lead to more substantial differences in absolute risk when applied in populations with a higher prevalence of certain phenotypes (as opposed to the low population prevalence of these phenotypes) [85]. Finally, more research should tackle the lack of current knowledge on the impact on quality of life in patients and their families after genetic testing in the context of psychiatry [140].

Developing new guidelines

First, we propose an update on current diagnostic guidelines that build on previous efforts, analogous to those published for ASD and ID [166, 167]. A statement on genetic testing is also available from the International Society of Psychiatric Genetics website (last updated in 2019) [168]. Furthermore, treatment guidelines should incorporate pharmacogenomic recommendations from the CPIC clinical guidelines [169] that are already available and further guidelines should be developed as new evidence arises for other drug classes, e.g., antipsychotics. The Dutch Pharmacogenetics Working Group [157] has called for a Europe-wide implementation of its pharmacogenetic guidelines, which would aid in their homologation and widespread use [170].

Moreover, genetic testing and counseling may be included in guidelines of psychiatric associations across the globe [171]. These guidelines should encompass special considerations for situations involving people with psychiatric disorders, including those with impaired mental competence. For example, in such guidelines ethical case deliberation sessions may be suggested for situations

where obtaining informed consent is not possible [172]. Procedures should be standardized and should aim to uphold human rights and bioethical principles, while at the same time accounting for cultural differences across the world.

Empowering patients and families

For successful implementation of clinical genetic testing, it is essential that patients, families, and caretakers' associations are involved in the process of development, implementation, and evaluation of genetic testing. These key stakeholders should be actively empowered and encouraged to provide voices and input that shape public mental health policy, clinical guidelines, and research proposals. By doing so, barriers to access genomic testing and genetic counseling may be overcome. Genetic counseling for psychiatric disorders has proven to be effective in increasing empowerment in both patients and family members [140, 149, 173]. We recommend that the next step is to make genetic counseling widely available for patients and families. The Genetic Counselling Outcome Scale or its abbreviated version, the Genomics Outcome Scale, may be used to measure patient-reported outcomes when evaluating genetic counseling and testing services [174].

CONCLUSIONS

With the advancement of new genetic testing methodologies, more discoveries can be made at a rapid pace in the field of psychiatric genetics. Several challenges currently hamper the implementation of psychiatric testing, be it broad or more targeted genetic testing in clinical settings. We are optimistic about the implementation of genetic testing in clinical psychiatry around the world as a variety of recommendations can be followed to overcome such barriers. To achieve this, it will be essential that all relevant stakeholders, and especially patients and family, are actively involved. We encourage future research projects to investigate the potential beneficial effects of these recommendations on genetic counseling settings and the quality of life of patients and their relatives around the world.

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AUTHOR CONTRIBUTIONS

All authors conceived and designed the review. JP-E, MvdH, and JJL wrote the manuscript. JZ, JA, CA, AB, PS, and JV revised the manuscript. JJL provided supervision. All authors have read and approved the final version of the manuscript.

COMPETING INTERESTS

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Discussion

A. Synthesis of Findings

The results from these studies collectively highlight significant advancements in our understanding of schizophrenia and its treatment. By integrating genetic, real-world, and neuroimaging data, this thesis offers a holistic perspective on the complex nature of schizophrenia and underscores the importance of personalized treatment approaches.

In **Chapter 1**, we explored how PRS enhance our understanding of schizophrenia's genetic underpinnings. Our findings suggest that individuals with higher PRS are more likely to require intensive treatments such as clozapine. This highlights the potential of PRS as a predictive tool for identifying those at greatest risk of severe clinical outcomes. Integrating PRS into clinical practice could enable earlier interventions tailored to an individual's genetic risk profile, offering a promising step toward personalized medicine in psychiatry (101).

In **Chapter 2**, we were able to finally quantify the age-old question of clinicians worldwide, *"To what percentage of my patients do RCTs results really apply?"* Our study addresses the representativeness of clinical trials in schizophrenia research. We found that 80% of real-world schizophrenia patients would be ineligible for participation in standard relapse prevention RCTs, raising concerns about the applicability of RCT findings to the broader patient population. Our results reveal that RCT-ineligible patients generally experience worse outcomes, supporting the need for more inclusive trial designs that reflect the heterogeneity of real-world schizophrenia patients (104).

In **Chapter 3**, we combined real-world evidence (RWE) with RCT data, challenging the notion that all antipsychotics are equally effective in practice (172). Our findings revealed significant differences in effectiveness, with clozapine and long-acting injectables (LAIs) such as olanzapine and aripiprazole demonstrating superior relapse prevention (105). These results suggest that existing treatment guidelines need to be updated to better reflect real-world outcomes.

Chapter 4 provided insights into the neurobiological basis of early-onset psychosis, where our neuroimaging findings indicate a higher prevalence of radiological abnormalities in youth with psychosis compared to healthy controls (106). This suggests a distinct neurobiological trajectory in early-onset psychosis, underscoring the potential of neuroimaging in early diagnosis and management.

Lastly, **Chapter 5** highlighted the healthcare disparities faced by individuals with psychiatric disorders during the COVID-19 pandemic. However, contrary to our hypothesis, our findings revealed that individuals with mental disorders, despite being tested more frequently, were less likely to test positive for the virus compared to those without psychiatric diagnoses (173). Results notwithstanding, it further served to set the stage for research and replication, and raise awareness on the need for more inclusive health policies that ensure vulnerable populations receive adequate healthcare during public health crises (161,163,173).

1. Genetic Contributions: Polygenic Risk Scores-Schizophrenia (PRS-SCZ) Study

The exploration of polygenic risk scores (PRS) in this thesis aligns with the latest advancements in understanding the genetic architecture of schizophrenia. Recent studies underscore that schizophrenia is influenced by a complex interplay of multiple genetic variants, each contributing modestly to the overall risk (175). The use of PRS has become increasingly valuable in stratifying patients based on their genetic liability to schizophrenia. Our research highlights that individuals with higher PRS are more likely to exhibit severe clinical phenotypes, necessitating treatments such as clozapine earlier in their therapeutic journey (101). This aligns with recent meta-analyses demonstrating the utility of PRS in predicting clinical outcomes in psychiatric disorders, including schizophrenia (176).

By incorporating PRS into treatment protocols, clinicians could better predict which patients are likely to respond to specific therapies, thus enhancing treatment efficacy and reducing the reliance on trial-and-error prescribing. In the case of schizophrenia,

where treatment resistance remains a significant challenge, the ability to anticipate clozapine response through PRS could revolutionize patient care by ensuring that the most effective treatment is administered from the outset.

2. Representativeness in Schizophrenia Research

The issue of representativeness in schizophrenia research is a significant limitation of current clinical trials. Our research demonstrates that the majority of individuals with schizophrenia seen in real-world clinical settings would not meet the stringent eligibility criteria of RCTs, thus limiting the generalizability of these trials to the broader schizophrenia population. That is, up to 80% of individuals in the real world would not meet the requirements to be included –or not excluded—from participating in a modern schizophrenia maintenance treatment trial.

Patients with comorbid conditions, treatment resistance, or complex clinical presentations are often excluded from trials, which leads to biased outcomes and limits the applicability of findings in clinical practice. Our analysis calls for more inclusive study designs that reflect the diversity of the real-world schizophrenia patient population. By exploring different avenues to make RCTs more representative, like focusing on subpopulations or large-scale innovative designs (155,177), we can develop findings that are more applicable to everyday clinical settings, ultimately leading to improved treatment guidelines and better outcomes for patients (104).

3. Integration of Real-World Evidence and RCT Data

Our study highlights the methodological challenges involved in integrating real-world evidence (RWE) with RCT data. These challenges include differences in study populations, treatment effects, and outcome definitions, yet the integration of these data sources is essential for a more complete understanding of treatment efficacy. RCTs, while providing high internal validity, often do not reflect the heterogeneity of

patients in clinical practice. RWE complements this by capturing the diverse range of patients treated in everyday settings.

Overcoming all the methodological challenges, we devised a novel approach that is a landmark on integrating RWE with RCT findings. We were able to conclusively demonstrate that clozapine and LAIs are more effective in preventing relapse compared to other antipsychotics in real-world scenarios. This is one of the first studies to match such large, high-quality, up-to-date datasets from RCTs and RWE and, by doing so, proved the effectiveness superiority of LAIs over oral formulations in real world settings.

These findings advocate for the use of both data sources when developing clinical guidelines, as this approach provides a more accurate reflection of treatment effectiveness in the broader patient population (102,104). The increasing use of RWE in psychiatric research reflects a broader shift towards more inclusive and generalizable study designs (178). Finally, our study may serve as a methodological blueprint for other fields of Medicine to elucidate their own clinical quandaries.

4. Neuroimaging and Early-Onset Psychosis

Our neuroimaging studies contribute to the neurodevelopmental hypothesis of schizophrenia, suggesting that early-onset cases may follow a distinct neurobiological trajectory. Advances in neuroimaging techniques have provided deeper insights into the structural abnormalities associated with schizophrenia, particularly in early-onset cases (179). Our findings are consistent with recent studies that have identified significant reductions in gray matter volume in critical brain regions, including the prefrontal cortex and hippocampus, in individuals at high risk for schizophrenia (180). The identification of these markers in youth with early-onset psychosis suggests that neuroimaging could play a pivotal role in early diagnosis and intervention, potentially improving long-term outcomes (181). It further supports the evidence advocating for routine brain MRI testing to remain an essential part of the medical evaluation recommended by clinical guidelines for diagnosing and treating early onset psychosis.

While neuroimaging has provided valuable insights into the neurobiological underpinnings of schizophrenia, our findings particularly emphasize the clinical relevance and applicability of these studies. Routine neuroimaging, without the need for super specialized machinery, equipment or training, was shown to be useful in identifying structural abnormalities that may underlie psychosis or other conditions. Furthermore, neuroimaging biomarkers may have the potential to significantly enhance early diagnosis and guide treatment strategies, especially in cases of early-onset psychosis. However, the focus should now shift towards translating these findings into practical tools that can be regularly used in clinical settings to improve patient outcomes.

5. Impact of COVID-19 on Schizophrenia

The COVID-19 pandemic highlighted the intersection between infectious diseases and psychiatric disorders. Contrary to our hypothesis, our study found that individuals with mental health disorders were more likely to be tested for COVID-19 at the beginning of the pandemic (173). This finding suggests that individuals with psychiatric conditions were tested more frequently than those without such diagnoses, a pattern that was particularly evident during the early stages of the pandemic when testing in the UK was largely limited to individuals exhibiting severe symptoms. This overrepresentation was seen across several categories of psychiatric disorders, but was especially prominent among individuals with substance use disorders, which showed significant associations with testing outcomes. Interestingly, our findings revealed that psychiatric disorders, particularly substance use disorder, were associated with negative COVID-19 test results. This means that individuals with psychiatric conditions, despite being tested more frequently, were less likely to test positive for the virus compared to those without psychiatric diagnoses. We consider these findings significant because they have the potential to reduce stigma. Although there may be public concerns that individuals with psychiatric disorders are less likely to follow containment measures and are therefore at higher risk of contracting COVID-19, our results challenge

this assumption. Additionally, our findings could alleviate worries about limited healthcare access preventing people with psychiatric disorders from being tested.

While our study did not find statistically significant associations between mental health questionnaire items and COVID-19 test results, it is important to note that this was a preliminary analysis, conducted during the early stages of the pandemic when testing availability was still limited. Published early in the pandemic, we called for future studies to investigate these relationships more comprehensively, particularly as more data became available and testing became more widespread. We also called for the need for continued investigation into how psychiatric disorders interact with infectious disease dynamics, particularly during public health crises, to better understand how to further prepare systems to respond in the best interest of vulnerable populations.

Subsequent observational studies on the relationship between COVID-19 and mental health provided contradicting evidence; however, one particular study by Luykx and Lin using Mendelian Randomization (MR) provided valuable insights. MR estimates causal effects using genetic variants, helping to address confounding factors and causality issues. Initially, findings suggested that genetic predispositions for both bipolar disorder and schizophrenia slightly increased COVID-19 risk. However, further analysis revealed that only genetic associations with BMI consistently influenced COVID-19 susceptibility. Thus, the authors concluded that there was no consistent evidence linking genetic liabilities to psychiatric disorders with COVID-19 risk, aligning with our study's results (182).

Other studies have shown that individuals with severe mental illnesses, including schizophrenia, are at increased risk of adverse outcomes from COVID-19, such as higher mortality rates (183). All in all, these results underscore the need for integrated care models that address both the physical and mental health needs of individuals with schizophrenia, particularly during public health crises (163).

B. Epistemological Implications of Integrating Diverse Research Findings

The integration of genetic, real-world, and neuroimaging data in this thesis presents critical epistemological implications for schizophrenia research, particularly in how we approach hypothesis testing frameworks. Traditionally, psychiatric research has relied on structured, linear models of hypothesis testing, often through RCTs, which prioritize controlled environments and isolated variables. However, schizophrenia, with its polygenic nature and variability in clinical presentation, demands a more nuanced approach that can capture its inherent complexity and heterogeneity.

By incorporating PRS, RWE, and neuroimaging, this research challenges the limitations of conventional frameworks. Each of these data streams offers a unique vantage point on schizophrenia: PRS provides insight into genetic predispositions, RWE reflects patient outcomes in actual clinical settings, and neuroimaging identifies structural brain changes related to potentially different schizophrenia neurodevelopmental phenotypes, especially in early-onset cases. Together, these sources present a multidimensional view of schizophrenia that traditional methods, such as RCTs, often fail to capture fully.

The inclusion of PRS highlights the need for genetic-based stratification in treatment, suggesting that genetic data can personalize care for those at higher risk of severe outcomes. RWE allows us to observe how these personalized treatments translate in real-world settings, moving beyond the narrow confines of trial populations to encompass the full spectrum of schizophrenia patients. Meanwhile, neuroimaging helps elucidate the neurobiological underpinnings of schizophrenia, particularly in relation to treatment resistance and disease progression.

Our findings support the intricate and iterative nature of hypothesis testing in the context of schizophrenia research. A key hypothesis tested was whether LAI antipsychotics outperform their oral counterparts in real-world settings, particularly in preventing relapse. The data from network meta-analyses and registry-based studies confirmed that LAIs are indeed more effective in routine clinical practice, aligning with

the hypothesis that these formulations benefit from improved patient adherence. This contrasts with the limited differences observed in RCTs, where the controlled environment often underestimates real-world challenges such as non-adherence.

Furthermore, this thesis tested the hypothesis that the efficacy observed in RCTs may not fully translate to real-world effectiveness. The results suggest that while there is a general concordance in the ranking of antipsychotic efficacy between RCTs and real-world data, the magnitude of the effects observed in RCTs tends to be larger. This confirms the existence of an "efficacy-effectiveness gap," particularly in populations that are less represented in RCTs, such as individuals with complex clinical profiles or lower adherence rates.

In the specific context of relapse prevention, the joint analysis of RCT and real-world evidence highlighted that clozapine and olanzapine and aripiprazole, particularly in their LAI formulations, consistently ranked among the most effective treatments. These findings support the hypothesis that certain antipsychotics, particularly those administered as LAIs, offer superior outcomes in real-world practice compared to what is suggested by RCT data alone. This reinforces the need for updated clinical guidelines that incorporate both RCT and real-world evidence to better inform treatment decisions.

The broader implication of these findings is that scientific knowledge in psychiatry, particularly in the treatment of schizophrenia, is built incrementally. Each study contributes to a more nuanced understanding of how treatments perform across different contexts, reinforcing the importance of ongoing hypothesis testing and revision. This thesis underscores the value of integrating real-world evidence into psychiatric research, as it provides a more comprehensive picture of treatment effectiveness in everyday clinical practice.

The epistemological future challenge here lies in adapting research methodologies to accommodate these intersecting layers of complexity. The integration of diverse findings suggests the need for flexible and robust research designs that move beyond rigid, single hypothesis-driven models. This approach emphasizes the importance of comprehensive, inclusive frameworks that account for the interrelated

variables influencing schizophrenia outcomes, rather than testing these variables in isolation.

Thus, this research advocates for a shift in schizophrenia studies toward more holistic, integrative methodologies. These new frameworks are better suited to the complexity of schizophrenia and offer a more accurate and inclusive reflection of the disorder, ultimately paving the way for more targeted and effective interventions. By challenging traditional approaches, we can open new avenues for understanding and treating schizophrenia in ways that reflect its full biological, clinical, and societal dimensions.

C. Implications for Clinical Practice

The findings presented in this thesis underscore the growing importance of personalized medicine in the treatment of schizophrenia, particularly through the lens of stratification. Our results demonstrate that polygenic risk scores (PRS) can serve as a powerful tool for stratifying patients based on their genetic predisposition to schizophrenia (101). This stratification could enable more tailored interventions, particularly for individuals at greater risk of severe, treatment-resistant forms of the disorder (184,185). Early identification of these high-risk patients through PRS-based stratification can help clinicians initiate more targeted treatments sooner, potentially improving long-term outcomes. However, clinical implementation of PRS requires further refinement, especially in terms of establishing standardized guidelines, addressing ethical considerations, and providing genetic counseling to support patients in understanding their risk (85,186). Further research is needed to establish standardized guidelines for the use of PRS in clinical practice (185).

Our research also highlights the potential of early intervention, supported by findings in neuroimaging, where youth with early-onset psychosis exhibited distinct structural abnormalities (106). These results reinforce the value of stratifying patients based on neurobiological markers, particularly in younger populations, to enable earlier and more precise interventions. By combining genetic and neuroimaging data, we can

develop stratified early intervention strategies that are tailored to individuals' specific risk factors, potentially delaying or preventing the onset of full-blown psychosis. This aligns with current research advocating for the early detection of neurobiological vulnerabilities in at-risk populations to improve clinical outcomes (187). Advances in neuroimaging, combined with genetic risk profiling, could enable the development of early intervention strategies tailored to individuals' specific risk profiles, potentially delaying or even preventing the onset of full-blown psychosis (47).

The growing body of evidence from RWE studies, including our own, suggests that current treatment guidelines may not adequately address the needs of the broader patient population seen in clinical practice. Recent discussions in the psychiatric community have called for more inclusive guidelines that reflect the diversity of patient presentations, particularly in light of findings that many patients excluded from RCTs experience worse outcomes (178). Our research contributes to this ongoing dialogue, emphasizing the need for guidelines that are informed by real-world data and that are applicable to the full spectrum of schizophrenia patients. Moreover, our findings show that a large proportion of real-world patients, who often have complex clinical profiles, are excluded from traditional RCTs (104). This discrepancy underscores the importance of revising treatment guidelines to incorporate insights from RWE, which more accurately reflects the heterogeneity of schizophrenia patients in routine clinical practice. For instance, our findings on the effectiveness of clozapine and long-acting injectable formulations (LAIs), such as olanzapine LAI and aripiprazole LAI, in real-world settings suggest that current guidelines should be updated to account for these superior relapse prevention strategies (105).

In conclusion, this thesis supports the growing recognition of the need for stratified approaches in schizophrenia treatment, combining genetic, neuroimaging, and real-world data. Implementing these insights into clinical practice can enhance early detection, optimize treatment effectiveness, and ensure that clinical guidelines more accurately reflect the complexity and diversity of schizophrenia populations.

D. Implications for Research and Future Directions

Future research should focus on further refining PRS methodologies to enhance their predictive accuracy and exploring their integration with other biomarkers and environmental factors. This approach could lead to more comprehensive models of schizophrenia risk, enabling earlier and more targeted interventions (184). Moreover, longitudinal studies on neuroimaging biomarkers will be crucial in understanding the progression of schizophrenia from a neurodevelopmental perspective (175, 182). Focus could also be put on protective genetic factors. For example, recent publications have explored the concept of a "polygenic resilience score," identifying genetic variants that may confer protection against schizophrenia in individuals with high genetic risk. This innovative approach seeks to explain why some individuals with a high polygenic risk score do not develop schizophrenia, potentially opening new avenues for prevention and treatment (188).

Other research avenues may include identifying neuroimaging biomarkers that can improve early diagnosis or further disentangle the possibility of a differential neurodevelopmental track in early-onset psychosis. Longitudinal neuroimaging studies are critical for understanding the neurodevelopmental trajectory of schizophrenia. Such studies could provide insights into the early brain changes associated with the onset of psychosis and identify potential targets for intervention (179). Future research should also explore the interaction between genetic risk factors and neurodevelopmental processes, contributing to a more nuanced understanding of the pathophysiology of schizophrenia (187). If not diagnostic, then prognostic markers could help clinicians to tailor interventions more effectively to individual patients based on their neurobiological profile.

Furthermore, the expansion of real-world evidence in psychiatric research is essential for developing more inclusive treatment guidelines that reflect the diversity of patient presentations in clinical practice. Future studies should focus on underrepresented populations to ensure the broad applicability of research findings across all schizophrenia patients (178). The use of advanced data analytics, such as machine learning, could further enhance the utility of real-world data in psychiatric

research (102,189). Moreover, our innovative studies methodologies to integrate RCT and RWE evidence could further efforts in other fields of Medicine besides psychiatry to improve representation and generalizability of treatment efficacy and effectiveness.

Finally, building on the findings of this research, future studies should explore the development of integrated treatment models that combine genetic, neurobiological, and real-world data to inform clinical decisions. These models could lead to more personalized and effective treatment strategies, improving outcomes for individuals with schizophrenia (32,73). Additionally, research should focus on the implementation of these models in clinical practice, including the potential barriers and facilitators to their adoption (47).

E. Strengths and Limitations

One of the primary strengths of this thesis lies in its multi-faceted approach, integrating genetic, neurobiological, and real-world evidence (RWE) into a cohesive understanding of schizophrenia. By addressing multiple dimensions of the disorder—genetic predispositions, clinical outcomes, and neurobiological mechanisms—this research offers a more holistic perspective than many prior studies. This multidisciplinary methodology contributes to the growing recognition that complex psychiatric disorders like schizophrenia require a comprehensive, multi-level investigative framework (32).

Another key strength is the focus on real-world data, which brings an additional layer of relevance to clinical practice. By comparing randomized controlled trials (RCTs) with RWE, this thesis identifies critical discrepancies between idealized trial populations and the actual patient population seen in routine psychiatric practice (102). This makes the findings highly applicable for improving treatment guidelines, particularly for individuals who may not fit the traditional RCT profiles. Additionally, the emphasis on early-onset psychosis in the neuroimaging study addresses an important and under-researched population, providing actionable insights for clinicians managing younger patients with schizophrenia

Finally, the use of PRS represents a cutting-edge application of genetic research to psychiatric practice. By demonstrating that PRS can be used to predict more severe outcomes in schizophrenia, this research sets the stage for early, personalized medicine, where treatments are tailored to stratified genetic profiles. The implications for clinical practice are substantial, particularly in addressing the high burden of treatment-resistant schizophrenia (173, 180).

Despite these strengths, several limitations must be acknowledged. First, the predictive utility of PRS, while promising, remains an area of ongoing research. PRS currently offers limited predictive power at an individual level, which restricts its immediate clinical applicability. Additionally, the generalizability of PRS across diverse populations remains questionable, as most PRS studies, including this one, are based on data from primarily European populations. Further research is needed to validate the use of PRS in more diverse cohorts, ensuring its broader clinical relevance (185).

Another limitation is the reliance on real-world data, which introduces potential biases, such as selection bias and incomplete data, common in observational studies. While real-world evidence is invaluable for capturing the heterogeneity of clinical populations, it also comes with limitations in terms of data quality and consistency. The lack of control over confounding variables in real-world settings can affect the internal validity of the findings (178).

The neuroimaging component of the research, while insightful, is limited by its cross-sectional design. This restricts the ability to draw causal inferences regarding the relationship between brain structure and clinical outcomes. Longitudinal studies are necessary to better understand the dynamic changes in brain structure that accompany the progression of schizophrenia. Additionally, neuroimaging data can be expensive and resource-intensive to acquire, potentially limiting the scalability of these findings in routine clinical practice (179).

Finally, the COVID-19 pandemic study, while timely and relevant, was conducted under rapidly evolving conditions with limited testing availability and variable healthcare access, which may have influenced the outcomes. The disparities observed in

healthcare access during the pandemic highlight important systemic issues but may also reflect the unique context of an unprecedented global health crisis, limiting the generalizability of these findings to other public health challenges (173).

F. Closing Remarks

In conclusion, this thesis highlights the necessity of individualized approaches to the diagnosis, characterization, and treatment of schizophrenia and those affected by it. By integrating genetic data, RWE, and neuroimaging, we offer a comprehensive framework that addresses the complexity of the schizophrenia spectrum and the limitations of current diagnosis and treatment protocols. Our findings emphasize the potential for personalized medicine, particularly using PRS to stratify patients with schizophrenia and early neuroimaging markers to identify those at high risk for severe outcomes.

Despite these advances, many challenges remain. PRS requires further refinement for broader clinical use, and RWE, while invaluable, brings inherent limitations like selection bias. Additionally, the gap between RCTs and real-world outcomes suggests the need for more inclusive treatment guidelines that reflect the diversity of the schizophrenia population. Our findings also highlight the importance of addressing healthcare disparities and stigma, as seen in the context of the initial COVID-19 pandemic assumptions on individuals with psychiatric disorders.

I believe this doctoral thesis contributes to the body of clinically relevant research aimed at improving the standard of care for individuals with schizophrenia. By continuing to explore the complex interactions between genetic, neurobiological, and environmental factors, future research can further optimize schizophrenia diagnosis, treatment, and management, advancing the goal of personalized psychiatry.

Conclusions

1. **Polygenic Risk Scores (PRS) offer potential as a tool for patient stratification and personalized treatment in schizophrenia.** Individuals with higher PRS are more likely to present with severe clinical phenotypes, suggesting that genetic stratification through PRS could guide the timing and choice of interventions, such as clozapine.

2. **The use of real-world evidence highlights the limitations of randomized controlled trials (RCTs) in capturing the diversity of schizophrenia presentations in clinical practice.** Our study revealed that up to 80% patients seen in everyday clinical settings are not represented in RCTs, emphasizing the need for more inclusive research methodologies that inform treatment guidelines applicable to a broader patient population.

3. **Long-acting injectable (LAI) antipsychotics, particularly olanzapine LAI and aripiprazole LAI, demonstrate superior effectiveness in preventing relapse in real-world settings compared to their oral counterparts**, despite limited differences observed in randomized controlled trials (RCTs).

4. **Integrating data from RCTs and real-world settings can be successfully achieved to compare the efficacy and effectiveness of antipsychotics for relapse prevention in schizophrenia**. This allows for a paradigm-shift in treatment guidelines to include emphasis on evidence derived from routine clinical practice and stringent RCTs.

5. **There is a higher prevalence of structural abnormalities in routine MRI scans in patients with early-onset psychotic disorders compared to community controls.** This highlights the importance of neuroimaging in understanding the pathophysiology of early-onset psychosis and emphasizes the potential benefits

of routine MRI acquisition for early detection, intervention, and personalized management strategies.

6. **Individuals with psychiatric disorders were more frequently tested for COVID-19 during the early pandemic stages, and despite higher testing rates, they were less likely to test positive.** These findings challenge existing stereotypes and emphasize the need for accessible healthcare for all psychiatric patients during health crises.

7. **Expanding the use of real-world evidence in psychiatric research is essential for developing treatment guidelines that reflect the realities of clinical practice.** This approach will ensure that research findings are applicable to a wider range of patients, including those with comorbid conditions or treatment-resistant symptoms.

8. **Future public health strategies must account for the increased vulnerability of individuals with schizophrenia to adverse outcomes during crises.** This underscores the importance of integrated care models and the need for ongoing research into the long-term impact of events like the COVID-19 pandemic on mental health.

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