Ph.D. Doctor Europaeus in Behavioural Neurosciences

Sapienza University of Rome

Title: Insights from large real-world cohorts towards inflammatory versus metabolic phenotypes of schizophrenia spectrum disorders

Ph.D. Candidate: Dr. Martina Nicole Modesti

Supervisor (Sapienza University of Rome): Prof. Cecilia Guariglia

Co-supervisor (Sapienza University of Rome): Prof. Stefano Ferracuti

Index

Abstract

Background: Schizophrenia spectrum disorders (SSDs) are clinically coherent yet biologically heterogeneous. Converging evidence suggests that systemic inflammation may delineate an "inflammatory biotype", but the behavioural and clinically relevant correlates of inflammation in large real-world cohorts remain poorly characterized.

Methods: This retrospective cohort study utilized the TriNetX Analytics network. Data extraction and analysis were conducted on February 3, 2026. Adults with SSD diagnoses and documented antipsychotic exposure were included. Two cohorts were defined a priori: Higher Severity Schizophrenia Spectrum Disorders (HS-SSD) and Lower Severity Schizophrenia Spectrum Disorders (LS-SSD). The HS-SSD cohort was identified using electronic health record proxy indicators of recent clinical instability, including hospitalization in the last 6 months, intentional self-harm, hospital admission, hallucinations, and unspecified stupor, restlessness and agitation; the LS-SSD cohort met the same diagnostic and treatment criteria in the absence of these severity signs/events. The index event was the first recorded simultaneous presence of diagnostic criteria, antipsychotic treatment, and severity signs/events. Primary outcomes were all-cause mortality, hospitalization rates, and inflammatory state, defined as C-reactive protein (CRP) ≥ 3.00 mg/L and/or lactate dehydrogenase (LDH) ≥ 220 U/L (most recent available measurements). Secondary outcomes included diastolic blood pressure, QTc interval, HbA1c, and LDL cholesterol. Propensity score matching (1:1 nearest-neighbour) was performed on age, sex, ethnicity,

sleep disorders, body mass index, and systolic blood pressure, yielding two balanced cohorts (N = 140,862 each).

Results: All-cause mortality was 12.38% in HS-SSD and 11.58% in LS-SSD (RR = 1.068; 95% CI = 1.047–1.090; $p < 0.001$; HR = 1.096; 95% CI = 1.073–1.119). Hospitalizations were 0.56% vs 0.02% (RR = 24.594; 95% CI = 17.272–35.018; $p < 0.001$). Positive inflammatory markers were 12.55% vs 11.30% (RR = 1.110; 95% CI = 1.086–1.135; $p < 0.001$). Secondary outcomes differed significantly, with slightly lower mean HbA1c, LDL, blood pressure, and QTc in HS-SSD.

Conclusions: The results are consistent with the hypothesis of an inflammatory–behavioural phenotype within the psychosis spectrum, characterized by higher inflammatory burden alongside increased all-cause mortality and a persistence of an instability trajectory.

Introduction

1. Background: schizophrenia as a heterogeneous disorder

More than a century after Kraepelin's description of dementia praecox, the aetiology, neuropathology, and pathophysiology of schizophrenia remain largely elusive (1). Although standardized diagnostic criteria have improved clinical reliability, schizophrenia continues to represent a broad and heterogeneous syndrome encompassing a constellation of subjective experiences, behavioural impairments, and variable longitudinal trajectories rather than a single disease entity.

Over the decades, research has uncovered a wide array of putative biological correlates—ranging from cognitive dysfunctions and brain structural abnormalities to alterations in neurotransmission and neurodevelopment. Despite decades of neuroimaging, molecular, and genetic research, no single biomarker has demonstrated consistent diagnostic validity. This enduring absence of unifying biological evidence reinforces the view of schizophrenia as a heterogeneous syndrome, leading contemporary research to focus on biologically informed subtypes—neurodevelopmental, dopaminergic, metabolic, and inflammatory. Yet, dismantling the construct entirely would obscure the clinical and empirical coherence that still defines the syndrome—its characteristic course, recurrent symptomatic patterns, and non-random associations across cognition, affect, and behaviour. In this context, contemporary research increasingly emphasizes the dissection of schizophrenia into biologically informed dimensions or

endophenotypes, integrating neurocognitive, genetic, and immunoinflammatory markers. Such an approach—anchored in the principles of precision psychiatry—aims to identify biologically and clinically meaningful subgroups that may clarify mechanisms of disease and guide individualized treatment strategies.

Current evidence indicates that schizophrenia arises from the interplay between genetic susceptibility and environmental risk factors, including perinatal complications, infections, stress exposure, and substance use. Multiple genes contribute to vulnerability through polygenic inheritance and variable penetrance, with many risk genotypes remaining clinically silent. The disorder occurs at comparable rates across populations and historical periods (2), suggesting an ancient and stable genetic background rather than a recent environmental emergence.

This persistent absence of diagnostic biomarkers has pushed the field toward multidimensional approaches integrating clinical, neurocognitive, and biological data. Divergences between major diagnostic systems (ICD and DSM) further underscore this conceptual instability (3). Nonetheless, the recurrence of symptom clusters, typical age at onset, and characteristic longitudinal course sustain the syndrome's empirical coherence. Against this background, the ongoing debate on the nature of schizophrenia reflects a tension that has accompanied the field since its inception. This enduring tension (4) — how to reconcile the descriptive coherence of the syndrome with its elusive biological basis—has persisted since Kraepelin's original formulation of dementia praecox. At the end of the nineteenth century, during the so-called first biological era of psychiatry, Kraepelin sought

to overcome the failure of neuropathological research to identify reliable lesions in chronic psychoses. In response, he proposed a clinical-longitudinal classification based on symptom evolution and functional outcomes, distinguishing dementia praecox from manic-depressive insanity. This pragmatic shift from brain pathology to systematic clinical observation provided psychiatry with its first reproducible diagnostic categories but at the cost of detaching the construct from its biological underpinnings.

This historical tension—between phenomenological precision and biological uncertainty—still defines the schizophrenia construct today. Modern efforts to "reinvent" it (5–7) echo Kraepelin's original challenge: after decades of sophisticated genetic, neuroimaging, and molecular studies, no unifying biological marker has emerged. Within this framework, the identification of biologically meaningful subtypes—such as, for example, an inflammatory biotype—represents a contemporary continuation of Kraepelin's aim: to move beyond descriptive phenomenology toward a biological understanding of mental illness.

2. Neuroinflammation and immune dysregulation in psychosis

In recent years, converging evidence has positioned neuroinflammation as one of the most compelling and integrative mechanisms in psychosis, bridging immune dysregulation, genetic vulnerability, and altered neural connectivity (8–10). Traditionally regarded as a psychiatric condition rooted primarily in dopaminergic dysfunction (11,12), schizophrenia is now understood as a neuroimmune disorder, where chronic low-grade inflammation and aberrant immune activation

interact with genetic vulnerability to shape the onset, course, and clinical heterogeneity of the illness.

Neuroinflammation encompasses a series of inflammatory responses within the central nervous system, involving microglial activation, elevated proinflammatory cytokines, and blood–brain barrier dysfunction. These processes can lead to neuronal injury, synaptic disruption, and altered neurotransmission, ultimately contributing to dysregulation of cognitive, affective, and behavioural functioning (13–15).

Evidence from multiple domains supports the immune–inflammatory hypothesis of schizophrenia. Concordant signals emerge across modalities: peripheral and central cytokine elevations, imaging evidence of microglial activation, and genetic enrichment in immune-related loci. Studies have shown elevated concentrations of IL-6, TNF-α, and other proinflammatory mediators in both brain tissue and peripheral blood of affected individuals (16). Genome-wide association studies have identified immune-related loci that confer increased vulnerability (17,18), while positron emission tomography (PET) imaging has demonstrated excessive microglial activation in the prefrontal cortex and hippocampus, correlating with psychotic and cognitive symptom severity (19,20). Similarly, cerebrospinal fluid analyses have revealed higher levels of inflammatory cytokines, such as IL-6 and IL-8, associated with disease progression (21–25). Beyond innate immune activation, adaptive immune mechanisms have also been implicated in schizophrenia. Several studies have reported altered humoral responses and increased seropositivity to infectious agents, including Toxoplasma

gondii (26,27), suggesting that dysregulated antibody-mediated immunity may contribute to a subset of patients. This humoral activation may reflect either prior infectious exposures interacting with genetic vulnerability or an intrinsic immune imbalance within the psychosis spectrum (28).

Animal models provide further mechanistic insight: prenatal inflammatory insults can disrupt foetal neurodevelopment, leading to offspring with behavioural and neurochemical abnormalities reminiscent of schizophrenia (29,30). Likewise, chronic inflammatory states in rodents produce cognitive and social impairments mediated by dopaminergic dysregulation and synaptic loss (29,31). Collectively, this evidence supports neuroinflammation as a key biological mechanism and potential therapeutic target.

In fact, despite the centrality of dopamine D_2 receptor blockade in current treatment strategies (12,32), traditional antipsychotic medications remain partially effective against negative and cognitive symptoms, as approximately 20% of patients exhibit poor clinical response (33). These limitations, coupled with the growing recognition of neuroinflammation in schizophrenia, underscore the need for novel pathophysiological frameworks that could pave the way for targeted interventions beyond the dopaminergic model.

3. An inflammatory biotype: toward precision psychiatry

These converging data suggest that neuroinflammatory processes may not be uniformly distributed across patients but instead define biologically distinct subgroups within the psychosis spectrum.

Building upon converging evidence for immune dysregulation across psychotic disorders, one prominent framework—the neuroinflammation hypothesis—posits that psychotic disorders are characterized by elevated levels of proinflammatory cytokines resulting from microglial activation and secondary inflammatory cascades within the brain (8,34). Postmortem investigations support this view, with meta-analytic data showing increased expression of proinflammatory genes (IL1β, IL6, IL8, and TNFα), higher protein concentrations of IL-1β and TNF-α, and greater microglial density in patients compared to healthy controls (35). Complementary evidence implicates dysfunction of the brain's vascular interfaces—notably brain microvascular endothelial cells (BMECs) and choroid plexus epithelial cells (CPECs)—which constitute the blood–brain and blood–CSF barriers. Alterations in these structures may promote barrier leakage, allowing peripheral immune mediators to enter the CNS and activate resident glia, further amplifying the inflammatory response measurable in peripheral blood (36–39).

However, inflammation is not uniformly present across all individuals with psychosis. Rather, converging findings indicate that only a subset of patients exhibits a sustained peripheral inflammatory profile (40). This subgroup appears to account for roughly 30–50% of cases, and is associated with poorer response to antipsychotic treatment and potentially distinct neurobiological characteristics (41–44). Such data have led to the conceptualization of an "inflammatory biotype" of psychosis—patients in whom systemic and central inflammation play a central pathophysiological role.

The clinical implications of this biotype are substantial. In other psychiatric disorders, such as treatment-resistant depression, anti-inflammatory treatment with agents like the TNF-α antagonist infliximab has been shown to improve symptoms specifically in individuals with elevated C-reactive protein (CRP > 5 mg/L) (45,46). Similar stratification strategies in psychosis could enable the identification of patients most likely to benefit from adjunctive anti-inflammatory or immunomodulatory therapies, especially when conventional antipsychotics prove insufficient (40,47).

The existence of inflammatory subgroups has nevertheless been debated. A meta-analysis of 35 studies in antipsychotic-naïve first-episode psychosis (FEP) questioned the validity of inflammatory stratification, arguing that immune alterations may constitute a core feature of psychosis rather than a subgroup phenomenon (48). Yet, the interpretation of these findings is limited by diagnostic heterogeneity, variability in assay sensitivity, small sample sizes, and reliance on single cytokine measurements instead of integrated inflammatory signatures.

Data-driven studies have identified distinct inflammatory subtypes within the psychosis spectrum, typically distinguishing a high-inflammatory group, representing about one-third of patients, from a low-inflammatory group. The high-inflammatory subtype is characterized by elevated peripheral cytokine levels, alterations in cortical and subcortical morphology—possibly reflecting blood–brain barrier dysfunction—and poorer cognitive and inhibitory control performance compared with low-inflammatory cases (42). More recent evidence indicates that these inflammatory subtypes are already

detectable in antipsychotic-naïve first-episode schizophrenia, where individuals with elevated IL1β, IL6, IL8, and TNFα levels also display region-specific cortical thickening and reduced network efficiency (49).

Collectively, these findings support the presence of a replicable inflammatory biotype emerging from the earliest stages of psychosis and highlight peripheral inflammatory markers as promising tools for biological stratification and precision-guided interventions. Yet, the clinical and behavioural implications of biotypes findings remain poorly understood.

4. Clinical and behavioural correlates of inflammation

Although a growing body of research has demonstrated immune–inflammatory activation across major psychiatric disorders, including psychosis (47–52), the question of how inflammatory processes translate into specific behavioural phenotypes remains largely unanswered. Population-based longitudinal studies indicate that elevated inflammatory markers in childhood or adolescence—such as IL-6 and CRP—predict an increased risk of developing psychotic and affective symptoms in adulthood (50–54), suggesting that low-grade systemic inflammation may contribute not only to disease onset but also to long-term neurobehavioral vulnerability.

Most of the available evidence from clinical samples concerns major depressive disorder, where the association between low-grade systemic inflammation and illness severity is well established, primarily through elevated levels of peripheral markers such as C-reactive protein (CRP) and proinflammatory cytokines (46,55–57). In this context,

approximately one-third of acutely unwell patients with depression exhibit CRP concentrations above 3 mg/L, a threshold commonly used to define low-grade systemic inflammation. A smaller but growing body of evidence extends these findings to psychotic disorders (58) where similar inflammatory alterations have been reported, though with greater heterogeneity and less consistent replication. Nonetheless, within both diagnostic spectra, patients showing elevated inflammatory markers tend to present more severe clinical courses, poorer treatment response, and longer hospitalizations (41,59). Moreover, higher baseline levels of proinflammatory cytokines such as IL-6 have been linked to poorer response to antipsychotic therapy in psychoses (41) and to greater symptom persistence over time in major depressive disorder (60,61).

Several clinical trials have demonstrated the potential benefits of anti-inflammatory strategies in schizophrenia, including the use of sulforaphane (62,63), pentoxifylline (64,65), canakinumab (66), and other anti-inflammatory agents, although further research is needed (67).

However, the behavioural and clinical correlates of systemic inflammation in psychosis remain poorly characterized. Most studies have focused on biological and symptomatic dimensions: inflammatory activation has been linked to altered stress reactivity, premorbid cognitive impairment, and motivational deficits, potentially mediated by cytokine-induced dopaminergic and fronto-limbic dysconnectivity (68,69).

Among possible biomarkers, C-reactive protein (CRP) in particular has emerged as one of the most robust and accessible indicators of low-grade

inflammation, providing a pragmatic tool for stratifying patients according to their inflammatory status.

C-reactive protein (CRP) represents one of the most reliable and accessible peripheral markers of low-grade systemic inflammation. Elevated CRP levels have been consistently observed in patients with schizophrenia and related psychoses (70), supporting the hypothesis of immune–inflammatory dysregulation as a core biological mechanism of the disorder (71–73). A recent meta-analysis suggested that higher CRP concentrations are associated with positive rather than negative symptom dimensions (73), and with illness chronicity and insidious onset (74). Increased CRP has also been linked to cognitive deficits—including impaired working memory, processing speed, and executive function (75,76), as well as to metabolic syndrome, cardiovascular risk, and overall functional decline (71). However, results remain inconsistent, and no consensus has emerged on whether CRP elevation reflects a causal mechanism or a by-product of psychosis pathophysiology (72). Importantly, while isolated reports have described associations between high CRP and greater aggression in schizophrenia inpatients (77), this finding has not been replicated.

Beyond inflammatory markers such as C-reactive protein (CRP), alterations in metabolic enzymes like lactate dehydrogenase (LDH) further support the link between inflammation and disrupted bioenergetic homeostasis in psychosis. LDH catalyzes the interconversion of pyruvate and lactate, playing a key role in neuronal energy metabolism and redox balance. Elevated LDH levels have been reported in schizophrenia, reflecting mitochondrial dysfunction,

oxidative stress (78), and glial activation—mechanisms that converge with immune–inflammatory dysregulation in the pathophysiology of psychosis (79–82).

LDH is increasingly implicated in the pathophysiology of schizophrenia within the interconnected domains of neuroinflammation, metabolic dysregulation, and cell death signaling. Experimental evidence indicates that LDH release reflects loss of membrane integrity associated with inflammatory forms of programmed cell death, particularly pyroptosis, driven by NLRP3–caspase-1 pathway activation and increased IL-1β signaling (83). In parallel, neurodevelopmental and immune activation models relevant to schizophrenia show altered LDH dynamics and increased LDH release as an index of neurotoxicity and microglial activation, further supporting its role as a marker of inflammation-related cellular damage (84). At the brain level, proteomic alterations involving LDH isoforms, such as LDH-B, suggest disturbances in energy metabolism and oxidative pathways within fronto-subcortical circuits implicated in schizophrenia (85).

To date, no large-scale cohort studies have systematically investigated whether elevated CRP or LDH identify a subgroup of patients characterized by more severe behavioural dysregulation—such as agitation or aggression—or by poorer clinical outcomes.

Given that C-reactive protein is widely regarded as a more specific marker of systemic inflammation, whereas LDH is more closely related to tissue damage, hemolysis, and cell death, these biomarkers may reflect partially distinct yet biologically interconnected dimensions of the inflammatory response; in this context, their combined assessment could

provide a more comprehensive characterization of underlying pathophysiological processes, potentially improving the identification of an inflammatory subtype of schizophrenia beyond the use of either marker alone. Accordingly, the present study is based on the identification of an inflammatory subtype of schizophrenia by jointly considering both LDH and CRP levels.

Aggressive and violent behaviour represents a clinically relevant and socially significant manifestation of psychotic disorders. Individuals with schizophrenia are estimated to be four to seven times more likely to commit violent crimes, such as assault or homicide, and four to six times more likely to display general aggressive behaviours, including verbal or physical threats, compared with the general population (86–89). Several large cohort studies have consistently reported an increased incidence of violent conduct among individuals with schizophrenia (86,89–91), suggesting that behavioural discontrol and aggression may represent core features of the most severe psychotic forms.

Given their clinical and societal impact, these manifestations constitute a key behavioural dimension to investigate within the framework of inflammation-related psychosis. If systemic inflammation contributes to more severe or treatment-resistant disease trajectories, it may also underlie heightened impulsivity, agitation, and violent behaviour, providing a potential biological substrate for the behavioural dysregulation observed in high-risk psychotic subtypes. Understanding this relationship could therefore clarify whether the inflammatory biotype is not only biologically distinct but also clinically identifiable through specific behavioural patterns, potentially underpinning

treatment resistance and functional decline. Beyond behavioural manifestations, psychosis has also been linked to adverse cardiometabolic and physiological outcomes (92). Individuals with schizophrenia exhibit elevated rates of metabolic syndrome, cardiovascular disease, and premature mortality (93), a burden partly associated with inflammatory activation and its interaction with lifestyle factors and antipsychotic exposure. Inflammatory markers such as CRP have been historically associated with alterations in blood pressure (94), glycaemic control, lipid profiles (95) and cardiac conduction parameters (96), suggesting that inflammatory subgroups may also differ in their somatic risk trajectories. For this reason, the present study includes secondary physiological and laboratory outcomes—such as blood pressure, QTc interval, HbA1c, and LDL cholesterol—to explore whether the inflammatory phenotype is associated not only with behavioural severity but also with early indicators of cardiometabolic vulnerability. Clarifying these links—ideally in large real-world datasets—could bridge biological stratification and clinical translation, informing early, treatment-specifying strategies (e.g., LAIs or clozapine) for patients at higher biological and clinical risk.

5. Translational relevance of bio-typing inflammation in psychosis and potential therapeutic implications

If inflammatory activation could delineate a subgroup of psychotic patients characterized by more severe behavioural dysregulation and treatment resistance, this may have direct therapeutic implications. Evidence consistently indicates that treatment-resistant psychosis (TRP)

represents a distinct and prognostically unfavourable trajectory, with up to one-quarter of individuals with a first episode of psychosis (FEP) failing to respond to two adequate trials of antipsychotics (97). Clozapine, the most effective treatment for TRP (98), remains underutilized despite robust evidence for its superiority across domains including symptom remission, relapse prevention, and reduced early mortality (99–101). Moreover, clozapine exerts unique anti-suicidal effects, with multiple studies in schizophrenia and schizoaffective disorder demonstrating reductions in suicidal ideation and behaviour. Evidence from the landmark International Suicide Prevention Trial (InterSePT) (102) led the U.S. Food and Drug Administration (FDA) to approve clozapine as the only medication indicated for the treatment of suicidality in these populations (103).

Barriers include concerns about rare but serious adverse events such as myocarditis (104), bowel obstruction (105), and agranulocytosis (106), as well as the burden of mandatory haematological monitoring (107). In addition to rare but severe adverse events, clozapine is also associated with frequent metabolic complications (108), including weight gain, insulin resistance, and constipation (109), which may require proactive management. In selected high-risk individuals, early introduction of metformin has been proposed to mitigate metabolic deterioration (110). Nonetheless, survey data suggest that most patients would not refuse clozapine if appropriately informed (111). Instead, reluctance often stems from clinician-level factors, with some psychiatrists preferring high-dose antipsychotic polypharmacy despite the lack of supporting evidence (112).

Because treatment resistance can be identified within three to four months of illness onset (113), early intervention services provide an ideal setting for clozapine initiation and close monitoring of metabolic and inflammatory parameters. This approach is supported by longitudinal evidence from specialized early psychosis programs (114,115), showing that the proportion of FEP patients who will later meet TRP criteria remains relatively stable (~10%), underscoring the feasibility of early detection and stratified treatment.

Parallel to this, long-acting injectable antipsychotics (LAIs) represent another strategy that may address the clinical challenges associated with inflammatory and behaviourally severe psychoses. LAIs were developed to mitigate the high rates of non-adherence (116) and relapse observed with oral antipsychotics (117,118), which are particularly frequent in early illness phases (119,120). Recent evidence demonstrates that LAIs reduce rehospitalization, relapse, and treatment failure compared with oral formulations (121–124).

Importantly, both systematic reviews and real-world data suggest that LAIs may be particularly beneficial in early psychosis (125–130), improving symptom control and adherence while reducing relapse risk (127,129).

In summary, if inflammatory activation delineates a subgroup of psychotic patients who are more behaviourally severe and more treatment-resistant, then recognizing these individuals from the very first episode becomes clinically crucial. When elevated peripheral markers (e.g., CRP) co-occur with signs of behavioural dysregulation—such as agitation, impulsivity, or the need for coercive interventions—

early identification of an inflammatory–behavioural phenotype could immediately inform the use of therapeutic strategies already proven to be most effective in severe psychoses, such as clozapine and long-acting injectable antipsychotics (LAIs). Implementing these approaches earlier may reduce relapse rates, hospitalizations, and overall clinical burden.

To achieve this level of early stratification, it is first necessary to demonstrate the existence of this phenotype in real-world cohorts and to establish its association with poorer behavioural outcomes. This is precisely the aim of the present study: to leverage real-world data to identify a subgroup of patients with elevated systemic inflammation and greater behavioural severity compared with non-inflammatory cases. Within this framework, TriNetX, a global federated network of anonymized electronic health records, provides the scale and granularity needed to detect and validate this phenotype in real clinical populations—paving the way for an evidence-based approach to precision psychiatry from illness onset.

6. The rationale for using real-world data (TriNetX)

Investigating complex psychiatric phenotypes requires large, ecologically valid datasets that capture the heterogeneity often excluded from randomized trials; real-world evidence bridges experimental rigor and clinical practice, enabling the study of longitudinal trajectories, treatment patterns, and outcome variability in naturalistic settings. TriNetX (www.trinetx.com) represents one of the most advanced federated, cloud-based research networks currently available, integrating anonymized electronic health records (EHRs) from a broad

consortium of healthcare organizations, including hospitals, primary care systems, and specialized treatment centres. Approximately two-thirds of its contributors are academic health institutions, ensuring both high data quality and clinical granularity. Through its web-based analytics platform, TriNetX enables the creation of cohorts, the application of propensity score matching, and comparative outcome analyses, all while adhering to strict ethical and legal governance standards. The identity of participating institutions and their individual data contributions remain undisclosed to preserve institutional confidentiality.

The present study utilizes the TriNetX Analytics network, which aggregates data from approximately 58.6 million patients aged 18–90 years across 54 healthcare organizations in the United States. The database offers comprehensive longitudinal information on demographics, diagnoses (based on ICD-10 codes), medications, procedures, and laboratory parameters, enabling the integration of biological, behavioural, and pharmacological dimensions in large-scale analyses.

A retrospective, multicentric cohort design of this magnitude is essential to explore the existence of an inflammatory phenotype of psychosis. This design allows simultaneous assessment of biological and behavioural markers across heterogeneous real-world populations, increasing both the validity and generalizability of findings.

Different studies on schizophrenia spectrum disorders have used TriNetX data across pharmacological (131–133), forensic (134),

epidemiological (135), and consultation-liaison psychiatry (136,137) domains.

To date, no multicentric cohort study has systematically examined the relationship between systemic inflammation and behavioural severity in psychosis, nor attempted to empirically delineate a phenotype characterized by inflammatory activation and more severe disease patterns. Thus, this research represents the first real-world investigation aimed at identifying the trajectory towards a psychosis biotype—an endeavour with direct therapeutic implications.

7. Aims and hypothesis

In summary, converging evidence indicates that schizophrenia and related psychoses encompass multiple biological subtypes, among which immune–inflammatory dysregulation has emerged as a promising determinant of clinical heterogeneity. Increasing data suggest that systemic low-grade inflammation may define a subgroup of patients with more severe symptomatology, cognitive impairment, and poorer treatment response. However, the behavioural correlates of inflammation—particularly regarding agitation, impulsivity, and aggression—remain insufficiently explored, despite their substantial clinical and societal relevance.

The primary hypothesis of this study is that two cohorts of clinically distinct phenotypes defined a priori—Higher Severity Schizophrenia Spectrum Disorders (HS-SSDs) and Lower Severity Schizophrenia Spectrum Disorders (LS-SSDs)—would differ in terms of all-cause mortality, hospitalization rates, and indicators of systemic inflammation.

More specifically, we hypothesized that the higher-severity phenotype would be associated with increased inflammatory burden and worse clinical outcomes, consistent with the presence of a biologically more severe inflammatory subgroup within the schizophrenia spectrum.

As secondary objectives, we explored whether somatic risk indicators, including QTc interval, metabolic parameters, and blood pressure, differed between the two groups, in order to assess whether the putative inflammatory phenotype also corresponded to a more adverse traditional cardiometabolic profile.

Accordingly, the objective of this study was to compare long-term clinical and safety outcomes associated with the severity of SSDs in a large real-world population, focusing on epidemiologically and medico-legally relevant endpoints such as mortality and hospitalization.

Methods

This retrospective cohort study utilized data from the TriNetX network and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting clinical research (138). The dataset provided comprehensive information on patient diagnoses, pharmacological treatments, and clinical outcomes, enabling an in-depth analysis of long-term clinical and safety outcomes in adults with schizophrenia spectrum disorders with documented antipsychotic exposure in the electronic health record. Data extraction and analysis were conducted on February 3, 2026, from electronic medical records obtained from healthcare organizations across multiple countries, with most data originating from institutions in the United States. A total of 139 providers responded for the HS-SSD cohort and 153 for the LS-SSD cohort. The final HS-SSD cohort included 139,281 patients, and the LS-SSD cohort included 803,899 patients, totalling 943,180 patients in the study.

The analysis process consisted of two main stages: defining the cohorts using specified query criteria and setting up and performing the statistical analyses. The first stage involved defining the inclusion criteria for both cohorts. Patients in the HS-SSD cohort were identified based on the diagnoses (schizophrenia; delusional disorders; brief psychotic disorder; schizoaffective disorders; other psychotic disorder not due to a substance or known physiological condition; unspecified psychosis not due to a substance or known physiological condition), current antipsychotic treatments, at least one of the following signs/events: hospitalization in the last 6 months, intentional self-harm, hospital

admission, hallucinations, and unspecified stupor, restlessness and agitation. Patients in the LS-SSD cohort were identified based on the same diagnoses and antipsychotic treatments and the absence of the above reported severity signs/events. The HS-SSD cohort was intentionally operationalized using pragmatic EHR-based indicators of recent clinical instability, including agitation/restlessness codes, self-harm events, and hospitalization-related codes within a defined time window. This approach was adopted to approximate, in real-world data, a clinically meaningful "high-instability" trajectory that cannot be directly captured through standardized symptom scales in TriNetX. Accordingly, subsequent hospitalization was not conceptualized as a fully independent endpoint, but rather as a severity-validating outcome reflecting the persistence of clinical instability over longitudinal follow-up.

The index event, marking the initiation of the observation period, was defined as the first recorded simultaneous presence of the diagnostic criteria, antipsychotic treatment, and severity signs/events. Patients whose index event occurred more than 20 years prior to the analysis date were excluded from the study to ensure data relevance; no subjects were excluded for this reason.

The second stage involved defining the observation period and outcomes of interest. Outcomes were assessed starting one day after the index event, no end date was specified, and all outcomes after the first occurrence of the index event were included. The primary outcomes included all-cause mortality, hospitalization rates, and inflammatory state. Mortality was defined as any recorded death during the

observation period. Hospitalization rates were defined as any recorded hospital admission event during the observation period.

Inflammatory states were defined by C-reactive protein [mass/volume] levels ≥ 3.00 mg/L (139) in serum, plasma, or blood and lactate dehydrogenase [enzymatic activity/volume] levels ≥ 220 U/L (140) in serum or plasma, using the most recent available measurements.

The secondary outcomes focused on physiological and laboratory-based measures. These included diastolic blood pressure, QTc interval, HbA1c levels, and LDL cholesterol. Laboratory values were assessed based on the most recent available measurements recorded during the observation window.

Propensity score matching was used to balance baseline sociodemographic and clinical characteristics between the two cohorts (141). To control for potential confounding, propensity scores were estimated using logistic regression based on key baseline covariates: age, sex, ethnicity, presence of sleep disorders, body mass index (BMI), and systolic blood pressure. These variables were selected based on their potential association with both disease severity and clinical outcomes. A 1:1 nearest-neighbor matching algorithm without replacement was applied to generate two balanced cohorts of 140,862 patients each. Matching was conducted using the estimated propensity scores, and balance between cohorts was confirmed through standardized differences. Patients with pre-existing outcomes prior to the index event were excluded from the analysis to ensure that observed events reflected new-onset outcomes during the follow-up period. This approach reduces bias and enhances clarity in assessing treatment effects, which is

particularly valuable in retrospective studies where randomization is not feasible (141).

Statistical analyses included measures of association, Kaplan-Meier survival analysis, number of instances analysis, and laboratory results analyses. Measures of association calculated risk differences, risk ratios, and odds ratios. Survival probabilities were estimated using Kaplan-Meier analysis (142), with hazard ratios derived from Cox models (143). Number of instances analysis assessed the burden of each outcome over the observation window, while laboratory results analyses considered mean values, standard deviations, and conducted t-tests for independent groups. The complete study methods are detailed in Appendix 1.

Data completeness and quality were ensured through the standardized approach of the TriNetX network, which maintains consistency in coding, event timing, and data sanitization across participating healthcare organizations.

All analyses were performed on de-identified data, adhering to privacy regulations, with no need for ethical approval or patient consent.

Results

Starting from a total of 943,180 patients, we included in the final analysis two balanced cohorts of 140,862 patients each, following the application of exclusion criteria and propensity score matching.

Both cohorts included 56.75% males and 43,25% females with a mean age of 46.2 years (SD = 19.7) (Table 1).

All study outcomes showed significant differences between the HS-SSD and LS-SSD cohorts over the five-year observation period. All-cause mortality was observed in 12.38% of patients in the HS-SSD cohort and 11.58% in the LS-SSD cohort (risk ratio [RR] = 1.068; 95% CI = 1.047-1.09; $p < 0.001$), indicating a higher risk of mortality in the HS-SSD cohort (risk difference [RD] = 0.008; z = 6.469; $p < 0.001$). Kaplan-Meier analysis confirmed these findings with a slightly higher mortality risk in the HS-SSD over about 20 years (hazard ratio [HR] = 1.096; 95% CI = 1.073-1.119; chi-squared=4.887; p = 0.027) (Tables 2 and 3, Figure 1).

Hospitalizations were 0.56% in the HS-SSD cohort and 0.02% in the LS-SSD cohort (RR = 24.594; 95% CI = 17.272-35.018; $p < 0.001$), reflecting a higher risk of hospitalization in the HS-SSD cohort across the observation period with a RD of 0.005 (z = 26.420; $p < 0.001$). For inflammation, patients in the HS-SSD cohort showed a higher risk of having positive inflammatory markers (12.55%) as compared to the LS-SSD cohort (11.3%) (RR = 1.11; 95% CI = 1.086-1.135; $p < 0.001$) with a RD of 0.012 (z = 9.375; $p < 0.001$).

Focusing on secondary outcomes, QTc interval values were slightly lower in the HS-SSD cohort (mean = 432.564; SD = 34.607 ms) compared to the LS-SSD cohort (mean = 434.841; SD = 35.56 ms) (t = -6.939; $p < 0.001$).

Abnormal HbA1c levels were lower in the HS-SSD cohort (mean = 5.88; SD = 1.418) compared to the LS-SSD cohort (mean = 5.977; SD = 1.49) (t = -11.325; $p < 0.001$). LDL levels were lower in the HS-SSD cohort (mean = 90.836; SD = 35.147) compared to the LS-SSD cohort (mean = 92.882; SD = 36.413) (t = -9.777; $p < 0.001$). Other secondary outcomes showed statistically significant differences (Table 3). Figure 1 below displays Kaplan-Meier survival analysis comparing higher-severity (green) and lower-severity (purple) schizophrenia spectrum disorder (SSD) cohorts.

Table 1. Baseline characteristics after Propensity Score Matching (N = 140,862 per cohort)

Characteristic	HS-SSD (Higher Severity)	LS-SSD (Lower Severity)
Number of patients	140,862	140,862
Mean age (SD)	46.2 (19.7)	46.2 (19.7)
Male (%)	56.7%	56.8%
Not Hispanic or Latino (%)	70.4%	70.4%
Sleep disorders (%)	24.3%	24.3%
BMI (mean, SD)	27.7 (7.4)	28.3 (7.8)
Systolic BP (mean, SD)	125.6 (19.7)	126.0 (19.2)

Table 2. Primary Clinical Outcomes

Outcome	HS-SSD (%)	LS-SSD (%)	Risk Ratio (95% CI)	Risk Difference	p-value
All-cause mortality	12.38	11.58	1.068 (1.047–1.090)	0.008	<0.001
Hospitalization	0.56	0.02	24.594 (17.272–35.018)	0.005	<0.001
Inflammation markers[a]	12.55	11.30	1.110 (1.086–1.135)	0.012	<0.001

[a] Based on CRP ≥ 3.0 mg/L or LDH ≥ 220 U/L; excludes patients with prior inflammation: HS-SSD (N = 117,687), LS-SSD (N = 120,726)

Table 3. Secondary Outcomes

Outcome	HS-SSD (Mean ± SD)	LS-SSD (Mean ± SD)	t-statistic	p-value
HbA1c (%)	5.88 ± 1.42	5.98 ± 1.49	-11.33	<0.001
QTc interval (ms)	432.56 ± 34.61	434.84 ± 35.56	-6.94	<0.001
LDL cholesterol (mg/dL)	90.84 ± 35.15	92.88 ± 36.41	-9.78	<0.001
Diastolic BP (mmHg)	74.44 ± 14.38	74.57 ± 14.17	-2.02	0.044

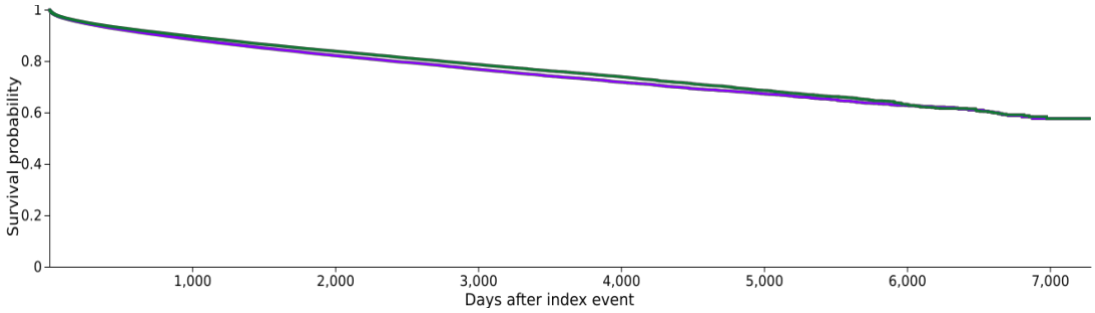


Figure 1. Kaplan-Meier survival analysis comparing higher-severity (green) and lower-severity (purple) schizophrenia spectrum disorder (SSD) cohorts. Each cohort included 140,862 patients. All-cause mortality occurred in 17,433 patients (12.38%) in the higher-severity (HS-SSD) cohort and 16,318 patients (11.58%) in the lower-severity (LS-SSD) cohort. Median survival was not reached in either group. The estimated survival probability at the end of the observation period was 57.62% for HS-SSD and 57.60% for LS-SSD. The log-rank test showed a statistically significant difference between survival curves ($\chi^2 = 70.493$, df = 1, $p < 0.001$). The hazard ratio was 1.096 (95% CI: 1.073–1.119), indicating a modest but significant increased risk of mortality in the HS-SSD cohort (proportionality test: $\chi^2 = 4.887$, df = 1, $p = 0.027$).

Discussion

1. Main results interpretation

The results are consistent with the hypothesis of an inflammatory–behavioural phenotype within the psychosis spectrum. Specifically, patients in the higher-severity schizophrenia spectrum disorders (HS-SSD), cohort had a significantly greater prevalence of positive inflammatory markers compared to those in the lower-severity (LS-SSD) cohort, even after applying rigorous exclusion criteria and achieving balanced groups through propensity score matching. Although the absolute differences in risk were relatively small, the consistent and statistically significant elevation in inflammation, all-cause mortality, and hospitalization rates in the HS-SSD group suggests a clinically meaningful association between illness severity and adverse health outcomes. These findings were further corroborated by the Kaplan-Meier survival analysis, which demonstrated a sustained and statistically significant increase in long-term mortality risk among patients with HS-SSD. Although an alternative analytic strategy could have involved modelling inflammatory markers continuously across the entire sample, we opted for an a priori severity-based stratification to approximate clinically meaningful trajectories identifiable in real-world practice. This approach reflects a translational logic: clinicians encounter patients in terms of instability patterns rather than isolated biomarker values.

2. Towards the inflammatory biotype

The present findings are broadly consistent with previous studies suggesting the existence of an inflammatory subgroup within the psychosis spectrum. Several investigations have reported that only a subset of patients shows persistent peripheral inflammatory activation, and that this subgroup is associated with severe negative symptoms (144), altered brain structure (145), and reduced response to antipsychotic treatment (146). These observations have supported the hypothesis of an inflammatory biotype contributing to the biological heterogeneity of psychotic disorders.

However, most of the available evidence derives from relatively small or highly selected samples and has focused mainly on neurobiological or cognitive correlates, rather than on global clinical severity and real-world outcomes. In this context, the present study extends previous findings by showing, in a large multicentric real-world cohort, that higher clinical severity within the schizophrenia spectrum is associated with a greater prevalence of systemic inflammation, as well as with increased mortality and hospitalization rates. The results support the interpretation of systemic inflammation as a marker of a clinically more severe subgroup of psychotic patients. Rather than representing a nonspecific epiphenomenon, inflammatory activation may reflect a distinct pathophysiological trajectory associated with worse outcomes, in line with models conceptualizing psychosis as a heterogeneous syndrome composed of partially distinct biological subtypes.

3. Inflammation and clinically relevant behaviour

The implications of these findings are not merely interpretative or classificatory. The identification of a greater inflammatory burden in the higher-severity schizophrenia spectrum cohort was accompanied by consistently worse clinical outcomes, including higher all-cause mortality and a markedly increased rate of hospitalization events. In parallel, positive inflammatory markers (CRP ≥ 3 mg/L or LDH ≥ 220 U/L) were observed more frequently in the HS-SSD group. Taken together, these results suggest that systemic inflammation may be associated with a more malignant illness trajectory within the schizophrenia spectrum. Nevertheless, an increase in natural cause-mortality associated with higher CRP in schizophrenia populations had already been established in smaller samples (147).

This interpretation is broadly consistent with previous studies linking elevated inflammatory markers to greater symptom severity (148–150) and treatment resistance (151). Instead, hospitalization rate differences were never previously investigated in large population studies, but hospitalized patients with higher CRP levels were more aggressive (152). Earlier investigations have also suggested that a subset of patients with psychosis may exhibit an inflammatory–behavioural phenotype, in which biological dysregulation is reflected not only in laboratory abnormalities but also in increased clinical instability (153) and poorer functional outcomes, such as worse working memory (154) and cognitive function (155) which, in routine clinical viewpoints, are strongly associated with long-term disability. Moreover, in some cases, clinical instability may manifest as aggressive behaviour (156) - underlying the

need for coercive or intensive interventions in hospitalized settings. Interestingly, previous data have associated lower cholesterol levels with increased hetero-aggressive behaviour in psychiatric populations (157). In this perspective, the slightly lower LDL levels observed in the HS-SSD cohort may not necessarily indicate a protective metabolic profile but could reflect biological correlates of behavioural dysregulation. These results strengthen the rationale for considering inflammation not only as a biological correlate of psychosis, but also as a potential marker of clinical risk, with direct implications for early stratification and treatment planning.

4. Mortality outcome

Beyond behavioural severity, the present findings also indicate a modest but consistent increase in all-cause mortality among patients in the higher-severity schizophrenia spectrum cohort. Over the observation period, mortality was observed in 12.38% of HS-SSD patients compared with 11.58% of LS-SSD patients (RR = 1.068; 95% CI = 1.047–1.09), with survival analysis confirming a sustained increase in long-term mortality risk. At the same time, the HS-SSD cohort showed a higher prevalence of positive inflammatory markers, suggesting a convergence between clinical severity, inflammatory activation, and adverse somatic outcomes. The very large between-cohort difference in hospitalization should be interpreted in light of the study design. Because the HS-SSD cohort was defined using indicators of recent clinical instability that include hospitalization-related codes, the hospitalization outcome captures, in part, the longitudinal persistence of an instability trajectory

rather than representing an entirely independent clinical endpoint. Importantly, however, the observation window extended beyond the index definition, supporting the interpretation that the HS-SSD group represents a clinically distinct trajectory characterized by recurrent service needs. In this context, hospitalization primarily functions as a construct-validating marker of severity, whereas the key inferential outcomes of the study concern mortality and inflammatory burden.

These findings are in line with a large body of literature showing that individuals with schizophrenia experience substantially reduced life expectancy (158), largely driven by cardiovascular and metabolic comorbidities (159). Systemic inflammation has been repeatedly implicated as a shared biological mechanism linking psychopathology severity, metabolism dysregulation, and premature mortality (160,161). Chronic low-grade inflammation may contribute both to the progression of psychotic illness—through neuroimmune and neurotoxic mechanisms (162)—and to the development of cardiometabolic conditions that represent the leading causes of death in this population (163). Furthermore, as suicide accounts for 5% of death causes in schizophrenia populations (164), the fact that neuroinflammation plays an established role in suicidal behaviour as well supports the results of the present study (165).

Notably, the HS-SSD cohort also showed a modestly higher prevalence of positive inflammatory markers compared with LS-SSD. This pattern is consistent with the hypothesis that clinical instability in psychosis may co-occur with higher systemic inflammatory burden in a subset of patients. Given the heterogeneity of real-world cohorts and the

nonspecific nature of CRP/LDH, these findings should be considered hypothesis-generating rather than definitive evidence of a discrete inflammatory biotype. Within this framework, the coexistence of greater clinical severity, higher inflammatory burden, and increased mortality in the HS-SSD cohort supports the hypothesis that inflammation may represent a common biological pathway underlying both mental and somatic deterioration. Rather than being limited to symptom expression, inflammatory dysregulation may characterize a subgroup of patients with a more globally aggressive disease trajectory, affecting both behavioural stability and long-term physical health outcomes.

5. Somatic outcomes

With regard to secondary somatic outcomes, the HS-SSD cohort showed statistically significant but quantitatively small differences compared with the LS-SSD group across all measured parameters. Patients in the higher-severity cohort displayed slightly lower: mean HbA1c levels, LDL cholesterol concentrations, diastolic blood pressure; and slightly shorter QTc intervals.

At first glance, these findings may appear counterintuitive, as the literature consistently shows that patients with more severe schizophrenia tend to present higher cardiometabolic risk (166), including impaired glucose metabolism (167), dyslipidaemia (168), and increased cardiovascular mortality (169). However, the present results indicate that, despite slightly more favourable traditional metabolic markers, the HS-SSD cohort still exhibited both higher inflammatory burden and increased all-cause mortality. This apparent dissociation

suggests that standard cardiometabolic indicators may not fully capture the mechanisms underlying somatic risk in more severe forms of psychosis.

One possible explanatory framework is the existence of partially distinct biological trajectories within the schizophrenia spectrum. While some patients appear to follow a more classical cardiometabolic pathway—characterized by weight gain, insulin resistance, dyslipidaemia, and long-term treatment effects (170)— others may exhibit a predominantly inflammatory or immune-driven profile (171). In this latter subgroup, systemic inflammation may represent an early and primary pathophysiological process, associated with greater clinical instability and higher mortality risk. This distinction may also be compatible with a temporal model of illness progression. Early or biologically more aggressive forms of psychosis may be dominated by immune activation (172,173), stress-related neuroinflammatory mechanisms, and recurrent acute episodes (174), whereas distinct phenotypes characterized by more prominent negative or deficit-like features (175) may be increasingly shaped by treatment-related metabolic changes and sedentary lifestyle (176). It is plausible that patients with more stable courses were more adherent to antipsychotics with prominent antihistaminergic properties, potentially favouring metabolic changes while partially reducing inflammatory activation. From this perspective, the coexistence of higher inflammatory burden, greater hospitalization, and increased mortality—despite slightly more favourable metabolic markers—in the HS-SSD cohort may reflect a primarily immune-driven disease trajectory, rather than a metabolically mediated one.

The direction of the differences is therefore conceptually relevant. Because the propensity score matching procedure balanced key metabolic covariates—such as BMI and systolic blood pressure—between cohorts, these findings cannot simply be attributed to baseline metabolic imbalance. Rather, they suggest that the inflammatory signal observed in the HS-SSD group may reflect a biological vulnerability that is at least partially independent from classical metabolic risk factors. Such a pattern could be related to underlying neuroimmune or genetic mechanisms, including polygenic or haplotypic susceptibilities (177,178), that are not adequately reflected by routine clinical markers. It is also noteworthy that several antipsychotics with stronger antihistaminergic properties (e.g., olanzapine, clozapine) have been associated both with greater weight gain and with anti-inflammatory effects. Therefore, greater exposure to these compounds in more clinically stable patients could theoretically contribute to a metabolic worsening accompanied by partial attenuation of inflammatory markers. This pharmacodynamic dissociation may partly account for the observed divergence between metabolic and inflammatory indices across cohorts.

In this perspective, inflammation may represent an upstream pathophysiological process, whose clinical consequences are more clearly expressed through mortality as a hard outcome than through small differences in cross-sectional laboratory averages. This pattern is compatible with the hypothesis that the inflammatory–behavioural phenotype represents a biologically distinct subgroup within the schizophrenia spectrum, not merely a more metabolically compromised one. Building on previous evidence that inflammation may characterize

only a subset of patients with schizophrenia (179), the present results suggest that this subgroup may follow a biological trajectory partially distinct from the classical cardiometabolic pathway, supporting the hypothesis of partially independent inflammatory and metabolic phenotypes within the schizophrenia spectrum.

From a longitudinal perspective, these findings should not be interpreted as a simple cross-sectional metabolic advantage in the HS-SSD cohort. As key metabolic covariates such as BMI and blood pressure were balanced at baseline, the slightly lower cardiometabolic indices observed in the higher-severity cohort are unlikely to be explained solely by differences in baseline metabolic status or treatment exposure. Instead, these results may point to partially distinct biological trajectories within the schizophrenia spectrum. The HS-SSD cohort was characterized by higher inflammatory burden, greater hospitalization, and increased mortality across the observation period, despite comparable baseline metabolic profiles. This pattern suggests that, in a subset of patients, illness severity and excess mortality may be primarily driven by immune–inflammatory mechanisms rather than by classical cardiometabolic risk factors. In other words, the subgroup with the highest inflammatory activation also exhibited the worst longitudinal outcomes, even in the absence of a more adverse traditional metabolic profile. In this perspective, inflammatory and metabolic alterations may reflect parallel but only partially overlapping pathophysiological pathways. Some patients may follow a predominantly inflammatory trajectory, marked by greater clinical instability, more frequent relapses, and higher mortality, even in the absence of pronounced metabolic derangement. Others may present a

more metabolically driven profile, characterized by chronic functional impairment and higher cardiometabolic burden, but a comparatively more stable clinical course. The present findings are consistent with the hypothesis that these trajectories represent biologically distinct subgroups within the schizophrenia spectrum, rather than different stages of a single metabolic progression.

An additional, non–mutually exclusive explanation concerns treatment exposure and adherence patterns. In routine clinical practice, patients with a more chronic, deficit-oriented course often show greater treatment continuity and cumulative exposure to antipsychotic medication, which is known to increase weight, insulin resistance, and lipid abnormalities. Conversely, patients with more unstable or relapsing trajectories may experience discontinuous treatment, frequent switches, or shorter cumulative exposure, which could attenuate the emergence of overt metabolic abnormalities despite greater clinical severity. Although this hypothesis cannot be directly tested in the present dataset, it may partly account for the dissociation observed between inflammatory burden, clinical outcomes, and traditional metabolic indicators.

Taken together, the coexistence of higher inflammatory burden, greater hospitalization, and increased mortality in the HS-SSD cohort—despite slightly more favourable metabolic markers—supports the interpretation of an inflammatory–behavioural phenotype characterized by intrinsically higher biological vulnerability. This pattern suggests that excess mortality in more severe psychosis may not be fully explained by conventional cardiometabolic risk factors but may also reflect immune–

inflammatory mechanisms that are only partially captured by standard metabolic measures. Accordingly, these secondary outcomes should be interpreted as exploratory and hypothesis-generating, highlighting the need for future longitudinal studies focusing on incident cardiometabolic events and integrated biological profiles.

6. Translational implications: early stratification and precision-guided treatment

Taken together, the present findings point to a clinically meaningful pattern: the HS-SSD cohort showed a convergence of increased inflammatory burden, greater hospitalization, and higher all-cause mortality. While the absolute differences in inflammation and mortality were modest, their consistency across endpoints—within a large, balanced real-world sample—supports the interpretation that a subgroup of patients may follow a more malignant trajectory characterized by both biological vulnerability and clinical instability. In practical terms, this pattern aligns with the concept of an inflammatory–behavioural phenotype: a subset in which systemic inflammatory activation co-occurs with markers of higher severity and adverse outcomes.

This interpretation is broadly coherent with existing evidence indicating that treatment-resistant psychosis constitutes a distinct and prognostically unfavourable course that can often be identified early in the illness (180,181), and that earlier use of high-efficacy or adherence-enhancing strategies may improve long-term outcomes. Clozapine remains the most effective intervention for treatment-resistant psychosis,

yet delays in initiation are common despite data supporting benefits on relapse, hospitalization, and mortality-related endpoints (182). In parallel, long-acting injectable antipsychotics have repeatedly been associated with improved adherence and reduced relapse and rehospitalization, with signals suggesting particular utility in early phases where non-adherence is a key driver of relapse (183). Within this framework, identifying a biologically more severe subgroup is not simply a classificatory exercise: it has direct implications for how psychosis should be managed from the early stages.

The specific contribution of the present study is to connect this translational logic to a scalable stratification approach. Rather than relying on small, highly selected samples or on purely symptomatic definitions, the present results suggest that even routinely available inflammatory markers—together with real-world indicators of severity—may help delineate a subgroup at increased clinical risk within the schizophrenia spectrum. If inflammatory activation marks patients who are more unstable, more frequently hospitalized, and at higher mortality risk, then inflammation becomes a candidate "treatment-specifying" signal: a biomarker that can support earlier escalation to interventions already known to be most effective in severe trajectories, including earlier consideration of clozapine and/or earlier adoption of LAIs to mitigate relapse risk driven by discontinuation.

In this sense, the findings strengthen the precision psychiatry rationale outlined in the Introduction: heterogeneity in psychosis is not only theoretical, but potentially actionable. Demonstrating that biological

stratification (inflammation) maps onto clinically meaningful severity patterns in real-world cohorts is a necessary step toward implementing early, stratified care pathways—aimed at reducing relapse, hospitalization burden, coercive interventions, and premature mortality in the subgroup that stands to lose the most from delayed optimization of treatment.

7. Future perspectives

Taken together, the present findings may support a model in which schizophrenia spectrum disorders encompass at least partially distinct biological trajectories. In the current dataset, a subgroup of patients characterized by higher clinical instability showed increased inflammatory burden, greater hospitalization rates, and higher mortality, despite slightly more favourable traditional metabolic indicators. This pattern is consistent with the hypothesis of a predominantly immune–inflammatory phenotype, biologically distinct from a metabolic trajectory.

Emerging evidence from neuroimaging studies also points in a similar direction. For instance, large-scale structural analyses have identified at least two neuroanatomical patterns within the psychosis spectrum, characterized by different cortical and subcortical alterations (diffuse vs basal ganglia centred degeneration), suggesting the presence of biologically heterogeneous subtypes rather than a single disease process (184). Moreover, more aggressive and severe forms of schizophrenia may present with a higher Local Gyrification Index (LGI), suggesting distinguished neurodevelopmental trajectories influencing symptoms

development (185). Aggressive and severe forms of schizophrenia have also historically shown to onset at an earlier age in comparison with classical forms of the disease (186–188). In this context, the inflammatory and metabolic trajectories observed in the present study may represent partially overlapping but distinct pathophysiological pathways.

From a historical and psychopathological perspective, this conceptual distinction may also echo classical descriptions of different clinical forms of schizophrenia, such as more disorganized or catatonic presentations versus more deficit-oriented or paranoid forms, which were recognized in earlier nosological systems (189). Although these traditional categories were abandoned in modern diagnostic manuals, the convergence of biological, neuroanatomical, and clinical evidence may suggest that such heterogeneity reflects underlying pathophysiological diversity rather than purely descriptive variation.

Within this framework, the inflammatory–behavioural phenotype identified in the present study may represent a more aggressive trajectory, distinct from a more metabolically driven and clinically stable course, further supporting the need for biologically informed stratification approaches in psychosis. Table 4 below summarizes the main differences in support of the hypothesis of different phenotypes.

DOMAIN	**INFLAMMATORY PHENOTYPE**	**METABOLIC PHENOTYPE**
Laboratory profile	Inflammatory alterations	Metabolic alterations
Earlier nosology/presentation	Hebephrenic / catatonic	Simplex / paranoid
Behavioural profile	Greater aggressiveness	Lower aggressiveness

Epidemiology	Earlier onset	Standard onset
Course of illness	More frequent hospitalizations	Fewer hospitalizations
Neuroanatomical pattern	Diffuse degeneration	Basal ganglia–predominant degeneration
Neurodevelopmental features	Increased gyrification	Reduced gyrification

Table 4. Summary of main differences in the hypothesis of schizophrenia inflammatory vs metabolic phenotypes

Strengths and limitations

The present study has several strengths. First, it is based on a large, multicentric real-world cohort, including more than 280,000 individuals with schizophrenia spectrum disorders after propensity score matching. The scale of the sample provides substantial statistical power and allows the inclusion of heterogeneous clinical profiles, more closely reflecting routine psychiatric populations than highly selected clinical trials. Second, the study integrates biological, clinical, and outcome-related variables within the same analytic framework. By combining inflammatory markers with indicators of illness severity, hospitalization, and mortality, it offers a more comprehensive view of the possible inflammatory–behavioural phenotype, extending previous studies that were limited to smaller samples or to single biological domains. Third, the use of propensity score matching enabled the construction of two balanced cohorts, reducing major sociodemographic and clinical imbalances and strengthening the internal validity of the comparisons. Fourth, the very large sample size and the real-world nature of the dataset increase the external validity of the findings and reduce the likelihood that observed associations are driven by small-sample artefacts or highly selected clinical subgroups. In large-scale observational cohorts, random confounding factors and local clinical practices tend to distribute more evenly across groups, making consistent differences across multiple endpoints less likely to reflect spurious associations. In this sense, the convergence of inflammatory, mortality, and hospitalization outcomes within a large, heterogeneous population represents a particularly robust signal.

Several limitations should also be considered. First, although propensity score matching was applied, the adjustment was restricted to a limited number of baseline variables. Residual confounding related to unmeasured factors—such as illness duration, substance use, medication exposure, or socioeconomic conditions—cannot be excluded, though can be partially overcome by the large number of individuals per each cohort. However, these conditions may have partially distinct etiological pathways, which could introduce heterogeneity within the cohort. We were unable to comprehensively control for non-metabolic medical comorbidities (e.g., cardiac arrhythmias, autoimmune disorders), which may differ across severity groups and independently influence inflammatory markers and mortality risk. The dataset did not allow for a detailed analysis of concomitant lipid-lowering or anti-inflammatory medications (e.g., statins), which may influence both metabolic and inflammatory markers. Differential prescription patterns across severity groups could therefore partially contribute to the observed laboratory differences. Moreover, the inclusion of related psychotic diagnoses such as schizoaffective and delusional disorders reflects a pragmatic "psychosis spectrum" approach based on shared treatment exposure and clinical instability patterns. Therefore, findings should be interpreted within a broader psychosis spectrum framework rather than as strictly limited to DSM-defined schizophrenia. Second, clinical severity was operationalized through proxy indicators available in electronic health records, such as hospitalization, agitation, or self-harm codes. These markers reflect clinically meaningful events but do not replace standardized symptom scales and therefore provide an indirect estimate

of behavioural severity. Third, the secondary somatic outcomes were based on cross-sectional laboratory and physiological parameters rather than incident cardiometabolic events. This limits conclusions about longitudinal cardiometabolic risk and may partly account for the apparent dissociation between slightly more favourable metabolic indices and higher mortality in the higher-severity cohort. Fourth, clinical severity was operationalized using EHR-based proxy indicators of recent clinical instability, including hospitalization-related codes. Consequently, analyses involving subsequent hospitalization are subject to partial definitional overlap and may overestimate between-cohort differences. Therefore, hospitalization results should be interpreted primarily as supporting the persistence of an instability trajectory (construct validation), rather than as an independent causal outcome. In contrast, mortality and inflammatory outcomes do not enter the cohort definition and provide more independent evidence of longitudinal differences between groups. Finally, as with all retrospective real-world studies, the analysis is subject to potential variability in coding practices, missing data, and limited information on treatment adherence, dosing, and illness course. The observational design also precludes causal inferences regarding the relationship between inflammation, severity, and outcomes.

Despite these limitations, the convergence of increased inflammatory burden, higher hospitalization rates, and greater mortality within a large, matched cohort supports the internal consistency of the findings and provides a solid basis for future prospective studies.

Conclusions

In this large real-world cohort of individuals with schizophrenia spectrum disorders, higher clinical severity was consistently associated with increased systemic inflammation, greater hospitalization burden, and elevated all-cause mortality. These findings support the hypothesis that a subgroup of patients may follow a more malignant trajectory characterized by the convergence of biological vulnerability and clinical instability.

The results are consistent with the hypothesis of an inflammatory–behavioural phenotype within the psychosis spectrum, in which systemic inflammatory activation is linked to more severe clinical and somatic outcomes. Importantly, this association emerged in a large, balanced real-world population, extending previous observations from smaller or more selected samples.

At the same time, the observation that the higher-severity cohort showed greater inflammatory burden and worse outcomes despite slightly more favourable traditional metabolic indices suggests that inflammatory and cardiometabolic alterations may represent partially distinct biological pathways within the schizophrenia spectrum. This pattern is compatible with the hypothesis that the inflammatory phenotype reflects a biologically more aggressive trajectory, not necessarily mediated by classical metabolic risk factors.

From a translational perspective, the identification of such a phenotype has direct clinical implications. If inflammatory activation marks patients at higher risk of adverse trajectories from the earliest stages of illness, it may serve as a practical stratification signal to guide earlier

implementation of high-efficacy or adherence-enhancing treatments, such as clozapine or long-acting injectable antipsychotics. Further prospective and mechanistic studies are needed to clarify the biological pathways underlying this association and to determine whether inflammation-guided treatment strategies can improve long-term outcomes in psychosis. Perhaps, the search for different biotypes brings us one step closer to the biological distinctions that Kraepelin had already intuited more than a century ago.

Bibliography

1. Kurtz MM. Kraepelin, schizophrenia and the first biological era in psychiatry. Schizophrenia Research. 2022;244:69–70. DOI: 10.1016/j.schres.2022.05.007

2. Jablensky A. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. Dialogues Clin Neurosci. 2010;12(3):271–87. DOI: 10.31887/DCNS.2010.12.3/ajablensky

3. Jablensky A. Subtyping schizophrenia: implications for genetic research. Mol Psychiatry. 2006;11(9):815–36. DOI: 10.1038/sj.mp.4001857

4. Tandon R. Agreement on the contours of schizophrenia: The first order of business. Schizophrenia Research. 2022;242:135–7. DOI: 10.1016/j.schres.2022.01.003

5. Cannon TD. Psychosis, schizophrenia, and states vs. traits. Schizophrenia Research. 2022;242:12–4. DOI: 10.1016/j.schres.2021.12.001

6. Carpenter WT. Schizophrenia: A view of immediate future. Schizophrenia Research. 2022;242:15–6. DOI: 10.1016/j.schres.2021.12.004

7. Van Os J, Guloksuz S. Schizophrenia as a symptom of psychiatry's reluctance to enter the moral era of medicine. Schizophrenia Research. 2022;242:138–40. DOI: 10.1016/j.schres.2021.12.017

8. Buckley PF. Neuroinflammation and Schizophrenia. Curr Psychiatry Rep. 2019;21(8):72. DOI: 10.1007/s11920-019-1050-z

9. Müller N. Inflammation in Schizophrenia: Pathogenetic Aspects and Therapeutic Considerations. Schizophrenia Bulletin. 2018;44(5):973–82. DOI: 10.1093/schbul/sby024

10. Doorduin J, De Vries EFJ, Willemsen ATM, De Groot JC, Dierckx RA, Klein HC. Neuroinflammation in Schizophrenia-Related Psychosis: A PET Study. J Nucl Med. 2009;50(11):1801–7. DOI: 10.2967/jnumed.109.066647

11. Rantala MJ, Luoto S, Borráz-León JI, Krams I. Schizophrenia: The new etiological synthesis. Neuroscience & Biobehavioral Reviews. 2022;142:104894. DOI: 10.1016/j.neubiorev.2022.104894

12. Howes OD, Shatalina E. Integrating the Neurodevelopmental and Dopamine Hypotheses of Schizophrenia and the Role of Cortical Excitation-Inhibition Balance. Biological Psychiatry. 2022;92(6):501–13. DOI: 10.1016/j.biopsych.2022.06.017

13. Arnold SE. Neurodevelopmental abnormalities in schizophrenia: insights from neuropathology. Dev Psychopathol. 1999;11(3):439–56. DOI: 10.1017/s095457949900214x

14. Chen C-H, Cheng M-C, Huang A, Hu T-M, Ping L-Y, Chang Y-S. Detection of Rare Methyl-CpG Binding Protein 2 Gene Missense Mutations in Patients With Schizophrenia. Front Genet. 2020;11:476. DOI: 10.3389/fgene.2020.00476

15. Qing L, Liu L, Zhou L, Zhang F, Gao C, Hu L, et al. Sex-dependent association of mineralocorticoid receptor gene (NR3C2) DNA methylation and schizophrenia. Psychiatry Research. 2020;292:113318. DOI: 10.1016/j.psychres.2020.113318

16. Romeo B, Brunet-Lecomte M, Martelli C, Benyamina A. Kinetics of Cytokine Levels during Antipsychotic Treatment in Schizophrenia: A Meta-Analysis. International Journal of Neuropsychopharmacology. 2018;21(9):828–36. DOI: 10.1093/ijnp/pyy062

17. Wang J, Xu H, Wang D, Wei G, Zhou H, Wang L, et al. The interactive effect of genetic polymorphisms of IL-10 and COMT on cognitive function in schizophrenia. J Psychiatr Res. 2021;136:501–7. DOI: 10.1016/j.jpsychires.2020.10.021

18. Wang J, Su P, Yang J, Xu L, Yuan A, Li C, et al. The D2R-DISC1 protein complex and associated proteins are altered in schizophrenia and normalized with antipsychotic treatment. J Psychiatry Neurosci. 2022;47(2):E134–47. DOI: 10.1503/jpn.210145

19. Chamera K, Trojan E, Kotarska K, Szuster-Głuszczak M, Bryniarska N, Tylek K, et al. Role of Polyinosinic:Polycytidylic Acid-Induced Maternal Immune Activation and Subsequent Immune Challenge in the Behaviour and Microglial Cell Trajectory in Adult Offspring: A Study of the Neurodevelopmental Model of Schizophrenia. Int J Mol Sci. 2021;22(4):1558. DOI: 10.3390/ijms22041558

20. De Picker LJ, Morrens M, Chance SA, Boche D. Microglia and Brain Plasticity in Acute Psychosis and Schizophrenia Illness Course: A Meta-Review. Front Psychiatry. 2017;8:238. DOI: 10.3389/fpsyt.2017.00238

21. Su Y, Lian J, Chen S, Zhang W, Deng C. Epigenetic histone acetylation modulating prenatal Poly I:C induced neuroinflammation in the prefrontal cortex of rats: a study in a maternal immune activation model. Front Cell Neurosci. 2022;16:1037105. DOI: 10.3389/fncel.2022.1037105

22. Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res. 2008;42(2):151–7. DOI: 10.1016/j.jpsychires.2006.10.013

23. Estes ML, McAllister AK. Maternal immune activation: Implications for neuropsychiatric disorders. Science. 2016;353(6301):772–7. DOI: 10.1126/science.aag3194

24. Bray NJ. Gene expression in the etiology of schizophrenia. Schizophr Bull. 2008;34(3):412–8. DOI: 10.1093/schbul/sbn013

25. Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol Psychiatry. 2016;21(8):1009–26. DOI: 10.1038/mp.2016.90

26. Andreou D, Steen NE, Jørgensen KN, Nerland S, Ueland T, Wortinger LA, et al. Toxoplasma gondii associated with psychotic symptom load and cortisol in severe mental illness. Schizophr. 2025;11(1):80. DOI: 10.1038/s41537-025-00630-0

27. Alvim PHP, Cavalari VC, Bianchini AJ, Frizon GF, Ferreira GM, Savian HFH, et al. Toxoplasmosis infection and schizophrenia: Elevated IgM reactivity index as a predictor of symptom worsening in chronic schizophrenia. Schizophrenia Research. 2025;278:20–5. DOI: 10.1016/j.schres.2025.03.008

28. Ahmed GK, Ramadan HK-A, Elbeh K, Haridy NA. The role of infections and inflammation in schizophrenia: review of the evidence. Middle East Curr Psychiatry. 2024;31(1):9. DOI: 10.1186/s43045-024-00397-7

29. Mattei D, Djodari-Irani A, Hadar R, Pelz A, de Cossío LF, Goetz T, et al. Minocycline rescues decrease in neurogenesis, increase in microglia cytokines and deficits in sensorimotor gating in an animal model of schizophrenia. Brain Behav Immun. 2014;38:175–84. DOI: 10.1016/j.bbi.2014.01.019

30. Chaves C, Marque CR, Trzesniak C, Machado de Sousa JP, Zuardi AW, Crippa J a. S, et al. Glutamate-N-methyl-D-aspartate receptor modulation and minocycline for the treatment of patients with schizophrenia: an update. Braz J Med Biol Res. 2009;42(11):1002–14. DOI: 10.1590/S0100-879X2009001100002

31. Hashimoto K. Microglial activation in schizophrenia and minocycline treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(7):1758–9; author reply 1760. DOI: 10.1016/j.pnpbp.2008.06.012

32. Leucht S, Chaimani A, Krause M, Schneider-Thoma J, Wang D, Dong S, et al. The response of subgroups of patients with schizophrenia to different antipsychotic drugs: a systematic review and meta-analysis. Lancet Psychiatry. 2022;9(11):884–93. DOI: 10.1016/S2215-0366(22)00304-2

33. Lähteenvuo M, Tiihonen J. Antipsychotic Polypharmacy for the Management of Schizophrenia: Evidence and Recommendations. Drugs. 2021;81(11):1273–84. DOI: 10.1007/s40265-021-01556-4

34. Monji A, Kato T, Kanba S. Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. Psychiatry Clin Neurosci. 2009;63(3):257–65. DOI: 10.1111/j.1440-1819.2009.01945.x

35. van Kesteren CFMG, Gremmels H, de Witte LD, Hol EM, Van Gool AR, Falkai PG, et al. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl Psychiatry. 2017;7(3):e1075. DOI: 10.1038/tp.2017.4

36. Pong S, Karmacharya R, Sofman M, Bishop JR, Lizano P. The Role of Brain Microvascular Endothelial Cell and Blood-Brain Barrier Dysfunction in Schizophrenia. Complex Psychiatry. 2020;6(1–2):30–46. DOI: 10.1159/000511552

37. Millett CE, Burdick KE, Kubicki MR. The Effects of Peripheral Inflammation on the Brain-A Neuroimaging Perspective. Harv Rev Psychiatry. 2022;30(1):54–8. DOI: 10.1097/HRP.0000000000000323

38. Lizano P, Lutz O, Ling G, Lee AM, Eum S, Bishop JR, et al. Association of Choroid Plexus Enlargement With Cognitive, Inflammatory, and Structural Phenotypes Across the Psychosis Spectrum. Am J Psychiatry. 2019;176(7):564–72. DOI: 10.1176/appi.ajp.2019.18070825

39. Balusu S, Van Wonterghem E, De Rycke R, Raemdonck K, Stremersch S, Gevaert K, et al. Identification of a novel mechanism of blood-brain communication during peripheral inflammation via choroid plexus-derived extracellular vesicles. EMBO Mol Med. 2016;8(10):1162–83. DOI: 10.15252/emmm.201606271

40. Bishop JR, Zhang L, Lizano P. Inflammation Subtypes and Translating Inflammation-Related Genetic Findings in Schizophrenia and Related

Psychoses: A Perspective on Pathways for Treatment Stratification and Novel Therapies. Harv Rev Psychiatry. 2022;30(1):59–70. DOI: 10.1097/HRP.0000000000000321

41. Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, Giordano A, et al. Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis. Schizophr Bull. 2015;41(5):1162–70. DOI: 10.1093/schbul/sbv028

42. Lizano P, Lutz O, Xu Y, Rubin LH, Paskowitz L, Lee AM, et al. Multivariate relationships between peripheral inflammatory marker subtypes and cognitive and brain structural measures in psychosis. Mol Psychiatry. 2021;26(7):3430–43. DOI: 10.1038/s41380-020-00914-0

43. Fillman SG, Sinclair D, Fung SJ, Webster MJ, Shannon Weickert C. Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. Transl Psychiatry. 2014;4(2):e365. DOI: 10.1038/tp.2014.8

44. Boerrigter D, Weickert TW, Lenroot R, O'Donnell M, Galletly C, Liu D, et al. Using blood cytokine measures to define high inflammatory biotype of schizophrenia and schizoaffective disorder. J Neuroinflammation. 2017;14(1):188. DOI: 10.1186/s12974-017-0962-y

45. Weinberger JF, Raison CL, Rye DB, Montague AR, Woolwine BJ, Felger JC, et al. Inhibition of tumor necrosis factor improves sleep continuity in patients with treatment resistant depression and high inflammation. Brain Behav Immun. 2015;47:193–200. DOI: 10.1016/j.bbi.2014.12.016

46. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist

infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70(1):31–41. DOI: 10.1001/2013.jamapsychiatry.4

47. Barbosa S, Martinuzzi E, Sommer IE, Dazzan P, McGuire P, Arango C, et al. Baseline Levels of C-Reactive Protein and Proinflammatory Cytokines Are Not Associated With Early Response to Amisulpride in Patients With First Episode Psychosis: The OPTiMiSE Cohort Study. Schizophrenia Bulletin Open. 2021;2(1):sgab017. DOI: 10.1093/schizbullopen/sgab017

48. Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD. A Meta-analysis of Immune Parameters, Variability, and Assessment of Modal Distribution in Psychosis and Test of the Immune Subgroup Hypothesis. Schizophr Bull. 2019;45(5):1120–33. DOI: 10.1093/schbul/sby160

49. Hoang D, Xu Y, Lutz O, Bannai D, Zeng V, Bishop JR, et al. Inflammatory Subtypes in Antipsychotic-Naïve First-Episode Schizophrenia are Associated with Altered Brain Morphology and Topological Organization. Brain Behav Immun. 2022;100:297–308. DOI: 10.1016/j.bbi.2021.11.019

50. Metcalf SA, Jones PB, Nordstrom T, Timonen M, Mäki P, Miettunen J, et al. Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: A prospective birth cohort study. Brain Behav Immun. 2017;59:253–9. DOI: 10.1016/j.bbi.2016.09.008

51. Khandaker GM, Zimbron J, Dalman C, Lewis G, Jones PB. Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. Schizophr Res. 2012;139(1–3):161–8. DOI: 10.1016/j.schres.2012.05.023

52. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med. 2013;43(2):239–57. DOI: 10.1017/S0033291712000736

53. Hayes JF, Khandaker GM, Anderson J, Mackay D, Zammit S, Lewis G, et al. Childhood interleukin-6, C-reactive protein and atopic disorders as risk factors for hypomanic symptoms in young adulthood: a longitudinal birth cohort study. Psychol Med. 2017;47(1):23–33. DOI: 10.1017/S0033291716001574

54. Dalman C, Allebeck P, Gunnell D, Harrison G, Kristensson K, Lewis G, et al. Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swedish subjects. Am J Psychiatry. 2008;165(1):59–65. DOI: 10.1176/appi.ajp.2007.07050740

55. Wium-Andersen MK, Ørsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. JAMA Psychiatry. 2013;70(2):176–84. DOI: 10.1001/2013.jamapsychiatry.102

56. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry. 2014;171(12):1278–86. DOI: 10.1176/appi.ajp.2014.14010094

57. Cizza G, Eskandari F, Coyle M, Krishnamurthy P, Wright EC, Mistry S, et al. Plasma CRP levels in premenopausal women with major depression: a 12-month controlled study. Horm Metab Res. 2009;41(8):641–8. DOI: 10.1055/s-0029-1220717

58. Wysokiński A, Margulska A, Strzelecki D, Kłoszewska I. Levels of C-reactive protein (CRP) in patients with schizophrenia, unipolar depression and bipolar disorder. Nord J Psychiatry. 2015;69(5):346–53. DOI: 10.3109/08039488.2014.984755

59. Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E, et al. The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr Res. 1998;32(1):9–15. DOI: 10.1016/s0920-9964(98)00034-6

60. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine. 1997;9(11):853–8. DOI: 10.1006/cyto.1997.0238

61. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology. 2000;22(4):370–9. DOI: 10.1016/S0893-133X(99)00134-7

62. Huang J, Chen A, Jin H, Liu F, Hei G, Teng Z, et al. Efficacy and Safety of Sulforaphane Added to Antipsychotics for the Treatment of Negative Symptoms of Schizophrenia: A Randomized Controlled Trial. J Clin Psychiatry. 2025;86(1):24m15272. DOI: 10.4088/JCP.24m15272

63. Chen H, Lu J, Zou T, Teng Z, Qin Y, Wu R, et al. Effects of sulforaphane on negative symptoms and cognitive impairments in chronic schizophrenia patients: A randomized double-blind trial. J Psychiatr Res. 2025;184:464–72. DOI: 10.1016/j.jpsychires.2025.03.023

64. Sinichi F, Farid Hosseini F, Fayyazi-Bordbar M, Sinichi M, Jamali J, Mohammadpour A. Pentoxifylline as adjunctive therapy in cognitive deficits and symptoms of schizophrenia: A randomized double-blind placebo-controlled clinical trial. J Psychopharmacol. Oxford, England; 2023;37(10):1003–10. DOI: 10.1177/02698811231186760

65. Shamabadi A, Rafiei-Tabatabaei E-S, Kazemzadeh K, Farahmand K, Fallahpour B, Khodaei Ardakani M-R, et al. Pentoxifylline adjunct to risperidone for negative symptoms of stable schizophrenia: a randomized, double-blind, placebo-controlled trial. Int J Neuropsychopharmacol. 2024;28(1):pyae051. DOI: 10.1093/ijnp/pyae051

66. Weickert TW, Jacomb I, Lenroot R, Lappin J, Weinberg D, Brooks WS, et al. Adjunctive canakinumab reduces peripheral inflammation markers and improves positive symptoms in people with schizophrenia and inflammation: A randomized control trial. Brain Behav Immun. 2024;115:191–200. DOI: 10.1016/j.bbi.2023.10.012

67. Li H, Shen H, Duan X, Guo M, Liu X. Efficacy and safety of anti-inflammatory drug-assisted treatment of symptoms in patients with schizophrenia: a meta-analysis. BMC Psychiatry. 2026;26(1):161. DOI: 10.1186/s12888-026-07774-y

68. Goldsmith DR, Rapaport MH. Inflammation and Negative Symptoms of Schizophrenia: Implications for Reward Processing and Motivational Deficits. Front Psychiatry. 2020;11:46. DOI: 10.3389/fpsyt.2020.00046

69. Alexandros Lalousis P, Schmaal L, Wood SJ, L E P Reniers R, Cropley VL, Watson A, et al. Inflammatory subgroups of schizophrenia and their association with brain structure: A semi-supervised machine learning

examination of heterogeneity. Brain Behav Immun. 2023;113:166–75. DOI: 10.1016/j.bbi.2023.06.023

70. Fond G, Lançon C, Auquier P, Boyer L. C-Reactive Protein as a Peripheral Biomarker in Schizophrenia. An Updated Systematic Review. Front Psychiatry. 2018;9:392. DOI: 10.3389/fpsyt.2018.00392

71. Sicras-Mainar A, Rejas-Gutiérrez J, Navarro-Artieda R, Blanca-Tamayo M. C-reactive protein as a marker of cardiovascular disease in patients with a schizophrenia spectrum disorder treated in routine medical practice. Eur Psychiatry. 2013;28(3):161–7. DOI: 10.1016/j.eurpsy.2011.07.003

72. Prins BP, Abbasi A, Wong A, Vaez A, Nolte I, Franceschini N, et al. Investigating the Causal Relationship of C-Reactive Protein with 32 Complex Somatic and Psychiatric Outcomes: A Large-Scale Cross-Consortium Mendelian Randomization Study. PLoS Med. 2016;13(6):e1001976. DOI: 10.1371/journal.pmed.1001976

73. Fernandes BS, Steiner J, Bernstein H-G, Dodd S, Pasco JA, Dean OM, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry. 2016;21(4):554–64. DOI: 10.1038/mp.2015.87

74. Frydecka D, Misiak B, Pawlak-Adamska E, Karabon L, Tomkiewicz A, Sedlaczek P, et al. Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. Eur Arch Psychiatry Clin Neurosci. 2015;265(6):449–59. DOI: 10.1007/s00406-014-0533-5

75. Johnsen E, Fathian F, Kroken RA, Steen VM, Jørgensen HA, Gjestad R, et al. The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis. BMC Psychiatry. 2016;16:60. DOI: 10.1186/s12888-016-0769-x

76. Dorofeikova M, Neznanov N, Petrova N. Cognitive deficit in patients with paranoid schizophrenia: Its clinical and laboratory correlates. Psychiatry Res. 2018;262:542–8. DOI: 10.1016/j.psychres.2017.09.041

77. Barzilay R, Lobel T, Krivoy A, Shlosberg D, Weizman A, Katz N. Elevated C-reactive protein levels in schizophrenia inpatients is associated with aggressive behavior. Eur Psychiatry. 2016;31:8–12. DOI: 10.1016/j.eurpsy.2015.09.461

78. Leza JC, García-Bueno B, Bioque M, Arango C, Parellada M, Do K, et al. Inflammation in schizophrenia: A question of balance. Neurosci Biobehav Rev. 2015;55:612–26. DOI: 10.1016/j.neubiorev.2015.05.014

79. Li C, Wang A, Wang C, Ramamurthy J, Zhang E, Guadagno E, et al. Metabolomics in patients with psychosis: A systematic review. Am J Med Genet B Neuropsychiatr Genet. 2018;177(6):580–8. DOI: 10.1002/ajmg.b.32662

80. Pruett BS, Meador-Woodruff JH. Evidence for altered energy metabolism, increased lactate, and decreased pH in schizophrenia brain: A focused review and meta-analysis of human postmortem and magnetic resonance spectroscopy studies. Schizophr Res. 2020;223:29–42. DOI: 10.1016/j.schres.2020.09.003

81. Liu S, Zhang L, Fan X, Wang G, Liu Q, Yang Y, et al. Lactate levels in the brain and blood of schizophrenia patients: A systematic review and

meta-analysis. Schizophr Res. 2024;264:29–38. DOI: 10.1016/j.schres.2023.11.013

82. Dogan AE, Yuksel C, Du F, Chouinard V-A, Öngür D. Brain lactate and pH in schizophrenia and bipolar disorder: a systematic review of findings from magnetic resonance studies. Neuropsychopharmacology. 2018;43(8):1681–90. DOI: 10.1038/s41386-018-0041-9

83. Jia C, Zhang M, Wu X, Zhang X, Lv Z, Zhao K, et al. HERV-W Env Induces Neuron Pyroptosis via the NLRP3-CASP1-GSDMD Pathway in Recent-Onset Schizophrenia. Int J Mol Sci. 2025;26(2):520. DOI: 10.3390/ijms26020520

84. Chamera K, Curzytek K, Kamińska K, Trojan E, Leśkiewicz M, Tylek K, et al. Insights into the Potential Impact of Quetiapine on the Microglial Trajectory and Inflammatory Response in Organotypic Cortical Cultures Derived from Rat Offspring. Biomedicines. 2023;11(5):1405. DOI: 10.3390/biomedicines11051405

85. Deng MY, Lam S, Meyer U, Feldon J, Li Q, Wei R, et al. Frontal-subcortical protein expression following prenatal exposure to maternal inflammation. PLoS One. 2011;6(2):e16638. DOI: 10.1371/journal.pone.0016638

86. Tiihonen J, Isohanni M, Räsänen P, Koiranen M, Moring J. Specific major mental disorders and criminality: a 26-year prospective study of the 1966 northern Finland birth cohort. Am J Psychiatry. 1997;154(6):840–5. DOI: 10.1176/ajp.154.6.840

87. Lindqvist P, Allebeck P. Schizophrenia and crime. A longitudinal follow-up of 644 schizophrenics in Stockholm. Br J Psychiatry. 1990;157:345–50. DOI: 10.1192/bjp.157.3.345

88. Kooyman I, Dean K, Harvey S, Walsh E. Outcomes of public concern in schizophrenia. Br J Psychiatry Suppl. 2007;50:s29-36. DOI: 10.1192/bjp.191.50.s29

89. Joyal C, Dubreucq J-L, Gendron C, Millaud F. Major Mental Disorders and Violence: A Critical Update. CPSR. 2007;3(1):33–50. DOI: 10.2174/157340007779815628

90. Wallace C, Mullen PE, Burgess P. Criminal offending in schizophrenia over a 25-year period marked by deinstitutionalization and increasing prevalence of comorbid substance use disorders. Am J Psychiatry. 2004;161(4):716–27. DOI: 10.1176/appi.ajp.161.4.716

91. Arseneault L, Moffitt TE, Caspi A, Taylor PJ, Silva PA. Mental disorders and violence in a total birth cohort: results from the Dunedin Study. Arch Gen Psychiatry. 2000;57(10):979–86. DOI: 10.1001/archpsyc.57.10.979

92. Wu G, Dong Z, Li Z, Zhao Q, Chen S, Dong Q, et al. Comorbidity patterns and immune-metabolic differences in patients with acute-episode of schizophrenia spectrum disorders. Schizophr. 2025;11(1):102. DOI: 10.1038/s41537-025-00646-6

93. Polcwiartek C, Jensen SE, Frøkjær JB, Nielsen RE. Prevalence of cardiovascular risk factors and disease in patients with schizophrenia: baseline results from a prospective cohort study with long-term clinical follow-up. Schizophr. 2025;11(1):95. DOI: 10.1038/s41537-025-00642-w

94. Sesso HD. C-Reactive Protein and the Risk of Developing Hypertension. JAMA. 2003;290(22):2945. DOI: 10.1001/jama.290.22.2945

95. Ramos-Arellano LE, Matia-Garcia I, Marino-Ortega LA, Castro-Alarcón N, Muñoz-Valle JF, Salgado-Goytia L, et al. Obesity, dyslipidemia, and high blood pressure are associated with cardiovascular risk, determined using high-sensitivity C-reactive protein concentration, in young adults. J Int Med Res. 2020;48(12):300060520980596. DOI: 10.1177/0300060520980596

96. Wu L, Wu M, Zhao D, Chen S, Wang G, Xu L, et al. Elevated high-sensitivity C-reactive protein levels increase the risk of new-onset cardiac conduction disorders. Cardiovasc Diabetol. 2023;22(1):268. DOI: 10.1186/s12933-023-01987-1

97. Siskind D, Orr S, Sinha S, Yu O, Brijball B, Warren N, et al. Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. Br J Psychiatry. 2022;220(3):115–20. DOI: 10.1192/bjp.2021.61

98. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2016;209(5):385–92. DOI: 10.1192/bjp.bp.115.177261

99. Vermeulen JM, van Rooijen G, van de Kerkhof MPJ, Sutterland AL, Correll CU, de Haan L. Clozapine and Long-Term Mortality Risk in Patients With Schizophrenia: A Systematic Review and Meta-analysis of Studies Lasting 1.1-12.5 Years. Schizophr Bull. 2019;45(2):315–29. DOI: 10.1093/schbul/sby052

100. O'Donoghue B, Mora L, Bismark M, Thompson A, McGorry P. Identifying and managing treatment resistance early with the integration of a clozapine clinic within an early intervention for psychosis service. Early Interv Psychiatry. 2025;19(1):e13578. DOI: 10.1111/eip.13578

101. Land R, Siskind D, McArdle P, Kisely S, Winckel K, Hollingworth SA. The impact of clozapine on hospital use: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017;135(4):296–309. DOI: 10.1111/acps.12700

102. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry. 2003;60(1):82–91. DOI: 10.1001/archpsyc.60.1.82

103. U.S. Food and Drug Administration. 2002.

104. Siskind D, Sidhu A, Cross J, Chua Y-T, Myles N, Cohen D, et al. Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. Aust N Z J Psychiatry. 2020;54(5):467–81. DOI: 10.1177/0004867419898760

105. Hibbard KR, Propst A, Frank DE, Wyse J. Fatalities associated with clozapine-related constipation and bowel obstruction: a literature review and two case reports. Psychosomatics. 2009;50(4):416–9. DOI: 10.1176/appi.psy.50.4.416

106. Li X-H, Zhong X-M, Lu L, Zheng W, Wang S-B, Rao W-W, et al. The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. Psychol Med. 2020;50(4):583–94. DOI: 10.1017/S0033291719000369

107. Oloyede E, Blackman G, Mantell B, Harris E, Williams J, Taylor D, et al. What are the barriers and facilitators of clozapine use in early psychosis? A survey of UK early intervention clinicians. Schizophrenia (Heidelb). 2023;9(1):26. DOI: 10.1038/s41537-023-00353-0

108. Wang PS, Glynn RJ, Ganz DA, Schneeweiss S, Levin R, Avorn J. Clozapine use and risk of diabetes mellitus. J Clin Psychopharmacol. 2002;22(3):236–43. DOI: 10.1097/00004714-200206000-00002

109. Edinoff AN, Sauce E, Ochoa CO, Cross J, Cogburn M, Cornett EM, et al. Clozapine and Constipation: A Review of Clinical Considerations and Treatment Options. Psychiatry International. 2021;2(3):344–52. DOI: 10.3390/psychiatryint2030026

110. Stogios N, Maksyutynska K, Navagnanavel J, Sanches M, Powell V, Gerretsen P, et al. Metformin for the prevention of clozapine-induced weight gain: A retrospective naturalistic cohort study. Acta Psychiatr Scand. 2022;146(3):190–200. DOI: 10.1111/acps.13462

111. Gee SH, Shergill SS, Taylor DM. Patient attitudes to clozapine initiation. Int Clin Psychopharmacol. 2017;32(6):337–42. DOI: 10.1097/YIC.0000000000000188

112. Tungaraza TE, Farooq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. Ther Adv Psychopharmacol. 2015;5(2):88–96. DOI: 10.1177/2045125314566808

113. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJM, Birnbaum ML, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group

Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry. 2017;174(3):216–29. DOI: 10.1176/appi.ajp.2016.16050503

114. Thien K, Bowtell M, Eaton S, Bardell-Williams M, Downey L, Ratheesh A, et al. Clozapine use in early psychosis. Schizophr Res. 2018;199:374–9. DOI: 10.1016/j.schres.2018.02.054

115. Edwards J, Maude D, McGorry PD, Harrigan SM, Cocks JT. Prolonged recovery in first-episode psychosis. Br J Psychiatry Suppl. 1998;172(33):107–16.

116. Etienne M, Verdoux H. Impact of long-acting injectable antipsychotics in early psychosis: An umbrella review. Schizophr Res. 2025;277:140–50. DOI: 10.1016/j.schres.2025.03.002

117. Ostuzzi G, Bertolini F, Del Giovane C, Tedeschi F, Bovo C, Gastaldon C, et al. Maintenance Treatment With Long-Acting Injectable Antipsychotics for People With Nonaffective Psychoses: A Network Meta-Analysis. Am J Psychiatry. 2021;178(5):424–36. DOI: 10.1176/appi.ajp.2020.20071120

118. Khan AY, Salaria S, Ovais M, Ide GD. Depot antipsychotics: Where do we stand? Ann Clin Psychiatry. 2016;28(4):289–98.

119. Pelayo-Terán JM, Gajardo Galán VG, de la Ortiz-García de la Foz V, Martínez-García O, Tabarés-Seisdedos R, Crespo-Facorro B, et al. Rates and predictors of relapse in first-episode non-affective psychosis: a 3-year longitudinal study in a specialized intervention program (PAFIP). Eur Arch Psychiatry Clin Neurosci. 2017;267(4):315–23. DOI: 10.1007/s00406-016-0740-3

120. Alvarez-Jimenez M, Priede A, Hetrick SE, Bendall S, Killackey E, Parker AG, et al. Risk factors for relapse following treatment for first episode

psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res. 2012;139(1–3):116–28. DOI: 10.1016/j.schres.2012.05.007

121. Verdoux H, Pambrun E, Tournier M, Bezin J, Pariente A. Risk of discontinuation of antipsychotic long-acting injections vs. oral antipsychotics in real-life prescribing practice: a community-based study. Acta Psychiatr Scand. 2017;135(5):429–38. DOI: 10.1111/acps.12722

122. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, et al. Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia. JAMA Psychiatry. 2017;74(7):686–93. DOI: 10.1001/jamapsychiatry.2017.1322

123. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. Lancet Psychiatry. 2021;8(5):387–404. DOI: 10.1016/S2215-0366(21)00039-0

124. Hamina A, Taipale H, Lieslehto J, Lähteenvuo M, Tanskanen A, Mittendorfer-Rutz E, et al. Comparative Effectiveness of Antipsychotics in Patients With Schizophrenia Spectrum Disorder. JAMA Netw Open. 2024;7(10):e2438358. DOI: 10.1001/jamanetworkopen.2024.38358

125. Zhornitsky S, Stip E. Oral versus Long-Acting Injectable Antipsychotics in the Treatment of Schizophrenia and Special Populations at Risk for Treatment Nonadherence: A Systematic Review. Schizophr Res Treatment. 2012;2012:407171. DOI: 10.1155/2012/407171

126. Taylor M, Ng KYB. Should long-acting (depot) antipsychotics be used in early schizophrenia? A systematic review. Aust N Z J Psychiatry. 2013;47(7):624–30. DOI: 10.1177/0004867412470010

127. Salgueiro M, Segarra R. Long-acting injectable second-generation antipsychotics in first-episode psychosis: a narrative review. Int Clin Psychopharmacol. 2019;34(2):51–6. DOI: 10.1097/YIC.0000000000000249

128. Lian L, Kim DD, Procyshyn RM, Fredrikson DH, Cázares D, Honer WG, et al. Efficacy of long-acting injectable versus oral antipsychotic drugs in early psychosis: A systematic review and meta-analysis. Early Interv Psychiatry. 2022;16(6):589–99. DOI: 10.1111/eip.13202

129. Lian L, Kim DD, Procyshyn RM, Cázares D, Honer WG, Barr AM. Long-acting injectable antipsychotics for early psychosis: A comprehensive systematic review. PLoS One. 2022;17(4):e0267808. DOI: 10.1371/journal.pone.0267808

130. Emsley R, Chiliza B, Asmal L, Mashile M, Fusar-Poli P. Long-acting injectable antipsychotics in early psychosis: a literature review. Early Interv Psychiatry. 2013;7(3):247–54. DOI: 10.1111/eip.12027

131. Yeh Y-T, Lo S-C, Huang C-N, Yang Y-S, Liao P-L, Kornelius E. Comparative cardiovascular outcomes of aripiprazole vs. risperidone in patients with type 2 diabetes and schizophrenia: a retrospective cohort study. Front Pharmacol. 2025;16:1617534. DOI: 10.3389/fphar.2025.1617534

132. Liu T-H, Hsu C-H, Wu J-Y, Huang P-Y, Chang C-C, Lai C-C. Association between tirzepatide use and risk of mortality, hospitalization, and suicidal behavior in patients with schizophrenia spectrum disorders: A

one-year retrospective cohort study of 3618 patients. Eur Neuropsychopharmacol. 2026;103:112739. DOI: 10.1016/j.euroneuro.2025.11.016

133. Ahmed S, Beyene E, Bisrat M, Falegan T, Hemphill A, Mack A, et al. Incidence and demographic patterns of neutropenia in clozapine-treated patients with schizophrenia: A 20-year retrospective cohort study. J Natl Med Assoc. 2026;118(1):149–55. DOI: 10.1016/j.jnma.2025.11.010

134. Das N, Dhamija R, Mistak D, Diaz LD, Kaelber DC, Mulloy K, et al. Epidemiological analysis of schizophrenia and incarceration: A multi-center exploration of the criminalization of mental illness in the United States. Schizophr Res. 2026;287:73–81. DOI: 10.1016/j.schres.2025.11.001

135. Israel A, Weizman A, Israel S, Stokar J, Ashkenazi S, Vinker S, et al. Systematic screening identifies medication and disease factors associated with schizophrenia risk. Brain Behav Immun. 2026;131:106135. DOI: 10.1016/j.bbi.2025.106135

136. Montalbano G, Kung VM, Franco-Paredes C, Vargas Barahona L, Chastain DB, Tuells J, et al. Positive Toxoplasma IgG Serology Is Associated with Increased Overall Mortality - A Propensity Score-Matched Analysis. Am J Trop Med Hyg. 2024;110(2):238–45. DOI: 10.4269/ajtmh.23-0537

137. Den J, Nelson N, Klimberg VS. Analysis of the incidence and outcomes of breast cancer in women with schizophrenia. Am J Surg. 2025;239:116050. DOI: 10.1016/j.amjsurg.2024.116050

138. Uhlig K, Menon V, Schmid CH. Recommendations for reporting of clinical research studies. Am J Kidney Dis. 2007;49(1):3–7. DOI: 10.1053/j.ajkd.2006.10.012

139. Pagana KD, Pagana TJ, Pagana TN. Mosby's Diagnostic & Laboratory Test Reference. In: Mosby's. 17th ed. ed. St. Louis: Elsevier; 2024. p. 289–90.

140. Sepulveda JL. Challenges in routine clinical chemistry analysis. In: Accurate Results in the Clinical Laboratory. Elsevier; 2019. DOI: 10.1016/B978-0-12-813776-5.00010-8

141. Kane LT, Fang T, Galetta MS, Goyal DKC, Nicholson KJ, Kepler CK, et al. Propensity Score Matching: A Statistical Method. Clin Spine Surg. 2020;33(3):120–2. DOI: 10.1097/BSD.0000000000000932

142. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association. 1958;53(282):457–81. DOI: 10.1080/01621459.1958.10501452

143. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society Series B: Statistical Methodology. 1972;34(2):187–202. DOI: 10.1111/j.2517-6161.1972.tb00899.x

144. Ermakov EA, Melamud MM, Boiko AS, Kamaeva DA, Ivanova SA, Nevinsky GA, et al. Association of Peripheral Inflammatory Biomarkers and Growth Factors Levels with Sex, Therapy and Other Clinical Factors in Schizophrenia and Patient Stratification Based on These Data. Brain Sci. 2023;13(5):836. DOI: 10.3390/brainsci13050836

145. Williams JA, Burgess S, Suckling J, Lalousis PA, Batool F, Griffiths SL, et al. Inflammation and Brain Structure in Schizophrenia and Other Neuropsychiatric Disorders: A Mendelian Randomization Study. JAMA Psychiatry. 2022;79(5):498–507. DOI: 10.1001/jamapsychiatry.2022.0407

146. Leboyer M, Godin O, Terro E, Boukouaci W, Lu C-L, Andre M, et al. Immune Signatures of Treatment-Resistant Schizophrenia: A

FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) Study. Schizophr Bull Open. 2021;2(1):sgab012. DOI: 10.1093/schizbullopen/sgab012

147. Fathian F, Divkovic I, Fagerbakke Strømme M, Mykletun A, Kroken RA, Bartz-Johannessen CA, et al. Natural-cause mortality and C-reactive protein levels in patients with schizophrenia spectrum disorders: A prospective total cohort study. Brain, Behavior, & Immunity - Health. 2025;50:101133. DOI: 10.1016/j.bbih.2025.101133

148. Fawzi MH, Fawzi MM, Fawzi MM, Said NS. C-reactive protein serum level in drug-free male Egyptian patients with schizophrenia. Psychiatry Res. 2011;190(1):91–7. DOI: 10.1016/j.psychres.2011.05.010

149. Fan X, Pristach C, Liu EY, Freudenreich O, Henderson DC, Goff DC. Elevated serum levels of C-reactive protein are associated with more severe psychopathology in a subgroup of patients with schizophrenia. Psychiatry Res. 2007;149(1–3):267–71. DOI: 10.1016/j.psychres.2006.07.011

150. Dimitrov DH, Lee S, Yantis J, Honaker C, Braida N, Walss-Bass C. Elevated serum levels of high-sensitivity C-reactive proteins are associated with severe delusional symptoms in a subgroup of patients with schizophrenia. J Clin Psychiatry. 2016;77(1):131–2. DOI: 10.4088/JCP.15l09833

151. Fond G, Lançon C, Korchia T, Auquier P, Boyer L. The Role of Inflammation in the Treatment of Schizophrenia. Front Psychiatry. 2020;11:160. DOI: 10.3389/fpsyt.2020.00160

152. Barzilay R, Lobel T, Krivoy A, Shlosberg D, Weizman A, Katz N. Elevated C-reactive protein levels in schizophrenia inpatients is associated with aggressive behavior. Eur psychiatr. 2016;31:8–12. DOI: 10.1016/j.eurpsy.2015.09.461

153. Fathian F, Løberg E-M, Gjestad R, Steen VM, Kroken RA, Jørgensen HA, et al. Associations between C-reactive protein levels and cognition during the first 6 months after acute psychosis. Acta Neuropsychiatr. 2019;31(1):36–45. DOI: 10.1017/neu.2018.25

154. Jacomb I, Stanton C, Vasudevan R, Powell H, O'Donnell M, Lenroot R, et al. C-Reactive Protein: Higher During Acute Psychotic Episodes and Related to Cortical Thickness in Schizophrenia and Healthy Controls. Front Immunol. 2018;9:2230. DOI: 10.3389/fimmu.2018.02230

155. Pan L-H, Qian M, Qu W, Tang Q, Yan Y. Serum C-Reactive Protein in Patients with Deficit Schizophrenia and the Relationship with Cognitive Function. Neuropsychiatr Dis Treat. 2020;16:2891–7. DOI: 10.2147/NDT.S284149

156. Gao Q, Zhu P, Hu H. Factors associated with aggressive behavior in patients with schizophrenia: a systematic review and meta-analysis. BMC Psychol. 2026;14(1):154. DOI: 10.1186/s40359-025-03936-x

157. Sen P, Waheed M-N, Taylor F, Mottram R, Haque Q, Blakemore AI, et al. Low cholesterol and risk of violence in forensic inpatients with schizophrenia, personality disorder or dual diagnosis: same or different? Eur Psychiatr. 2025;68(1):e87. DOI: 10.1192/j.eurpsy.2025.10051

158. Wildgust HJ, Hodgson R, Beary M. The paradox of premature mortality in schizophrenia: new research questions. J Psychopharmacol. Oxford, England; 2010;24(4 Suppl):9–15. DOI: 10.1177/1359786810382149

159. Polcwiartek C, Jensen SE, Frøkjær JB, Nielsen RE. Prevalence of cardiovascular risk factors and disease in patients with schizophrenia: baseline results from a prospective cohort study with long-term clinical follow-up. Schizophr. 2025;11(1):95. DOI: 10.1038/s41537-025-00642-w

160. Chen S, Tan Y, Tian L. Immunophenotypes in psychosis: is it a premature inflamm-aging disorder? Mol Psychiatry. 2024;29(9):2834–48. DOI: 10.1038/s41380-024-02539-z

161. Chung K-H, Chen P-H, Kuo C-J, Tsai S-Y, Huang S-H, Wu W-C. Risk factors for early circulatory mortality in patients with schizophrenia. Psychiatry Research. 2018;267:7–11. DOI: 10.1016/j.psychres.2018.05.044

162. Boos HBM, Postma HD, Cahn W. Neurotoxicity and Schizophrenia. In: Stolerman IP, Price LH, editors. Encyclopedia of Psychopharmacology. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014. DOI: 10.1007/978-3-642-27772-6_260-2

163. Popa A-V, Ifteni PI, Ţâbian D, Petric PS, Teodorescu A. What is behind the 17-year life expectancy gap between individuals with schizophrenia and the general population? Schizophr. 2025;11(1):117. DOI: 10.1038/s41537-025-00667-1

164. Hor K, Taylor M. Review: Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol. 2010;24(4_suppl):81–90. DOI: 10.1177/1359786810385490

165. Courtet P, Giner L, Seneque M, Guillaume S, Olie E, Ducasse D. Neuroinflammation in suicide: Toward a comprehensive model. The World Journal of Biological Psychiatry. 2016;17(8):564–86. DOI: 10.3109/15622975.2015.1054879

166. Polcwiartek C, Jensen SE, Frøkjær JB, Nielsen RE. Prevalence of cardiovascular risk factors and disease in patients with schizophrenia: baseline results from a prospective cohort study with long-term clinical follow-up. Schizophrenia (Heidelb). Heidelberg, Germany; 2025;11(1):95. DOI: 10.1038/s41537-025-00642-w

167. Bryll A, Skrzypek J, Krzyściak W, Szelągowska M, Śmierciak N, Kozicz T, et al. Oxidative-Antioxidant Imbalance and Impaired Glucose Metabolism in Schizophrenia. Biomolecules. 2020;10(3):384. DOI: 10.3390/biom10030384

168. Modesti MN, Arena JF, Del Casale A, Gentile G, Borro M, Parmigiani G, et al. Lipidomics and genomics in mental health: insights into major depressive disorder, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. Lipids Health Dis. 2025;24(1):89. DOI: 10.1186/s12944-025-02512-x

169. Westman J, Eriksson SV, Gissler M, Hällgren J, Prieto ML, Bobo WV, et al. Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. Epidemiol Psychiatr Sci. 2018;27(5):519–27. DOI: 10.1017/S2045796017000166

170. Ventriglio A, Gentile A, Stella E, Bellomo A. Metabolic issues in patients affected by schizophrenia: clinical characteristics and medical management. Front Neurosci. 2015;9. DOI: 10.3389/fnins.2015.00297

171. Miller BJ, Goldsmith DR. Inflammatory biomarkers in schizophrenia: Implications for heterogeneity and neurobiology. Biomarkers in Neuropsychiatry. 2019;1:100006. DOI: 10.1016/j.bionps.2019.100006

172. Hughes HK, Yang H, Lesh TA, Carter CS, Ashwood P. Evidence of innate immune dysfunction in first-episode psychosis patients with accompanying mood disorder. J Neuroinflammation. 2022;19(1):287. DOI: 10.1186/s12974-022-02648-y

173. Noto MN, Maes M, Nunes SOV, Ota VK, Rossaneis AC, Verri WA, et al. Activation of the immune-inflammatory response system and the compensatory immune-regulatory system in antipsychotic naive first episode psychosis. Eur Neuropsychopharmacol. 2019;29(3):416–31. DOI: 10.1016/j.euroneuro.2018.12.008

174. Miller BJ, Buckley PF. Is Relapse in Schizophrenia an Immune-Mediated Effect? FOC. 2012;10(2):115–23. DOI: 10.1176/appi.focus.10.2.115

175. Andreasen NC. Positive and Negative Symptoms in Schizophrenia: A Critical Reappraisal. Arch Gen Psychiatry. 1990;47(7):615. DOI: 10.1001/archpsyc.1990.01810190015002

176. Vázquez-Bourgon J, Gómez-Revuelta M, Mayoral-van Son J, Labad J, Ortiz-García De La Foz V, Setién-Suero E, et al. Pattern of long-term weight and metabolic changes after a first episode of psychosis: Results from a 10-year prospective follow-up of the PAFIP program for early intervention in psychosis cohort. Eur Psychiatr. 2022;65(1):e48. DOI: 10.1192/j.eurpsy.2022.2308

177. Rødevand L, Rahman Z, Hindley GFL, Smeland OB, Frei O, Tekin TF, et al. Characterizing the Shared Genetic Underpinnings of Schizophrenia

and Cardiovascular Disease Risk Factors. Am J Psychiatry. 2023;180(11):815–26. DOI: 10.1176/appi.ajp.20220660

178. Pillinger T, Osimo EF, De Marvao A, Shah M, Francis C, Huang J, et al. Effect of polygenic risk for schizophrenia on cardiac structure and function: a UK Biobank observational study. The Lancet Psychiatry. 2023;10(2):98–107. DOI: 10.1016/S2215-0366(22)00403-5

179. Miller BJ, Goldsmith DR. Inflammatory biomarkers in schizophrenia: Implications for heterogeneity and neurobiology. Biomarkers in Neuropsychiatry. 2019;1:100006. DOI: 10.1016/j.bionps.2019.100006

180. Kane JM, Agid O, Baldwin ML, Howes O, Lindenmayer J-P, Marder S, et al. Clinical Guidance on the Identification and Management of Treatment-Resistant Schizophrenia. J Clin Psychiatry. 2019;80(2):18com12123. DOI: 10.4088/JCP.18com12123

181. Dempster K, Li A, Sabesan P, Norman R, Palaniyappan L. Treatment Resistance: A Time-Based Approach for Early Identification in First Episode Psychosis. J Pers Med. 2021;11(8):711. DOI: 10.3390/jpm11080711

182. Siskind D, Northwood K, McCutcheon RA. Clozapine and treatment-resistant schizophrenia: efficacy versus effectiveness. The Lancet Psychiatry. 2025;12(4):240–1. DOI: 10.1016/S2215-0366(25)00032-X

183. Kane JM, Agid O, Castle DJ, Citrome L, Fagiolini A, Kishimoto T, et al. The Use of Long-Acting Injectables for People with Schizophrenia: Consensus Panel Recommendations for Overcoming Barriers and Implementing Treatment. Neurol Ther. 2025;14(6):2551–81. DOI: 10.1007/s40120-025-00838-3

184. Chand GB, Dwyer DB, Erus G, Sotiras A, Varol E, Srinivasan D, et al. Two distinct neuroanatomical subtypes of schizophrenia revealed using machine learning. Brain. 2020;143(3):1027–38. DOI: 10.1093/brain/awaa025

185. Ferracuti S, Del Casale A, Romano A, Gualtieri I, Lucignani M, Napolitano A, et al. Correlations between cortical gyrification and schizophrenia symptoms with and without comorbid hostility symptoms. Front Psychiatry. 2022;13:1092784. DOI: 10.3389/fpsyt.2022.1092784

186. Gao Q, Zhu P, Hu H. Factors associated with aggressive behavior in patients with schizophrenia: a systematic review and meta-analysis. BMC Psychol. 2026;14(1):154. DOI: 10.1186/s40359-025-03936-x

187. Huber CG, Hochstrasser L, Meister K, Schimmelmann BG, Lambert M. Evidence for an agitated-aggressive syndrome in early-onset psychosis correlated with antisocial personality disorder, forensic history, and substance use disorder. Schizophr Res. 2016;175(1–3):198–203. DOI: 10.1016/j.schres.2016.04.027

188. Sandyk R. Aggressive behavior in schizophrenia: relationship to age of onset and cortical atrophy. Int J Neurosci. 1993;68(1–2):1–10. DOI: 10.3109/00207459308994254

189. McGlashan TH, Fenton WS. Classical Subtypes for Schizophrenia: Literature Review for DSM-IV. Schizophrenia Bulletin. 1991;17(4):609–32. DOI: 10.1093/schbul/17.4.609

Appendix 1

Methods

The analysis process includes two main steps: 1) Defining the cohorts through query criteria; 2) Setting up and running the analysis. Setting up the analysis requires definitions for the index event, outcomes criteria, and the time frame. Compare outcomes supports four analyses: Measures of Association, Survival, Number of Instances and Lab result distribution. These analyses have additional options that are listed in the Outcomes Definitions and Analyses Specifications section below. Furthermore, characteristics of the cohorts that are balanced using propensity score matching are also included in the Propensity Score Matching section.

Cohorts definition

This section lists all terms used in the definitions of the two cohorts.

Query Criteria for Cohort 1 (query name: high-severity)

This query was run on the network Global Collaborative Network with 170 HCO(s) queried and 169 HCO(s) responded. A total of 139 provider(s) responded with patients. The final cohort included 139,281 patients who matched the query criteria listed in the table below. For the text representation of the query criteria please see Appendix A.

Group 1					
	Group 1A diagnoses				
	must have	any of	diagnosis	UMLS:ICD10CM:F20	Schizophrenia
			diagnosis	UMLS:ICD10CM:F22	Delusional disorders
			diagnosis	UMLS:ICD10CM:F23	Brief psychotic disorder
			diagnosis	UMLS:ICD10CM:F25	Schizoaffective disorders
			diagnosis	UMLS:ICD10CM:F28	Other psychotic disorder not due to a substance or known physiological condition
			diagnosis	UMLS:ICD10CM:F29	Unspecified psychosis not due to a substance or known physiological condition
		and	medication	NLM:ATC:N05A	ANTIPSYCHOTICS
	date constraint		The terms in this group occurred at any time		
	event relationship		Any instance of severity signs occurred within 6 months on or before any instance of diagnoses		
	Group 1B severity signs				

must have	any of	laboratory	UMLS:LNC:93681-5	Number of times hospitalized in last 6 months (between 1.00 and 5.00 {#})
		diagnosis	UMLS:ICD10CM:X71-X83	Intentional self-harm
		procedure	UMLS:SNOMED:32485007	Hospital admission
		diagnosis	UMLS:ICD10CM:R44.3	Hallucinations, unspecified
		diagnosis	UMLS:ICD10CM:R40.1	Stupor
		diagnosis	UMLS:ICD10CM:R45.1	Restlessness and agitation

Query Criteria for Cohort 2 (query name: low-severity)

This query was run on the network Global Collaborative Network with 170 HCO(s) queried and 169 HCO(s) responded. A total of 153 provider(s) responded with patients. The final cohort included 803,899 patients who matched the query criteria listed in the table below.

Group 1				
Group 1A diagnoses				
must have	any of	diagnosis	UMLS:ICD10CM:F20	Schizophrenia
		diagnosis	UMLS:ICD10CM:F22	Delusional disorders
		diagnosis	UMLS:ICD10CM:F23	Brief psychotic disorder
		diagnosis	UMLS:ICD10CM:F25	Schizoaffective disorders
		diagnosis	UMLS:ICD10CM:F28	Other psychotic disorder not due to a substance or known physiological condition
		diagnosis	UMLS:ICD10CM:F29	Unspecified psychosis not due to a substance or known physiological condition
	and	medication	NLM:ATC:N05A	ANTIPSYCHOTICS
date constraint		The terms in this group occurred at any time		
event relationship		Any instance of severity signs occurred within 6 months on or before any instance of diagnoses		
Group 1B severity signs				
cannot have		procedure	UMLS:SNOMED:32485007	Hospital admission
	or	laboratory	UMLS:LNC:93681-5	Number of times hospitalized in last 6 months (between 1.00 and 5.00 {#})
	or	diagnosis	UMLS:ICD10CM:R44.3	Hallucinations, unspecified
	or	diagnosis	UMLS:ICD10CM:R40.1	Stupor
	or	diagnosis	UMLS:ICD10CM:X71-X83	Intentional self-harm
	or	diagnosis	UMLS:ICD10CM:R45.1	Restlessness and agitation

Analysis Setup

This section contains the Index Event and Time Window definitions and a list of selected outcomes and the analyses.

Index Event & Time Window Definitions

The index event defines the point in time when each patient in the cohort enters the analysis. To define an index event for the cohort, one or more criteria for the cohort must be selected. The index date for each patient within a cohort is the day on which the patient first met the selected criteria for the cohort (listed in the table below).

As the index event defines the earliest time point after which outcomes are analyzed, the time window defines the duration during which outcomes are analyzed. The time window can start on the same day as the index event or at any specified time interval after the index event. The time window can end any time after the start date. Outcomes are defined as diagnoses, medications, procedures, or laboratory values that happened in the time window starting after the first occurrence of the index event.

Time Window Used in this Analysis

This analysis included outcomes that occurred in the time window that started 1 day after the first occurrence of the index event. Since no end date was specified all outcomes after the first occurrence of the index event were included.

The index event only includes events that occurred up to 20 years ago. Patients whose index event occurred 20 years or more ago are excluded. In this analysis, 0 patients in Cohort 1 and 0 patients in Cohort 2 were excluded because they met the index event more than 20 years ago.

Index Events Used in this Analysis

Index events for the Compare Outcomes analysis were derived from the cohort definitions. Index events were defined separately for each cohort and were based on the criteria used in the original cohort definition. Please see Appendix B for the text representation of the index event definition.

The index event for Cohort 1 (query name: high-severity) was defined as the following:

Group 1				
Group 1A diagnoses				
must have	any of	diagnosis	UMLS:ICD10CM:F20	Schizophrenia
		diagnosis	UMLS:ICD10CM:F22	Delusional disorders
		diagnosis	UMLS:ICD10CM:F23	Brief psychotic disorder

		diagnosis	UMLS:ICD10CM:F25	Schizoaffective disorders
		diagnosis	UMLS:ICD10CM:F28	Other psychotic disorder not due to a substance or known physiological condition
		diagnosis	UMLS:ICD10CM:F29	Unspecified psychosis not due to a substance or known physiological condition
	and	medication	NLM:ATC:N05A	ANTIPSYCHOTICS
date constraint		The terms in this group occurred at any time		
event relationship		Any instance of severity signs occurred within 6 months on or before any instance of diagnoses		
Group 1B severity signs				
must have	any of	laboratory	UMLS:LNC:93681-5	Number of times hospitalized in last 6 months (between 1.00 and 5.00 {#})
		diagnosis	UMLS:ICD10CM:X71-X83	Intentional self-harm
		procedure	UMLS:SNOMED:32485007	Hospital admission
		diagnosis	UMLS:ICD10CM:R44.3	Hallucinations, unspecified
		diagnosis	UMLS:ICD10CM:R40.1	Stupor
		diagnosis	UMLS:ICD10CM:R45.1	Restlessness and agitation

The index event for Cohort 2 (query name: low-severity) was defined as the following:

Group 1				
Group 1A diagnoses				
must have	any of	diagnosis	UMLS:ICD10CM:F20	Schizophrenia
		diagnosis	UMLS:ICD10CM:F22	Delusional disorders
		diagnosis	UMLS:ICD10CM:F23	Brief psychotic disorder
		diagnosis	UMLS:ICD10CM:F25	Schizoaffective disorders
		diagnosis	UMLS:ICD10CM:F28	Other psychotic disorder not due to a substance or known physiological condition
		diagnosis	UMLS:ICD10CM:F29	Unspecified psychosis not due to a substance or known physiological condition
	and	medication	NLM:ATC:N05A	ANTIPSYCHOTICS
date constraint		The terms in this group occurred at any time		
event relationship		Any instance of severity signs occurred within 6 months on or before any instance of diagnoses		
Group 1B severity signs				
cannot have		procedure	UMLS:SNOMED:32485007	Hospital admission
	or	laboratory	UMLS:LNC:93681-5	Number of times hospitalized in last 6 months (between 1.00 and 5.00 {#})
	or	diagnosis	UMLS:ICD10CM:R44.3	Hallucinations, unspecified
	or	diagnosis	UMLS:ICD10CM:R40.1	Stupor
	or	diagnosis	UMLS:ICD10CM:X71-X83	Intentional self-harm
	or	diagnosis	UMLS:ICD10CM:R45.1	Restlessness and agitation

Analyses Specifications

The Compare Outcomes Analytic supports four types of analyses: Measure of Association, Survival, Number of Instances, and Lab result distribution. The first three analyses support the “exclude patients with outcomes prior to the window” setting. This option can exclude patients from the analysis if they are not at risk for an outcome (e.g., if the outcome is a chronic disease). When "exclude patients with the outcome prior to the time window" is not checked, all patients in the cohort are included in the analysis, regardless of whether they had the outcome prior to the time window. When "exclude patients with the outcome prior to the time window" is checked, patients are excluded from the analysis if their record includes the outcome prior to the beginning of the time window. This selection will exclude all patients with the outcome prior to the index event. If the start of the time window for the analysis falls some days after the index event, patients will also be excluded if they have the outcome between the index event and the start of the time window.

Measure of Association Analysis

The Measure of Association Analysis calculates and compares the fraction of patients with the selected outcome. The output summary includes: Patients in each Cohort (count of patients meeting query criteria); Patients with Outcome in each Cohort (of the patients in the cohort, count of patients that had the outcome in the time window); and Risk (the fraction of patients in the cohort that have the outcome in the time window, i.e. Patients with Outcome / Patients in Cohort). In addition, Risk Difference (the difference in the risks in Cohort 1 and Cohort 2), Risk Ratio (the ratio of the risks in Cohort 1 and Cohort 2), and Odds Ratio (the ratio of the odds in Cohort 1 and Cohort 2). The bar chart shows the risk of the outcome for the both cohorts.

Survival Analysis

The Kaplan-Meier Analysis estimates probability of the outcome at a respective time interval (daily time interval is used in this analysis). In order to account for the patients who exited the cohort during the analysis period, and therefore should not be included in the analysis, censoring is applied. In this analysis, patients are removed from the analysis (censored) after the last fact in their record.

The output summary includes: Patients in each Cohort (count of patients meeting query criteria); Patients with Outcome (of the patients in the cohort, count of patients that had the outcome in the time window);

Median Survival (the number of days when the survival drops below 50%; the "-" indicates that survival does not drop below 50% during the time window); and Survival Probability at End of Time Window (the % survival at the end of the time window). In addition, Log-Rank test, Hazard Ratio and test for Proportionality.

Number of Instances Analysis

The Number of Instances Analysis calculates how many times the outcome occurred in the time window. This analysis includes two additional settings: include patients with zero instances; the definition of an instance.

Selecting to exclude patients with zero instances will remove these patients from the calculations for mean number of instances, standard deviation, or median. The histogram showing the distribution of patients by number of instances will not contain a bar for zero. Alternatively, by selecting to include patients with zero instances, the mean, standard deviation, and median for number of instances will reflect these patients. The histogram will contain a bar for zero patients.

The definition of an instance affects how counts are analyzed. By selecting Date, each calendar date on which any of the terms selected in the outcome are recorded will represent one instance. For example, if the outcome is "Med A or Med B," and a patient has "Med A" on January 3, then both medications on January 4, then "Med B" on January 6, then that patient is considered to have three instances– January 3, January 4, and January 6. Note that if an outcome occurs across several dates (e.g. Visit: inpatient encounter), then only the start date is tracked for the purpose of counting instances. A patient who begins at stay on January 1, ends that stay on January 3, begins another stay on January 10, and ends that stay on January 15, is considered to have two instances of the outcome.

Selecting Visit as an Instance will count any visit that includes the outcome as one instance, regardless of how many times it occurred. For instance, consider a patient administered an analgesic on each of the three days that make up an inpatient stay following some index event. If analgesic is an outcome, these three administrations will represent only one instance, because all three are associated with the same visit.

The output summary includes: Patients in Cohort (count of patients meeting query criteria); Patients with Outcome (of the patients in the cohort, count of patients that had the outcome in the time window); Mean

(mean of the counts); Standard Deviation (standard deviation of the counts); Median (median of the counts); and Median (1+ instances) when patients with zero instances included in the analysis. In addition, T-Test statistics testing for the difference between the cohorts is included.

Laboratory Results Analysis

Lab Results can be included in the analysis only for the outcomes that are labs. Only the most recent lab values in the time window are included. For the lab results that are numeric, the outcome summary includes: Patients in Cohort (count of patients meeting query criteria); Patients with Outcome (of the patients in the cohort, count of patients that had the outcome in the time window); Mean (mean of the counts); and Standard Deviation (the standard deviation for lab values across patients in the cohort). In addition, T-Test statistics testing for the difference between the cohorts is included.

For the non-numeric lab results, three values are reported: counts of Negative; Positives; and Unknowns.
The counts are represented in the bar chart as percentages of the total counts.

Outcome Definitions

Table below outlines the definitions for each outcome and the analysis specifications. For outcome definitions consisting of more than one term, at least one term must match. Please see Appendix C for the text representation of the outcome definitions.

death		
Outcome definition		
Demographics	Deceased	Deceased
Settings for the performed analyses		
Risk analysis		including patients with outcome prior to the time window
Kaplan - Meier survival analysis		including patients with outcome prior to the time window
hospitalization		
Outcome definition		
Laboratory	UMLS:LNC:93680-7	Hospitalized in the last 6 months ((most recent occurrence))
Procedure	UMLS:SNOMED:32485007	Hospital admission
Settings for the performed analyses		
Risk analysis		including patients with outcome prior to the time window
inflammation		
Outcome definition		

Laboratory	TNX:9063	C reactive protein [Mass/volume] in Serum, Plasma or Blood (at least 3.00 mg/L (most recent occurrence))
Laboratory	TNX:9052	Lactate dehydrogenase [Enzymatic activity/volume] in Serum or Plasma (at least 220.00 U/L (most recent occurrence))
Settings for the performed analyses		
Risk analysis		excluding patients with outcome prior to the time window
HbbA1c		
Outcome definition		
Laboratory	TNX:9037	Hemoglobin A1c/Hemoglobin.total in Blood ((most recent occurrence))
Settings for the performed analyses		
Lab values distribution		patient's most recent lab result in the selected time window
systolic		
Outcome definition		
Laboratory	TNX:9085	Blood Pressure, Systolic ((most recent occurrence))
Settings for the performed analyses		
Lab values distribution		patient's most recent lab result in the selected time window
diastolic		
Outcome definition		
Laboratory	TNX:9086	Blood Pressure, Diastolic ((most recent occurrence))
Settings for the performed analyses		
Lab values distribution		patient's most recent lab result in the selected time window
qtc		
Outcome definition		
Laboratory	TNX:FINDING:2001	Corrected QT Interval (QTc) ((most recent occurrence))
Settings for the performed analyses		
Lab values distribution		patient's most recent lab result in the selected time window
ldl		
Outcome definition		
Laboratory	TNX:9002	Cholesterol in LDL [Mass/volume] in Serum or Plasma ((most recent occurrence))
Settings for the performed analyses		
Lab values distribution		patient's most recent lab result in the selected time window

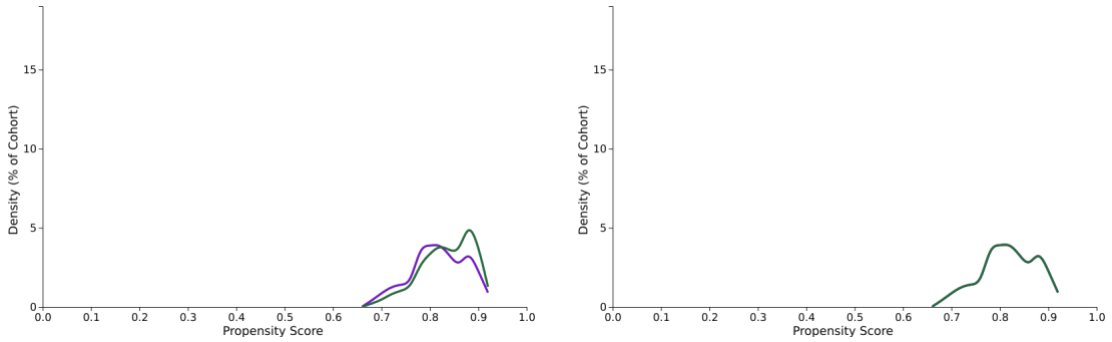
Propensity Score Matching

Propensity score matching was performed on all listed characteristics. Characteristics of the cohorts before and after matching are summarized in the table below.

Cohort 1 and cohort 2 patient count before and after propensity score matching

Cohort	Patient count before matching	Patient count after matching
1 - high-severity	141,728	140,862
2 - low-severity	757,956	140,862

Propensity score density function - Before and after matching (cohort 1 - purple, cohort 2 - green)



Cohort 1 (N = 141,728) and cohort 2 (N = 757,956) characteristics before propensity score matching

Demographics

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	AI	Age at Index	46.2 +/- 19.7 47.3 +/- 19.5	140,862 745,105	100% 100%	<0.001	0.058
1 2	UN	Unknown Ethnicity		30,622 190,819	21.7% 25.6%	<0.001	0.091
1 2	2186-5	Not Hispanic or Latino		99,144 494,657	70.4% 66.4%	<0.001	0.086
1 2	M	Male		79,937 394,271	56.7% 52.9%	<0.001	0.077

Diagnosis

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	G47	Sleep disorders		34,290 113,542	24.3% 15.2%	<0.001	0.230

Laboratory

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	9083	BMI	27.7 +/- 7.4 28.2 +/- 7.7	91,785 378,380	65.2% 50.8%	<0.001	0.065
1 2		0 - 0 kg/m2		91,826 378,695	65.2% 50.8%	<0.001	0.294
1 2	9085	Blood Pressure, Systolic	125.6 +/- 19.7 126.2 +/- 19.7	104,042 446,488	73.9% 59.9%	<0.001	0.031
1 2		0 - 0 mm[Hg]		104,045 446,505	73.9% 59.9%	<0.001	0.299

Cohort 1 (N = 140,862) and cohort 2 (N = 140,862) characteristics after propensity score matching

Demographics

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	AI	Age at Index	46.2 +/- 19.7 46.2 +/- 19.7	140,862 140,862	100% 100%	0.959	<0.001
1 2	UN	Unknown Ethnicity		30,622 30,624	21.7% 21.7%	0.993	<0.001

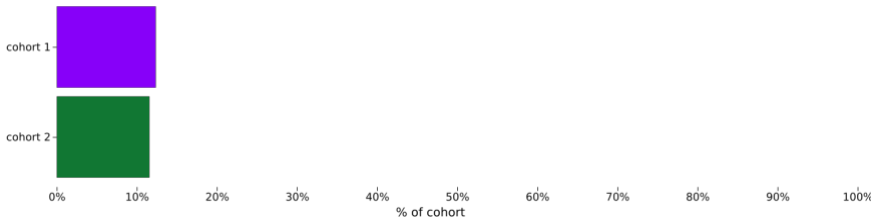
1 2	2186-5	Not Hispanic or Latino		99,144 99,181	70.4% 70.4%	0.879	0.001
1 2	M	Male		79,937 79,940	56.7% 56.8%	0.991	<0.001
Diagnosis							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	G47	Sleep disorders		34,290 34,282	24.3% 24.3%	0.972	<0.001
Laboratory							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	9083	BMI	27.7 +/- 7.4 28.3 +/- 7.8	91,785 91,755	65.2% 65.1%	<0.001	0.080
1 2		0 - 0 kg/m2		91,826 91,831	65.2% 65.2%	0.984	<0.001
1 2	9085	Blood Pressure, Systolic	125.6 +/- 19.7 126.0 +/- 19.2	104,042 104,049	73.9% 73.9%	<0.001	0.022
1 2		0 - 0 mm[Hg]		104,045 104,052	73.9% 73.9%	0.976	<0.001

Results

Results are summarized in the tables below. Outcomes analysis was performed on the cohorts after propensity score matching.

1 death					
Risk analysis					
Cohort		Patients in cohort	Patients with outcome	Risk	
1	high-severity	140,862	17,433	0.124	
2	low-severity	140,862	16,318	0.116	

		95% CI	z	p
Risk Difference	0.008	(0.006, 0.010)	6.469	0.000
Risk Ratio	1.068	(1.047, 1.090)	N/A	N/A
Odds Ratio	1.078	(1.054, 1.103)	N/A	N/A

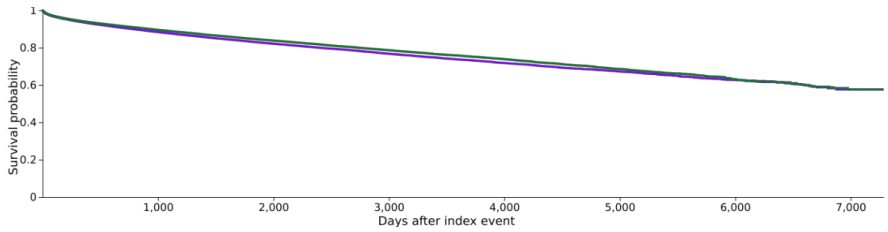


Kaplan - Meier survival analysis

Cohort		Patients in cohort	Patients with outcome	Median survival (days)	Survival probability at end of time window
1	high-severity	140,862	17,433	--	57.62%
2	low-severity	140,862	16,318	--	57.60%

	χ^2	df	p
Log-Rank Test	70.493	1	0.000

	Hazard Ratio	95% CI	χ^2	df	p
Hazard Ratio and Proportionality	1.096	(1.073, 1.119)	4.887	1	0.027

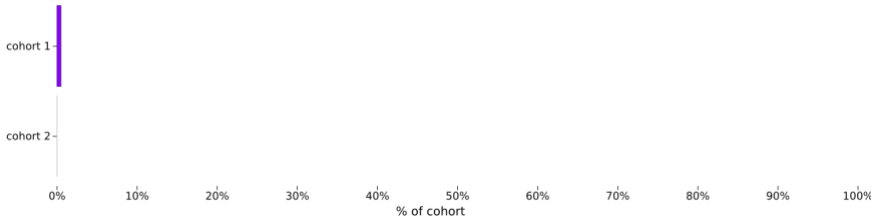


2 hospitalization

Risk analysis

Cohort		Patients in cohort	Patients with outcome	Risk
1	high-severity	140,862	787	0.006
2	low-severity	140,862	32	0.000

		95% CI	z	p
Risk Difference	0.005	(0.005, 0.006)	26.420	0.000
Risk Ratio	24.594	(17.272, 35.018)	N/A	N/A
Odds Ratio	24.726	(17.363, 35.213)	N/A	N/A

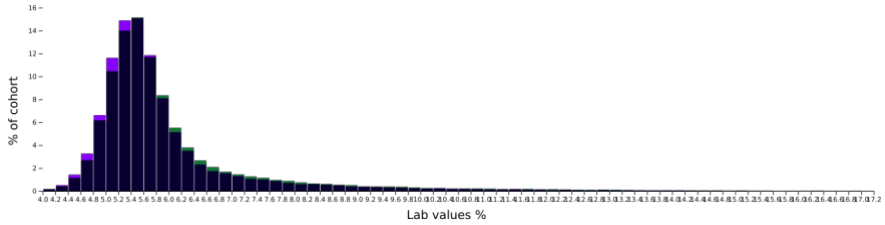


3 HbbA1c

Lab values distribution

Cohort		Patients in cohort	Patients with outcome	Mean	Standard Deviation
1	high-severity	140,862	59,678	5.880	1.418
2	low-severity	140,862	56,033	5.977	1.490

	t	df	p
Test Statistics	-11.325	115709	0.000



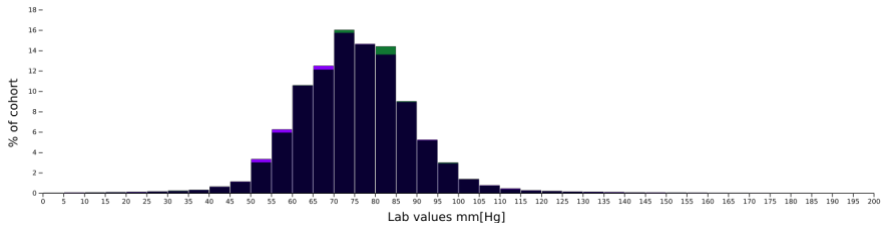
121 data points for Cohort 1 and 113 data points for Cohort 2 were omitted for display purposes.
For Cohort 1, 1,199 data points for 613 patients were excluded because they were invalid or fell outside the sanitization limit; of the 613 patients, 122 patients had no other lab in the time window.
For Cohort 2, 7,464 data points for 3,552 patients were excluded because they were invalid or fell outside the sanitization limit; of the 3,552 patients, 740 patients had no other lab in the time window.

4 diastolic

Lab values distribution

Cohort		Patients in cohort	Patients with outcome	Mean	Standard Deviation
1	high-severity	140,862	111,695	74.444	14.379
2	low-severity	140,862	107,936	74.567	14.173

	t	df	p
Test Statistics	-2.015	219629	0.044



For Cohort 1, 5,398 data points for 1,923 patients were excluded because they were invalid or fell outside the sanitization limit; of the 1,923 patients, 281 patients had no other lab in the time window.
For Cohort 2, 26,859 data points for 11,362 patients were excluded because they were invalid or fell outside the sanitization limit; of the 11,362 patients, 3,796 patients had no other lab in the time window.

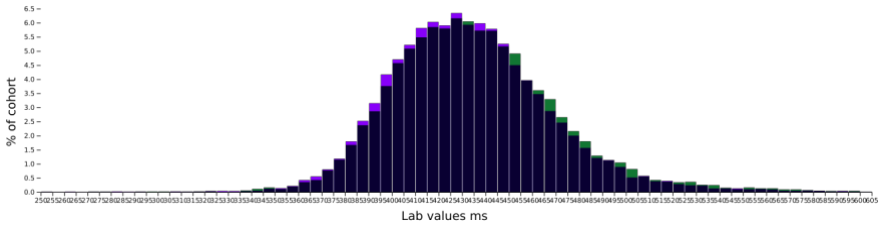
5 QTc

Lab values distribution

Cohort		Patients in cohort	Patients with outcome	Mean	Standard Deviation
1	high-severity	140,862	26,414	432.564	34.607

2	low-severity	140,862	20,023	434.841	35.560

	t	df	p
Test Statistics	-6.939	46435	0.000



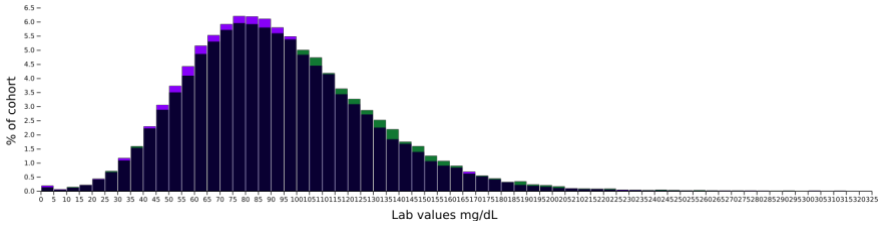
For Cohort 1, 13,486 data points for 1,793 patients were excluded because they were invalid or fell outside the sanitization limit; of the 1,793 patients, 114 patients had no other lab in the time window.
For Cohort 2, 47,336 data points for 5,992 patients were excluded because they were invalid or fell outside the sanitization limit; of the 5,992 patients, 565 patients had no other lab in the time window.

6 LDL

Lab values distribution

Cohort		Patients in cohort	Patients with outcome	Mean	Standard Deviation
1	high-severity	140,862	59,957	90.836	35.147
2	low-severity	140,862	56,902	92.882	36.413

	t	df	p
Test Statistics	-9.777	116857	0.000



8 data points for Cohort 1 and 10 data points for Cohort 2 were omitted for display purposes.
For Cohort 1, 1,446 data points for 721 patients were excluded because they were invalid or fell outside the sanitization limit; of the 721 patients, 93 patients had no other lab in the time window.
For Cohort 2, 9,718 data points for 4,539 patients were excluded because they were invalid or fell outside the sanitization limit; of the 4,539 patients, 677 patients had no other lab in the time window.

Appendix A – Text Representation of the Cohorts Definition

This section lists all terms used in the definitions of the two cohorts.

Query Criteria for Cohort 1 (query name: high-severity)

All the following must be satisfied: diagnoses: The terms in this group occurred at any time Patients must have: all of the following: any of the following: Schizophrenia (UMLS:ICD10CM:F20); or Delusional disorders (UMLS:ICD10CM:F22); or Brief psychotic disorder (UMLS:ICD10CM:F23); or Schizoaffective disorders (UMLS:ICD10CM:F25); or Other psychotic disorder not due to a substance or known physiological condition (UMLS:ICD10CM:F28); or Unspecified psychosis not due to a substance or known physiological condition (UMLS:ICD10CM:F29); and ANTIPSYCHOTICS (NLM:ATC:N05A). severity signs: Any instance of severity signs occurred within 6 months on or before any instance of diagnoses Patients must have: any of the following: Number of times hospitalized in last 6 months (UMLS:LNC:93681-5) (between 1.00 and 5.00); or Intentional self-harm (UMLS:ICD10CM:X71-X83); or Hospital admission (UMLS:SNOMED:32485007); or Hallucinations, unspecified (UMLS:ICD10CM:R44.3); or Stupor (UMLS:ICD10CM:R40.1); or Restlessness and agitation (UMLS:ICD10CM:R45.1).

Query Criteria for Cohort 2 (query name: low-severity)

All the following must be satisfied: diagnoses: The terms in this group occurred at any time Patients must have: all of the following: any of the following: Schizophrenia (UMLS:ICD10CM:F20); or Delusional disorders (UMLS:ICD10CM:F22); or Brief psychotic disorder (UMLS:ICD10CM:F23); or Schizoaffective disorders (UMLS:ICD10CM:F25); or Other psychotic disorder not due to a substance or known physiological condition (UMLS:ICD10CM:F28); or Unspecified psychosis not due to a substance or known physiological condition (UMLS:ICD10CM:F29); and ANTIPSYCHOTICS (NLM:ATC:N05A). severity signs: Any instance of severity signs occurred within 6 months on or before any instance of diagnoses Patients cannot have: any of the following: Hospital admission (UMLS:SNOMED:32485007); or Number of times hospitalized in last 6 months (UMLS:LNC:93681-5) (between 1.00 and 5.00); or Hallucinations, unspecified (UMLS:ICD10CM:R44.3); or Stupor

(UMLS:ICD10CM:R40.1); or Intentional self-harm (UMLS:ICD10CM:X71-X83); or Restlessness and agitation (UMLS:ICD10CM:R45.1).

Appendix B – Text Representation of the Analysis Setup

This section contains the Index Event definition for each cohort.

The index event for Cohort 1 (query name: high-severity) is defined as the following:
All the following must be satisfied: diagnoses: The terms in this group occurred at any time Patients must have: all of the following: any of the following: Schizophrenia (UMLS:ICD10CM:F20); or Delusional disorders (UMLS:ICD10CM:F22); or Brief psychotic disorder (UMLS:ICD10CM:F23); or Schizoaffective disorders (UMLS:ICD10CM:F25); or Other psychotic disorder not due to a substance or known physiological condition (UMLS:ICD10CM:F28); or Unspecified psychosis not due to a substance or known physiological condition (UMLS:ICD10CM:F29); and ANTIPSYCHOTICS (NLM:ATC:N05A). severity signs: Any instance of severity signs occurred within 6 months on or before any instance of diagnoses Patients must have: any of the following: Number of times hospitalized in last 6 months (UMLS:LNC:93681-5) (between 1.00 and 5.00); or Intentional self-harm (UMLS:ICD10CM:X71-X83); or Hospital admission (UMLS:SNOMED:32485007); or Hallucinations, unspecified (UMLS:ICD10CM:R44.3); or Stupor (UMLS:ICD10CM:R40.1); or Restlessness and agitation (UMLS:ICD10CM:R45.1).

The index event for Cohort 2 (query name: low-severity) is defined as the following:
All the following must be satisfied: diagnoses: The terms in this group occurred at any time Patients must have: all of the following: any of the following: Schizophrenia (UMLS:ICD10CM:F20); or Delusional disorders (UMLS:ICD10CM:F22); or Brief psychotic disorder (UMLS:ICD10CM:F23); or Schizoaffective disorders (UMLS:ICD10CM:F25); or Other psychotic disorder not due to a substance or known physiological condition (UMLS:ICD10CM:F28); or Unspecified psychosis not due to a substance or known physiological condition (UMLS:ICD10CM:F29); and ANTIPSYCHOTICS

(NLM:ATC:N05A). severity signs: Any instance of severity signs occurred within 6 months on or before any instance of diagnoses Patients cannot have: any of the following: Hospital admission (UMLS:SNOMED:32485007); or Number of times hospitalized in last 6 months (UMLS:LNC:93681-5) (between 1.00 and 5.00); or Hallucinations, unspecified (UMLS:ICD10CM:R44.3); or Stupor (UMLS:ICD10CM:R40.1); or Intentional self-harm (UMLS:ICD10CM:X71-X83); or Restlessness and agitation (UMLS:ICD10CM:R45.1).

Appendix C – Text Representation of the Outcomes Definition

This analysis includes the following outcomes:

death
  Patients must have:
    Deceased (Deceased).

hospitalization
  Patients must have:
    any of the following:
      Hospitalized in the last 6 months (UMLS:LNC:93680-7) ((most recent occurrence)); or
      Hospital admission (UMLS:SNOMED:32485007).

HbbA1c
  Patients must have:
    Hemoglobin A1c/Hemoglobin.total in Blood (TNX:9037) ((most recent occurrence)).

diastolic
  Patients must have:
    Blood Pressure, Diastolic (TNX:9086) ((most recent occurrence)).

QTc
  Patients must have:
    Corrected QT Interval (QTc) (TNX:FINDING:2001) ((most recent occurrence)).

LDL

Patients must have:
Cholesterol in LDL [Mass/volume] in Serum or Plasma (TNX:9002) (
(most recent occurrence))