The tryptophan catabolite pathway in major and simple neurocognitive psychosis: a double-edged sword with two sharpened edges

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Abstract

Objectives: There are differences in IgA responses to tryptophan catabolites (TRYCATs) in major neurocognitive psychosis (MNP) versus simple neurocognitive psychosis (SNP) and normal controls. MNP and SNP are distinct schizophrenia classes which are differentiated by neurocognitive deficits, phenome features, and biomarker pathways. Nevertheless, there is no data on serum concentrations of those TRYCATs in MNP and SNP. The aim of the present study is to examine serum concentrations of tryptophan and TRYCATs in MNP versus SNP and controls.

Methods: This case-control study examines serum levels of tryptophan and TRYCATs in 52 MNP patients, 68 SNP patients and 60 controls in association with overall severity of schizophrenia (OSOS).

Results: MNP patients show lower tryptophan, kynurenic acid (KA), 3-OH-anthranilic acid (3HAA), and higher anthranilic acid (AA) and quinolinic acid (QA) than SNP patients and controls. There were no differences between SNP and controls in these TRYCATs. Kynurenine (KYN) was lower in MNP+SNP than in controls. We found that 36.5% of the variance in OSOS was explained by the combined effects of lowered tryptophan, KA, and 3-HK, and increased QA and AA. The most important biomarkers of MNP and OSOS were the QA/KA ratio followed by the QA/3HAA ratio.

Conclusions: The alterations in serum TRYCAT levels further emphasize that MNP and SNP represent two biologically distinct subtypes of schizophrenia. The reductions in TRYCATs diminish the antioxidant and immunoregulatory functions of the TRYCAT pathway. Elevated QA levels may exacerbate the disruption of the blood-brain barrier and the immune-related and oxidative neurotoxicity in MNP.

Keywords: tryptophan, schizophrenia, neuroimmune, oxidative stress, inflammation, biomarkers.

Specific outcomes

- A significant portion of the variance in the overall severity of schizophrenia is accounted for by alterations in the TRYCAT pathway.

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- Particular alterations in TRYCAT levels across two clinically distinct subgroups of schizophrenia, specifically MNP and SNP, further corroborate this clinical differentiation.
- MNP is marked by elevated quinolinic acid levels and diminished tryptophan and other TRYCATs, such as kynurenic acid.
- The elevated ratio of quinolinic acid to kynurenic acid represents a novel pharmacological target for the treatment of patients with MNP.

Limitations

- The results derived from an Iraqi population necessitate validation across other cultures and nations.
- It would be intriguing to correlate the present findings in MNP with the assessment of serum lipopolysaccharide concentrations and M1 macrophage and T helper 1 cytokine levels.

The findings obtained on an Iraqi population should be validated in other cultures and countries. It would be interesting to associate the current findings in MNP with measurement of serum lipopolysaccharide levels and M1 macrophage and T helper 1 cytokines.

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Introduction

Schizophrenia is a neuropsychiatric disorder that is associated with a substantial socioeconomic burden (Vigo *et al.*, 2016) and has a debilitating impact on cognitive, behavioral, and affective functioning (Correll & Howes, 2021). The clinical characteristics that constitute the phenome of schizophrenia are negative symptoms and psychotic, hostility, excitation, and mannerism (PHEM) symptoms (Maes *et al.*, 2020; Sirivichayakul *et al.*, 2019b). Furthermore, we have demonstrated that a single factor or latent construct can be extracted from all of the aforementioned symptom domains in schizophrenia, which is indicative of the overall severity of schizophrenia (OSOS) (Almulla *et al.*, 2021; Maes *et al.*, 2019b).

There is currently evidence to suggest that schizophrenia should be divided into two distinct diagnostic groups: major neurocognitive psychosis (MNP) and simple neurocognitive psychosis (SNP) (Kanchanatawan *et al.*, 2018b; Kanchanatawan *et al.*, 2018c). Kraepelin's concept of "defect" schizophrenia (Maes, 2023) and the negative symptom cluster characterized by Snezhnevsky et al. (Snezhnevsky, 1971; Snezhnevsky *et al.*, 1970) are two concepts that MNP largely overlaps with. Using neurocognitive test results, symptom profiles, and biomarkers in machine learning models indicated that MNP and SNP are two qualitatively distinct classes (Kanchanatawan *et al.*, 2018b; Popov *et al.*, 2024). Maes et al.'s laboratory discovered that MNP is not only distinguished by elevated negative symptoms in comparison to SNP but also by elevated PHEM and OSOS scores (Almulla *et al.*, 2021; Maes, 2023; Maes *et al.*, 2020; Sirivichayakul *et al.*, 2019b). Additionally, MNP is distinguished by the activation of the immune-inflammatory response system (IRS) and deficiencies in the compensatory immune-regulatory system (CIRS) (Maes *et al.*, 2019b). The latter exerts negative feedback on the IRS, prevents hyperinflammation, and supports homeostasis, immune tolerance, and healing mechanisms after immune injuries (Maes *et al.*, 2012; Roomruangwong *et al.*, 2020). MNP is accompanied by activated IRS components, including M1 macrophage, T helper (Th)1, and Th17 immune profiles, increased oxidative stress, and increased translocation of Gram-negative bacteria or their lipopolysaccharides (LPS) (Maes *et al.*, 2019a; Maes *et al.*, 2021; Popov *et al.*, 2024). These pathways are more disrupted in MNP than in SNP and distinguish both MNP and SNP from healthy controls (Popov *et al.*, 2024). Additionally, MNP is distinguished by diminished CIRS functions, which may increase the susceptibility of patients with schizophrenia to the neurotoxic effects of IRS components (Roomruangwong *et al.*, 2020). Examples of

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suppressed CIRS functions in MNP versus SNP include reduced IgM responses to a variety of oxidative-specific epitopes or adducts and reduced paraoxonase 1 (PON1) activity in MNP versus SNP (Maes *et al.*, 2019b; Matsumoto *et al.*, 2021). In the past, it was demonstrated that IRS biomarkers, in conjunction with deficiencies in the CIRS pathways, account for a significant portion of the variance in PHEM and negative symptoms (Maes *et al.*, 2019c; Maes *et al.*, 2019d).

The catabolism of tryptophan into tryptophan catabolites (TRYCATs) may be induced by increased levels of proinflammatory cytokines, including interferons (IFNs), interleukin (IL-1)β, tumor necrosis factor (TNF)-α, oxidative stress, and LPS, through the stimulation of indoleamine-2,3-dioxygenase (IDO) (Almulla *et al.*, 2022). In general, the TRYCAT pathway is a component of the innate CIRS, as it safeguards against oxidative stress and IRS activation (Almulla *et al.*, 2022). Moreover, the majority of TRYCATs exhibit anti-inflammatory effects, while reduced tryptophan provides protection against viral and bacterial infections (Maes *et al.*, 2007). However, certain TRYCATs, such as kynurenine (KYN), 3-hydroxykynurenine (3HK), 3-hydroxyanthranilic acid (3HAA), and quinolinic acid (QA), may be neurotoxic at highly elevated levels. Conversely, kynurenic acid and anthranilic acid may possess neuroprotective properties (Almulla *et al.*, 2022).

A meta-analysis that included 2,313 schizophrenia patients and 2,948 healthy controls, showed that IDO stimulation is associated with lower serum levels of tryptophan and higher KA and KYN levels in the central nervous system of schizophrenia patients compared to normal controls (Almulla *et al.*, 2022). In addition, the KYN/tryptophan ratio (indicant of IDO activity) was significantly increased in schizophrenia. However, the TRYCAT pathway distinctions between schizophrenia patients divided into MNP and SNP and controls were only examined by one laboratory (Kanchanatawan *et al.*, 2018a). These authors measured the IgA responses to various TRYCATs and reported that the IgA responses to QA, picolinic acid (PA), and xanthurenic acid (XA) were higher in MNP than in SNP, while the IgA responses to KA and AA were relatively lower. This suggests that there may be an imbalance in the equilibrium between increased neurotoxic TRYCATs (QA, XA, PA) and diminished neuroprotective TRYCATs (AA and KA) in MNP versus SNP. These findings contribute to the hypothesis that MNP is distinguished by suppressed CIRS properties and increased immune-linked neurotoxicity (Roomruangwong *et al.*, 2020).

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However, no research has examined the serum concentrations of tryptophan and TRYCATs in MNP and SNP in comparison to healthy controls. Therefore, this investigation examines the serum levels of tryptophan and TRYCATS in MNP and SNP patients, as well as in controls. The a priori hypothesis, which is predicated on prior research, is that there will be a decrease in tryptophan and an increase in neurotoxic TRYCATs in MNP versus SNP and controls.

Subjects and Methods

Participants

In addition to 60 healthy controls, this investigation recruited 120 patients diagnosed with schizophrenia subtypes MNP or SNP. All participants were recruited from the same geographic region, specifically Baghdad City, Iraq. From January 2024 to April 2024, patients were recruited at the Ibn-Rushd Training Hospital for Psychiatric Medicine in Baghdad, Iraq. Individuals who were either staff members, their family members, or associates of staff members and patients comprised the controls. All patients with schizophrenia were in a stable phase of their illness and had not experienced any acute episodes in the year preceding the investigation. According to the DSM-IVTR criteria, patients were diagnosed with "schizophrenia." Additionally, we incorporated patients with schizophrenia who satisfied the diagnostic criteria of MNP as defined by Kanchanatawan et al. (2018a) (Kanchanatawan *et al.*, 2018b). Patients who did not meet these criteria were classified as SNP.

The following were the exclusion criteria for patients and controls: a) lifetime use of medications that interfere with immune functions, such as immunosuppressive drugs and glucocorticoids; b) recent intake of supplements containing ω3-polyunsaturated fatty acids or antioxidants within the month prior to the study; c) presence of neurodegenerative and neuroinflammatory disorders, such as Parkinson's disease, stroke, multiple sclerosis, and Alzheimer's disease; d) (auto)immune illnesses, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, and diabetes mellitus. Controls were denied inclusion if they had a family history of schizophrenia or psychosis or a current or lifetime diagnosis of DSM-IV-TR axis I disorders. Patients diagnosed with schizophrenia were excluded from this study if they had experienced psychotic episodes within the year preceding the study or if they had any axis-1 DSM-IV-TR disorders, including bipolar disorder, major depression,

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schizoaffective disorder, obsessive-compulsive disorder, psycho-organic disorders, and substance use disorders.

The study was conducted in accordance with Iraqi and international ethical and privacy laws. Written informed consent was obtained from all participants, as well as the first-degree relatives of schizophrenia participants (the legally authorized representatives are father, mother, spouse, son, or brother) before they participated in this study. Approval for the study was obtained from the ethics committee (IRB) of the College of Science, University of Kufa, Iraq (T4220/2023), which complies with the International Guideline for Human Research Protection as required by the Declaration of Helsinki.

Measurements

Clinical assessments

A semi-structured interview was conducted by a senior psychiatrist who specializes in schizophrenia to gather clinical and socio-demographic data from both patients and controls. The Mini-International Neuropsychiatric Interview (M.I.N.I.), a validated Arabic translation (Iraqi dialect), was employed to diagnose schizophrenia using the DSM-IV-TR diagnostic criteria. The Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987), the Scale for the Assessments of Negative Symptoms (SANS) (Andreasen, 1989), and the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) were also evaluated by the same psychiatrist. We utilized z-unit weighted composite scores to generate scores for the psychosis, hostility, excitation, and mannerism domains, as previously reported (Maes *et al.*, 2020; Sirivichayakul *et al.*, 2019a, 2019b). The total sum of the PANNS negative subscale was used as a severity index of negative symptoms. Subsequently, we computed the principal component (PC) scores from the first PC extracted from psychosis, hostility, excitation, mannerism, the negative PANNS subdomain score, and the total SANS score, as previously described (Almulla *et al.*, 2021; Maes *et al.*, 2019b). This PC analysis complies with stringent criteria, including KMO value > 0.8 (actually it is 0.933), significant Bartlett's test of sphericity is significant (χ^2=1534.446, df=15, p<0.001), explained variance > 50% (actually it is 87.20%), and all loadings of the first PC > 0.7 (actually all are higher than 0.852). The patients' medication status was assessed (as shown below). The DSM-IV-TR criteria were employed to establish the diagnosis of tobacco use disorder (TUD). The clinical interview was conducted concomitantly with the measurement of

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body mass index (BMI), which was determined by dividing body weight (kg) by squared height (m^2).

Assays

Five milliliters of fasting blood samples were collected in the morning hours (6.30 a.m. – 8.00 a.m.) from all participants. After a ten-minute waiting period, the clotted blood samples were centrifuged at 1100Xg for five minutes. The serum was then aliquoted into three Eppendorf tubes. Hemolyzed samples were excluded from the investigation. The tubes were then refrigerated at -80 °C until thawed for tests. We used an ELISA methodology to measure serum levels of tryptophan, kynurenine (KYN), kynurenic acid (KA), anthranilic acid (AA), 3-OH-AA (3HAA), 3 hydroxy kynurenine (3HK), and quinolinic acid (QA) with commercially available ELISA kits provided by Nanjing Pars Biochem Co., Ltd. (Nanjing, China). The intra-assay coefficient of variation (CV) for all ELISA kits was less than 10.0%. We used sample dilutions for specimens containing analytes at elevated quantities. Based on the measured serum levels we computed different composites reflecting enzymatic activities, and neurotoxic (NT) versus neuroprotective (NP) potential. Therefore, we used z-unit-based composite scores to reflect the activity of the whole TRYCAT pathway as z transformation of KYN (zKYN) + z3HK + zKA + zAA + z3HAA + zQA (z TRYCAT pathway). IDO activity was computed as z KYN – z tryptophan (z IDO). Kynurenine 3-monooxygenase (KMO) was estimated as z 3HK – z KYN (z KMO). Kynurenine aminotransferase (KAT) activity was estimated as z KA – z KYN (z KAT). 3 hydroxyanthranilate 3,4-dioxygenase (HAAO) activity was estimated as z QA – z 3HAA (z HAAO). We used the composite z QA – z KA (z NT/NP) to reflect NT versus NP potential (Kanchanatawan *et al.*, 2018b).

Statistics

The scale variables were compared between groups using a one-way analysis of variance, and the associations among categorical variables were evaluated using contingency tables (χ^2 tests). Pearson's product-moment correlation, Spearman's rank order correlation coefficients, or partial correlation coefficients were employed to assess the correlations between scale variables, with extraneous variables being adjusted. The associations between diagnostic groups (MNP, SNP, and controls) and the TRYCATs were examined using multivariate and univariate GLM

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analyses, which accounted for the effects of explanatory variables (age, sex, education, and drug status). The Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was employed to correct the false discovery rate (FDR) of multiple tests. Multiple regression analysis was employed to identify the significant biomarkers that predicted the symptom domains through manual and automatic sequential methods (p-to-entry of 0.05 and p-to-remove 0.06) while evaluating the R^2 change. Furthermore, the analysis was examined for homoscedasticity (using the White and Breusch-Pagan tests) and collinearity (using VIF and tolerance). Once the latter was rejected, we employed heteroscedasticity-consistent standard error (SE) or robust SE estimates using the HC3 method. In addition, the analyses were bootstrapped (n=2000), and the bootstrapped results are reported when discrepancies between the two approaches are observed.

Power analysis, conducted with G*Power 3.1.9.7, indicates that a minimum sample size of 130 is necessary for a multiple regression analysis with six covariates, an effect size of 0.111, an alpha of 0.05, and a power of 0.8.

Results.

Socio-demographic data

Table 1 demonstrates the socio-demographic and clinical data for SNP and MNP patients, as well as controls. The groups did not show any significant differences in terms of age, sex, BMI, and nicotine dependence. The levels of education and marriage status were lower in both patient groups compared to the control group. Patients had significantly higher scores on rating scales, including psychosis, hostility, excitement, mannerism, total PANSS negative, total SANS, total BPRS, and OSOS, in comparison to controls. The highest values were observed in the MNP patient group, and all rating scale scores were higher in MNP than in SNP.

GLM analysis

Electronic Supplementary File (ESF), Table 1, and **Table 2** show the results of GLM analyses examining the associations between serum levels of tryptophan and TRYCATs and schizophrenia versus controls (ESF, Table 1) and MNP, SNP, and controls (Table 2). ESF, Table 1 shows that TRP, KYN, 3HK, and KA are lower in schizophrenia than in controls, whereas AA and QA are higher. Table 2 shows that TRP is significantly different between the three groups and decreases from controls to SNP to MNP. 3HK is significantly lower in MNP than in controls.

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KA and 3HAA are significantly lower in MNP than in controls and SNP. AA and QA are significantly higher in MNP than in controls and SNP. There were no significant differences in KA, 3HAA, AA and QA between SNP patients and controls.

ESF, Table 1 and Table 2 show that there were no significant differences in TRYCAT ratios reflecting z IDO, z KAT and z KMO between schizophrenia patients and controls and between MNP, SNP or controls. The QA/KA ratio was significantly higher in patients than in controls (ESF, Table 1). The TRYCAT pathway index and the QA/KA ratio are significantly different between the three groups and decrease and increase, respectively, from HC to SNP to MNP. The z HAA ratio is higher than in SNP and controls. All above GLM analyses were adjusted for age, sex, BMI, and smoking. Multivariate GLM showed a significant effect of sex on the TRYCATs and ratios (F=3.06, df=7/167, p=0.055, R^2=0.114). There were significant effects of sex on KYN (F=12.12, df=1/173, p=0.001, R^2=0.065), AA (F=5.64, df=1/173, p=0.019, R^2=0.032), z TRYCAT pathway (F=16.56, df=1/173, p<0.001, R^2=0.087), and z IDO (F=7.30, df=1/173, p=0.008, R^2=0.040). The latter variables were lower in men than in women. All differences between MNP+SNP versus controls and between the three study groups (MNP, SNP and controls) remained significant after FDR p correction.

Using the drug status of the patients as a covariate, no significant effects could be found on any of the TRYCAT variables even without FDR p correction. Thus, olanzapine (n=73, F=1.37, df=7/110, p=0.227), clozapine (n=59, F=1.18, p=0.303), haloperidol (n=27, F=0.55, p=0.799), trifluoperazine (n=32, F=0.49, p=0.836), carbamazepine (n=45, F=0.70, p=0.671), escitalopram (n=33, F=1.61, p=0.139), and propranolol (n=56, F=0.58, p=0.775) did not have any significant effects of the TRYCAT variables (even without FDR p correction).

Prediction of schizophrenia and its subgroups using serum tryptophan and TRYCATs

Table 3 displays the outcomes of different binary logistic regression analyses with schizophrenia designated as the dependent variable and the control group serving as the reference group. Schizophrenia is significantly predicted by a decrease in tryptophan and 3HK and increases in AA and QA (χ^2=45.61, df=4, p<0.001, Nagelkerke R^2=0.311, overall accuracy=72.2%). MNP versus SNP was best predicted by lower levels of tryptophan, KA, 3HAA, and higher levels of QA (χ^2=50.04, df=4, p<0.001, Nagelkerke R^2=0.457, overall accuracy=70.7%).

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We have rerun the logistic regression analyses using the ratios. Schizophrenia versus controls was predicted by z IDO, z KMO and the QA/KA ratio (all three positively associated; χ^2=31.95, df=3, p<0.001, Nagelkerke R^2=0.226, overall accuracy=70.0%). MNP versus SNP was significantly associated with the QA/KA ratio (χ^2=30.80, df=1, p<0.001, Nagelkerke R^2=0.304, overall accuracy=69.2%).

Prediction of OSOS

Table 4 demonstrates the results of multiple regression analyses, in which OSOS serves as the dependent variable and the TRYCAT biomarkers function as the explanatory variables. In the first set of regressions, we used all separate TRYCATs and tryptophan (regressions #1 and 3), and in the second set of analyses we used the ratios reflecting enzyme activities and the QA/KA ratio (regressions #2 and #4). Regression #1 shows that 36.5% of the variance in the OSOS score was explained by the regression on tryptophan, KA, 3HK and KYN (all inversely associated) and QA and AA (both positively). **Figure 1** shows the partial regression of OSOS on serum tryptophan levels. **Figure 2** shows the partial regression of OSOS on serum KA levels. The same six TRYCAT variables explained 35.8% of the variance in psychosis (F=16.04, df=6/173, p<0.001), 33.9% in hostility (F=14.81, df=6/173, p<0.001), 31.6% in excitation (F=13.30, df=6/173, p<0.001), 23.0% in manneris n (F=8.63, df=6/173, p<0.001), and 31.7% in the total PANSS negative subdomain score (F=13.39, df=6/173, p<0.001).

Regression #2 indicates that 24.0% of the variance in OSOS was explained by the regression on QA/KA, z KMO and z IDO (all positively associated). **Figure 3** shows the partial regression of OSOS on the QA/KA ratio. Regression #3 reveals that, in the restricted group of schizophrenia patients, 21.1% of the variance in OSOS was explained by the combined effects of KA and tryptophan (both negatively). Regression #4 shows that in the restricted group of patients, 16.4% of the variance in OSOS was explained by the QA/KA ratio.

Discussion

Serum TRYCATs in MNP and SNP

The results of this study indicated that schizophrenia patients exhibited substantially lower levels of serum tryptophan, KYN, 3HK, and KA, as well as higher levels of QA and AA, in comparison to controls. Similarly, the QA/KA ratio and the HAAO index were substantially

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higher in schizophrenia than in controls. These results bolster the conclusions of a recent meta-analysis (Almulla *et al.*, 2022) that schizophrenia patients exhibited substantially lower peripheral blood tryptophan levels than controls. In the latter meta-analysis, there were no alterations in KA (either serum or plasma) in comparison to controls, and the same meta-analysis reported a lower KYN in plasma, but not serum. In our multivariate logistic regression analysis, IDO and KMO appeared to have modest effects on the diagnosis of MNP+SNP versus controls. The meta-analysis performed by Almulla et al. (2022) identified a modest positive correlation between schizophrenia and the KYN/tryptophan ratio, reflecting IDO activity (Almulla *et al.*, 2022).

Nevertheless, the results of the current study are consistent with those of recent publications that were published subsequent to the meta-analysis conducted by Almulla et al. (2022) (Almulla *et al.*, 2022). In the first investigation, serum KYN and KA levels were found to be lower than those of controls (Yang *et al.*, 2022). KYN levels were considerably lower in a combined patient group that included schizophrenia and bipolar disorder, according to a recent study conducted by Skorobogatov et al. (2023) (Skorobogatov *et al.*, 2023). Moreover, the latter authors concluded that lower levels of TRYCATs including KYN, XA, QA and PA should be regarded as a transdiagnostic feature of schizophrenia and bipolar disorder. They also found that aberrations in the TRYCAT pathway are associated with acute symptom severity and long-term illness. Liu et al. (2023) found that the peripheral blood of schizophrenia patients exhibited a decrease in tryptophan and N-formyl-kynurenine (Liu *et al.*, 2023). Markovic et al. (2023) have recently observed that plasma KYN and KA levels in schizophrenia patients are lower than those in controls (Marković *et al.*, 2023). These authors did not observe any variations in the KYN/tryptophan ratio between the two groups (Marković *et al.*, 2023). However, our current study has revealed that the QA/3HAA ratio and QA are higher in schizophrenia than in controls. These results may suggest that HAAO activity is elevated in schizophrenia.

Nevertheless, all results obtained in schizophrenia patients mentioned above are likely to be of little significance. In fact, the present investigation demonstrated that, when the patient group was divided into two mutually exclusive groups (MNP versus SNP), a fundamentally distinct pattern with regard to the TRYCAT pathway was discovered. As a result, serum tryptophan, KA, and 3HAA are considerably lower in MNP than in SNP, while AA and QA are significantly higher in MNP than in SNP. It is important to note that we were unable to identify

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any substantial differences in KA, 3HK, 3HAA, AA, and QA between SNP patients and the controls. The QA/KA ratio was substantially higher in MNP than in SNP and controls, whereas there was again no significant difference between SNP patients and controls. This suggests that the changes in the QA/KA ratio, as well as serum levels of tryptophan, KA, 3HAA, AA, and QA, are highly specific for MNP. Therefore, the presence of MNP patients in any "schizophrenia" study groups could result in either negligible differences from the controls (when mainly SNP patients are included) or significant changes (where mainly MNP are included). Consequently, studies that failed or fail to differentiate between MNP and SNP are, in fact, uninterpretable.

Only one laboratory has previously investigated the differences in the TRYCAT pathway between MNP, SNP, and controls (Kanchanatawan *et al.*, 2018a). However, this paper investigated IgA responses to TRYCATs, which indicate the immune system's capacity to respond to TRYCAT-adducts. Consequently, the serum measurements in the current investigation are not directly comparable to these results. Despite these differences, there are several noteworthy similarities. Both investigations identified elevated QA levels and QA/KA in MNP compared to SNP. Additionally, Kanchanatawan et al. reported that MNP exhibited higher levels of QA, XA, and PA than SNP (Kanchanatawan *et al.*, 2018a). The current research and the latter study both conclude that MNP is associated with a higher neurotoxic potential in comparison to SNP.

Serum TRYCATs and severity of illness.

In the present study, we discovered that a significant portion (36.5%) of the variance in OSOS (which is indicative of the overall severity of the illness) was accounted for by decreased tryptophan, KA, 3HK, and KYN levels, in conjunction with elevated QA and AA levels. Interestingly, the restricted MNP+SNP study group's multivariate analysis revealed that OSOS was positively correlated with the combined effects of the IDO and KMO indices, as well as with the QA/KA ratio. Our results may suggest that both increased IDO and KMO may contribute to MNP and SNP and an increased severity of illness, albeit with a very modest effect size. These results are, therefore, partially in accord with the meta-analysis conducted by Almulla et al. (2022), which suggests that "schizophrenia" may be accompanied by a modest increase in IDO in peripheral blood (Almulla *et al.*, 2022). In a previous report, it was observed that OSOS was predicted by increased IgA responses to neurotoxic TRYCATs (namely PA+XA+3HK) (Maes *et*

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al., 2019b). OSOS, as previously mentioned, is constructed by considering the severity of PHEM and negative symptoms to reflect the severity of schizophrenia. This is due to the fact that all PHEM and negative symptoms are firmly interrelated manifestations of SNP and MNP, which explains why a single reliable factor can be extracted from these diverse rating scale scores (Maes *et al.*, 2019b). This is further emphasized by the current study, which demonstrates that the same six TRYCAT variables (tryptophan, KA, 3HK, KYN, QA, and AA) predict a significant portion of the variance in psychosis, hostility, excitation, mannerism, and negative symptoms.

TRYCATs and the pathophysiology of MNP

The TRYCAT pathway plays a critical role in MNP, as evidenced by the findings of the current study and Kanchanatawan et al (2018a) (Kanchanatawan *et al.*, 2018b). As reviewed in the Introduction, the TRYCAT pathway exerts protective activities by starving invading microorganisms (e.g. lowered tryptophan), inhibiting the growth of microorganisms (e.g. 3HK and PA), mounting antioxidant defenses (the TRYCAT pathway per se, tryptophan, 3HAA, AA, PA), prevention of hyperinflammation (anti-inflammatory activities of KYN, KA, XA, 3HAA), and through its neuroprotective activities (e.g. tryptophan, AA, KA) (Dehhaghi *et al.*, 2019; Francisco-Marquez *et al.*, 2016; Krause *et al.*, 2011; Liaqat *et al.*, 2022; Maes *et al.*, 2011a; Maes *et al.*, 2007; Narui *et al.*, 2009; Xu *et al.*, 2018). Since serum tryptophan, KYN, 3HK, and AA contribute to their pools in the brain (Fukui *et al.*, 1991; Maes *et al.*, 2011a), the findings of the current study may also have consequences for the central nervous system of MNP patients. In fact, KYN and 3HK may penetrate the brain at a substantial rate through the L-system of the large neutral amino-acid carrier (Fukui *et al.*, 1991). In contrast, passive diffusion is demonstrated for AA at a substantial rate, while the diffusion of KA, QA, and 3HAA occurs at a slower pace (Fukui *et al.*, 1991). As a result, the effects of reduced serum tryptophan, KYN, 3HK, and KA may have significant implications for the CNS functions of MNP patients.

The reduction in tryptophan is a double-edged sword: lowered levels are an innate immunity protective mechanism; however, it may also reduce antioxidant defenses and disrupt the gut-brain axis, resulting in decreased neuroprotection (Liaqat *et al.*, 2022; Xu *et al.*, 2018). Furthermore, the alterations in TRYCAT levels may be perceived as a double-edged sword with two sharpened edges. Initially, our TRYCAT composite score, which is decreased in MNP,

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indicates that the antioxidant activities of the pathway have been diminished. For instance, lowered levels of KYN and KA may have lowered the reactive oxygen scavenging effects and anti-inflammatory effects of the TRYCAT pathway (Ramírez Ortega *et al.*, 2021). Therefore, it appears that MNP is associated with diminished protective CIRS activities, which may increase the risk of oxidative and inflammatory injuries. Conversely, elevated levels of QA and the QA/KA ratio may indicate increased neurotoxic potential. QA is a potent endogenous neurotoxin that activates the N-methyl-D-aspartate receptor, resulting in excitotoxic effects (Lugo-Huitrón *et al.*, 2013). Additionally, QA is a pro-inflammatory and pro-oxidant compound that has the potential to induce apoptotic, cytotoxic, neurotoxic, and gliotoxic effects, as well as increased oxidative stress (Guillemin, 2012; Lugo-Huitrón *et al.*, 2013). Furthermore, the blood-brain barrier may be compromised by elevated QA (Guillemin, 2012), which may be induced by other IRS-associated events in MNP, such as elevated levels of LPS, reactive oxygen species, and certain pro-inflammatory cytokines (Maes *et al.*, 2021; Najjar *et al.*, 2017). This is significant because the current investigation demonstrated that HAAO activity may be increased in MNP in comparison to SNP and controls. HAAO is a highly active enzyme in the TRYCAT pathway, resulting in the rapid catabolism of 3HAA into QA (Lehninger, 1980; Nishizuka & Hayaishi, 1963).

Limitations

The results of the current study, which was conducted in Iraq, are worthy of replication in MNP patients versus SNP patients and controls in other countries and cultures. If we had measured biomarkers of oxidative stress, Th1 and M1 macrophage cytokines, and the LPS load in peripheral blood, this study would have been even more intriguing. These substances have the potential to stimulate IDO and other enzymes of the TRYCAT pathway, including 3HAAO. It would have been intriguing to conduct an assay of PA in order to estimate the activity of 2–amino-3–carboxymuconate semialdehyde decarboxylase. In addition, even in the absence of meeting the criteria for type 2 diabetes mellitus or of prescribed medications, schizophrenia is frequently linked to hyperglycemia and hypertension as aspects of metabolic dysregulation (Fang et al., 2024). Similar to a highly dysregulated gut microbiome, both hyperglycemia and hypertension (Zhang et al., 2024) elevate levels of methylglyoxal, which binds tryptophan through protein-protein interactions (Samsuzzaman et al., 2024) and may be a contributing factor to suppressed tryptophan levels in schizophrenia. This necessitates further investigation in future

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studies, particularly in relation to the relevance of the tryptophan-melatonin pathway. The hippocampal melatonergic pathway is essential for neurocognition, including long-term potentiation, as demonstrated in preclinical studies (Karimi-Zandi et al., 2024). This would suggest that cognitive changes associated with the kynurenine pathway may be linked to changes in the tryptophan-melatonin pathway and necessitate further investigation in future studies.

Conclusions.

MNP patients have reduced levels of tryptophan, KA, and 3HAA, alongside elevated levels of AA and QA compared to SNP patients. We determined that 36.5% of the variance in OSOS was accounted for by the collective influences of diminished tryptophan, KA, and 3-HK, alongside elevated QA and AA. The primary biomarkers of MNP and OSOS were the QA/KA ratio, succeeded by the QA/3HAA ratio.

MNP and SNP constitute two physiologically different subtypes of schizophrenia with respect to alterations in the TRYCAT pathway. Increased QA levels may intensify the breakdown of the blood-brain barrier and the immune-related and oxidative neurotoxicity in MNP. The reductions in TRYCATs may compromise the antioxidant and immunoregulatory functions of the TRYCAT pathway. The TRYCAT pathway in MNP is a double-edged sword, characterized by heightened toxicity and diminished CIRS activity. As noted in the context of significant depression (Maes *et al.* 2011b), it is imprudent to attempt to modify the delicate balance among IDO, KMO, and KAT activities. At first glance, HAAO may seem to be a novel therapeutic target for the treatment of MNP. HAAO antagonists may reduce the elevated synthesis of QA, hence averting the disruption of the blood-brain barrier and subsequent neurotoxicity. Nonetheless, this method may inhibit NAD^+ synthesis and NAD-dependent enzymes (like sirtuins), elevate oxidative stress, and lead to dysfunctions in the mitochondrial electron transport chain due to heightened 3HAA concentrations (Schuck *et al.*, 2007).

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Conflict of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

Author's contributions

All the contributing authors have participated equally in the manuscript.

References

Almulla, A. F., Vasupanrajit, A., Tunvirachaisakul, C., Al-Hakeim, H. K., Solmi, M., Verkerk, R., et al. (2022). The tryptophan catabolite or kynurenine pathway in schizophrenia: meta-analysis reveals dissociations between central, serum, and plasma compartments. *Mol Psychiatry, 27*(9), 3679-3691. doi:10.1038/s41380-022-01552-4

Almulla, Abbas F, Al-Hakeim, Hussein K, & Maes, Michael. (2021). Schizophrenia phenomenology revisited: positive and negative symptoms are strongly related reflective manifestations of an underlying single trait indicating overall severity of schizophrenia. *CNS spectrums, 26*(4), 368-377.

Andreasen, Nancy C. (1989). The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *The British Journal of Psychiatry, 155*(S7), 49-52.

Bender, David A. (1980). Inhibition in vitro of the enzymes of the oxidative pathway of tryptophan metabolism and of nicotinamide nucleotide synthesis by benserazide, carbidopa and isoniazid. *Biochemical Pharmacology, 29*(5), 707-712.

Benjamini, Yoav, & Hochberg, Yosef. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological), 57*(1), 289-300.

Correll, Christoph U, & Howes, Oliver D. (2021). Treatment-resistant schizophrenia: definition, predictors, and therapy options. *The Journal of Clinical Psychiatry, 82*(5), 36608.

Accepted manuscript

https://doi.org/10.1017/neu.2025.5 Published online by Cambridge University Press

Dehhaghi, M., Kazemi Shariat Panahi, H., & Guillemin, G. J. (2019). Microorganisms, Tryptophan Metabolism, and Kynurenine Pathway: A Complex Interconnected Loop Influencing Human Health Status. *Int J Tryptophan Res, 12*, 1178646919852996. doi:10.1177/1178646919852996

Fang, Y.J., Lee, W.Y., Lin, C.L., Cheah, Y.C., Hsieh, H.H., Chen, C.H., Tsai, F.J., Tien, N., & Lim, Y.P. (2024). Association of antipsychotic drugs on type 2 diabetes mellitus risk in patients with schizophrenia: a population-based cohort and in vitro glucose homeostasis-related gene expression study. *BMC Psychiatry*, 30, 24(1):751.

Francisco-Marquez, Misaela, Aguilar-Fernández, Mario, & Galano, Annia. (2016). Anthranilic acid as a secondary antioxidant: Implications to the inhibition of OH production and the associated oxidative stress. *Computational and Theoretical Chemistry, 1077*, 18-24. doi:https://doi.org/10.1016/j.comptc.2015.09.025

Fukui, Shinsuke, Schwarcz, Robert, Rapoport, Stanley I., Takada, Yoshiaki, & Smith, Quentin R. (1991). Blood–brain barrier transport of kynurenines: implications for brain synthesis and metabolism. *Journal of neurochemistry, 56*(6), 2007-2017.

Guillemin, G. J. (2012). Quinolinic acid, the inescapable neurotoxin. *Febs j, 279*(8), 1356-1365. doi:10.1111/j.1742-4658.2012.08425.x

Kanchanatawan, B., Sirivichayakul, S., Ruxrungtham, K., Carvalho, A. F., Geffard, M., Ormstad, H., et al. (2018a). Deficit, but Not Nondeficit, Schizophrenia Is Characterized by Mucosa-Associated Activation of the Tryptophan Catabolite (TRYCAT) Pathway with Highly Specific Increases in IgA Responses Directed to Picolinic, Xanthurenic, and Quinolinic Acid. *Mol Neurobiol, 55*(2), 1524-1536. doi:10.1007/s12035-017-0417-6

Kanchanatawan, Buranee, Sriswasdi, Sira, Thika, Supaksorn, Sirivichayakul, Sunee, Carvalho, André F, Geffard, Michel, et al. (2018b). Deficit schizophrenia is a discrete diagnostic category defined by neuro-immune and neurocognitive features: results of supervised machine learning. *Metabolic Brain Disease, 33*, 1053-1067.

Kanchanatawan, Buranee, Sriswasdi, Sira, Thika, Supaksorn, Stoyanov, Drozdstoy, Sirivichayakul, Sunee, Carvalho, André F, et al. (2018c). Towards a new classification of stable phase schizophrenia into major and simple neuro-cognitive psychosis: Results of unsupervised machine learning analysis. *Journal of Evaluation in Clinical Practice, 24*(4), 879-891.

Accepted manuscript

https://doi.org/10.1017/neu.2025.5 Published online by Cambridge University Press

Karimi-Zandi, L., Ghorbandaiepour, T., Zahmatkesh, M., & Sadroddiny, E. (2024) GnRH protective effects against long-term potentiation impairment induced by AANAT-siRNA. *Neuropeptides*. 108, 102474. doi: 10.1016/j.npep.2024.102474. Epub 2024 Sep 18. PMID: 39305554.

Kay, Stanley R, Fiszbein, Abraham, & Opler, Lewis A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin, 13*(2), 261-276.

Krause, D., Suh, H. S., Tarassishin, L., Cui, Q. L., Durafourt, B. A., Choi, N., et al. (2011). The tryptophan metabolite 3-hydroxyanthranilic acid plays anti-inflammatory and neuroprotective roles during inflammation: role of hemeoxygenase-1. *Am J Pathol, 179*(3), 1360-1372. doi:10.1016/j.ajpath.2011.05.048

Liaqat, H., Parveen, A., & Kim, S. Y. (2022). Neuroprotective Natural Products' Regulatory Effects on Depression via Gut-Brain Axis Targeting Tryptophan. *Nutrients, 14*(16). doi:10.3390/nu14163270

Liu, J. C., Yu, H., Li, R., Zhou, C. H., Shi, Q. Q., Guo, L., et al. (2023). A Preliminary Comparison of Plasma Tryptophan Metabolites and Medium- and Long-Chain Fatty Acids in Adult Patients with Major Depressive Disorder and Schizophrenia. *Medicina (Kaunas), 59*(2). doi:10.3390/medicina59020413

Lugo-Huitrón, R., Ugalde Muñiz, P., Pineda, B., Pedraza-Chaverrí, J., Ríos, C., & Pérez-de la Cruz, V. (2013). Quinolinic acid: an endogenous neurotoxin with multiple targets. *Oxid Med Cell Longev, 2013*, 104024. doi:10.1155/2013/104024

Maes, M. (2023). Major neurocognitive psychosis: a novel schizophrenia endophenotype class that is based on machine learning and resembles Kraepelin's and Bleuler's conceptions. *Acta Neuropsychiatr, 35*(3), 123-137. doi:10.1017/neu.2022.32

Maes, M., Berk, M., Goehler, L., Song, C., Anderson, G., Gałecki, P., et al. (2012). Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med, 10*, 66. doi:10.1186/1741-7015-10-66

Maes, M., Kanchanatawan, B., Sirivichayakul, S., & Carvalho, A. F. (2019a). In Schizophrenia, Increased Plasma IgM/IgA Responses to Gut Commensal Bacteria Are Associated with Negative Symptoms, Neurocognitive Impairments, and the Deficit Phenotype. *Neurotox Res, 35*(3), 684-698. doi:10.1007/s12640-018-9987-y

Accepted manuscript

https://doi.org/10.1017/neu.2025.5 Published online by Cambridge University Press

Maes, M., Leonard, B. E., Myint, A. M., Kubera, M., & Verkerk, R. (2011a). The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog Neuropsychopharmacol Biol Psychiatry, 35*(3), 702-721. doi:10.1016/j.pnpbp.2010.12.017

Maes, M., Mihaylova, I., Ruyter, M. D., Kubera, M., & Bosmans, E. (2007). The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression - and other conditions characterized by tryptophan depletion induced by inflammation. *Neuro Endocrinol Lett, 28*(6), 826-831.

Maes, M., Vojdani, A., Geffard, M., Moreira, E. G., Barbosa, D. S., Michelin, A. P., et al. (2019b). Schizophrenia phenomenology comprises a bifactorial general severity and a single-group factor, which are differently associated with neurotoxic immune and immune-regulatory pathways. *Biomol Concepts, 10*(1), 209-225. doi:10.1515/bmc-2019-0023

Maes, M., Vojdani, A., Sirivichayakul, S., Barbosa, D. S., & Kanchanatawan, B. (2021). Inflammatory and Oxidative Pathways Are New Drug Targets in Multiple Episode Schizophrenia and Leaky Gut, Klebsiella pneumoniae, and C1q Immune Complexes Are Additional Drug Targets in First Episode Schizophrenia. *Mol Neurobiol, 58*(7), 3319-3334. doi:10.1007/s12035-021-02343-8

Maes, Michael, Galecki, Piotr, Verkerk, Robert, & Rief, Winfried. (2011b). Somatization, but not depression, is characterized by disorders in the tryptophan catabolite (TRYCAT) pathway, indicating increased indoleamine 2, 3-dioxygenase and lowered kynurenine aminotransferase activity. *Neuroendocrinol Lett, 32*(3), 264-273.

Maes, Michael, Moraes, Juliana Brum, Congio, Ana, Bonifacio, Kamila Landucci, Barbosa, Decio Sabbatini, Vargas, Heber Odebrecht, et al. (2019c). Development of a novel staging model for affective disorders using partial least squares bootstrapping: effects of lipid-associated antioxidant defenses and neuro-oxidative stress. *Molecular Neurobiology, 56*, 6626-6644.

Maes, Michael, Sirivichayakul, Sunee, Kanchanatawan, Buranee, & Carvalho, André F. (2020). In schizophrenia, psychomotor retardation is associated with executive and

Accepted manuscript

https://doi.org/10.1017/neu.2025.5 Published online by Cambridge University Press

memory impairments, negative and psychotic symptoms, neurotoxic immune products and lower natural IgM to malondialdehyde. *The World Journal of Biological Psychiatry, 21*(5), 383-401.

Maes, Michael, Sirivichayakul, Sunee, Kanchanatawan, Buranee, & Vodjani, Aristo. (2019d). Breakdown of the paracellular tight and adherens junctions in the gut and blood brain barrier and damage to the vascular barrier in patients with deficit schizophrenia. *Neurotox Res, 36*, 306-322.

Marković, Miloš, Petronijević, Nataša, Stašević, Milena, Stašević Karličić, Ivana, Velimirović, Milica, Stojković, Tihomir, et al. (2023). Decreased Plasma Levels of Kynurenine and Kynurenic Acid in Previously Treated and First-Episode Antipsychotic-Naive Schizophrenia Patients. *Cells, 12*(24), 2814.

Matsumoto, A. K., Maes, M., Supasitthumrong, T., Maes, A., Michelin, A. P., de Oliveira Semeão, L., et al. (2021). Deficit schizophrenia and its features are associated with PON1 Q192R genotypes and lowered paraoxonase-1 (PON1) enzymatic activity: effects on bacterial translocation. *CNS Spectr, 26*(4), 426-433. doi:10.1017/s1092852920001388

Najjar, S., Pahlajani, S., De Sanctis, V., Stern, J. N. H., Najjar, A., & Chong, D. (2017). Neurovascular Unit Dysfunction and Blood-Brain Barrier Hyperpermeability Contribute to Schizophrenia Neurobiology: A Theoretical Integration of Clinical and Experimental Evidence. *Front Psychiatry, 8*, 83. doi:10.3389/fpsyt.2017.00083

Narui, K., Noguchi, N., Saito, A., Kakimi, K., Motomura, N., Kubo, K., et al. (2009). Anti-infectious activity of tryptophan metabolites in the L-tryptophan-L-kynurenine pathway. *Biol Pharm Bull, 32*(1), 41-44. doi:10.1248/bpb.32.41

Nishizuka, Yasutomi, & Hayaishi, Osamu. (1963). Studies on the biosynthesis of nicotinamide adenine dinucleotide: I. Enzymic synthesis of niacin ribonucleotides from 3-hydroxyanthranilic acid in mammalian tissues. *Journal of Biological Chemistry, 238*(10), 3369-3377.

Overall, John E, & Gorham, Donald R. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*(3), 799-812.

Popov, P., Chen, C., Al-Hakeim, H. K., Al-Musawi, A. F., Al-Dujaili, A. H., Stoyanov, D., et al. (2024). The novel schizophrenia subgroup "major neurocognitive psychosis" is validated as a distinct class through the analysis of immune-linked neurotoxicity

Accepted manuscript

https://doi.org/10.1017/neu.2025.5 Published online by Cambridge University Press

biomarkers and neurocognitive deficits. *Brain Behav Immun Health, 40*, 100842. doi:10.1016/j.bbih.2024.100842

Ramírez Ortega, D., Ugalde Muñiz, P. E., Blanco Ayala, T., Vázquez Cervantes, G. I., Lugo Huitrón, R., Pineda, B., et al. (2021). On the Antioxidant Properties of L-Kynurenine: An Efficient ROS Scavenger and Enhancer of Rat Brain Antioxidant Defense. *Antioxidants (Basel), 11*(1). doi:10.3390/antiox11010031

Roomruangwong, C., Noto, C., Kanchanatawan, B., Anderson, G., Kubera, M., Carvalho, A. F., et al. (2020). The Role of Aberrations in the Immune-Inflammatory Response System (IRS) and the Compensatory Immune-Regulatory Reflex System (CIRS) in Different Phenotypes of Schizophrenia: the IRS-CIRS Theory of Schizophrenia. *Mol Neurobiol, 57*(2), 778-797. doi:10.1007/s12035-019-01737-z

Samsuzzaman, M.D., Hong, S.M., Lee, J.H., Park, H., Chang, K.A., Kim, H.B., Park, M.G., Eo, H., Oh, M.S., & Kim, S.Y. (2024). Depression like-behavior and memory loss induced by methylglyoxal is associated with tryptophan depletion and oxidative stress: a new in vivo model of neurodegeneration. *Biol Res*, 57(1), 87. doi: 10.1186/s40659-024-00572-4. PMID: 39574138; PMCID: PMC11580208.

Schuck, P. F., Tonin, A., da Costa Ferreira, G., Viegas, C. M., Latini, A., Duval Wannmacher, C. M., et al. (2007). Kynurenines impair energy metabolism in rat cerebral cortex. *Cell Mol Neurobiol, 27*(1), 147-160. doi:10.1007/s10571-006-9124-y

Sirivichayakul, Sunee, Kanchanatawan, Buranee, Thika, Supaksorn, Carvalho, André F, & Maes, Michael. (2019a). Eotaxin, an endogenous cognitive deteriorating chemokine (ECDC), is a major contributor to cognitive decline in normal people and to executive, memory, and sustained attention deficits, formal thought disorders, and psychopathology in schizophrenia patients. *Neurotox Res, 35*(1), 122-138.

Sirivichayakul, Sunee, Kanchanatawan, Buranee, Thika, Supaksorn, Carvalho, André F, & Maes, Michael. (2019b). A new schizophrenia model: immune activation is associated with the induction of different neurotoxic products which together determine memory impairments and schizophrenia symptom dimensions. *CNS Neurological Disorders-Drug Targets, 18*(2), 124-140.

Skorobogatov, K., Autier, V., Foiselle, M., Richard, J. R., Boukouaci, W., Wu, C. L., et al. (2023). Kynurenine pathway abnormalities are state-specific but not diagnosis-specific in

Accepted manuscript

https://doi.org/10.1017/neu.2025.5 Published online by Cambridge University Press

schizophrenia and bipolar disorder. *Brain Behav Immun Health, 27*, 100584. doi:10.1016/j.bbih.2022.100584

Snezhnevsky, A. V. (1971). Symptom, syndrome, disease: a clinical method in psychiatry. *The world biennial of psychiatry and psychotherapy*, 151-164.

Snezhnevsky, A. V., Vartanyan, M., & Himwich, H. E. (1970). The forms of schizophrenia and their biological correlates. *Biochemistry, Schizophrenias, and Affective Illnesses. Baltimore, MD: Williams & Wilkins*, 1-28.

Vigo, Daniel, Thornicroft, Graham, & Atun, Rifat. (2016). Estimating the true global burden of mental illness. *The Lancet Psychiatry, 3*(2), 171-178.

Xu, K., Liu, G., & Fu, C. (2018). The Tryptophan Pathway Targeting Antioxidant Capacity in the Placenta. *Oxid Med Cell Longev, 2018*, 1054797. doi:10.1155/2018/1054797

Yang, Q., Zhang, Y., Yang, K., Niu, Y., Fan, F., Chen, S., et al. (2022). Associations of the serum kynurenine pathway metabolites with P50 auditory gating in non-smoking patients with first-episode schizophrenia. *Front Psychiatry, 13*, 1036421. doi:10.3389/fpsyt.2022.1036421

Zhang, W.Y., Zhao, C.M., Wang, C.S., Xie, X., Li, Y.Q., Chen, B.B., Feng, L., & Jiang, P (2024) Methylglyoxal accumulation contributes to accelerated brain aging in spontaneously hypertensive rats. *Free Radic Biol Med*. 210, 108-119. doi: 10.1016/j.freeradbiomed.2023.11.012. Epub 2023 Nov 18. PMID: 37984752.

Accepted manuscript

https://doi.org/10.1017/neu.2025.5 Published online by Cambridge University Press

Table 1. Demographic and clinical data in healthy controls (HC), patients with major neuro-cognitive p*sychosis* (*MNP*), and simple neuro-cognitive p*sychosis* (S*NP*).

Variables	**HC (n=60)**[A]	**SNP (n=68)**[B]	**MNP (n=52)**[C]	**F/χ^2**	**df**	**p**
Age (years)	38.6 (10.9)	41.2 (10.9)	41.2 (8.6)	1.30	2/177	0.276
BMI (Kg/m^2)	27.36 (4.70)	27.74 (4.27)	27.81 (3.08)	0.202	2/177	0.818
Sex (Female/Male)	18/42	22/46	10/42	2.751	2	2.53
Single/Married	11/49 [B,C]	39/29 [A]	23/23 [A]	23.898	2	<0.001
TUD (No/Yes)	41/19	46/22	31/21	1.149	2	0.563
Education years	10.9 (3.7) [B,C]	7.7 (3.2) [A]	7.3 (3.7) [A]	18.80	2/177	<0.001
Duration of Disease (years)	-	15.1 (9.4)	17.3 (8.8)	1.751	1/119	0.108
Psychosis (z scores)	-6.625 (0.06) [B,C]	1.12±2.176 [A,C]	6.179 (1.987) [A,B]	KWT	-	<0.001
Hostility (z scores)	-5.364 (0.276) [B,C]	1.331±2.457 [A,C]	4.423 (2.233) [A,B]	KWT	-	<0.001
Excitement (z scores)	-4.083 (0.399) [B,C]	0.691±1.847 [A,C]	3.795 (1.984) [A,B]	KWT	-	<0.001
Mannerism (z scores)	-2.08 [B,C]	0.533±1.431 [A,C]	1.703 (1.684) [A,B]	KWT	-	<0.001
Total PANSS negative	0.4 (0.586) [B,C]	16.324±3.972 [A,C]	25.404 (5.026) [A,B]	KWT	-	<0.001
Total SANS	6.05 (4.316) [B,C]	65.62±9.451 [A,C]	84.9 (6.999) [A,B]	KWT	-	<0.001
Total BPRS score	19.6 (1.2) [B,C]	51.2 (8.8) [A,C]	78.8 (6.2) [A,B]	KWT	-	<0.001
OSOS (z score)	-1.252 (0.037) [B,C]	0.296 (0.307) [A,C]	1.103 (0.247) [A,B]	KWT	-	<0.001

All results are shown as mean (SD), all results of analysis of variance (F), Kruskal-Wallis test (KWT) or contingency analysis (χ^2).
[A,B,C]: post-hoc comparisons among group means (least significant difference).
BMI: body mass index, TUD: tobacco use disorder, PANSS: The Positive and Negative Syndrome Scale, SANS: The Scale for the Assessment of Negative Symptoms, BPRS: Brief Psychiatric Rating Scale, OSOS: overall severity of schizophrenia.

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Table 2. Serum levels of tryptophan and tryptophan catabolites (TRYCATs) in healthy controls (HC), patients with simple neuro-cognitive p*sychosis* (S*NP*) and with major neuro-cognitive p*sychosis* (*MNP*)

Variables	**HC (n=60)** [A]	**SNP (n=68)** [B]	**MNP (n=52)** [C]	**F (2/17[illegible])**	**p**	**Partial η^2**
Tryptophan (TRP) µM	62.25 (3.04) [B,C]	50.92 (2.84) [A,C]	40.085 (3.35) [A,B]	15.19	<0.001	0.132
Kynurenine (KYN) µM	2.457 (0.104) [B,C]	2.141 (0.097) [A]	1.935 (0.114) [A]	6.48	0.002	0.070
3-OH-Kynurenine (3HK) nM	20.49 (1.124) [C]	17.63 (1.05)	14.72 (1.24) [A]	6.55	0.002	0.092
Kynurenic acid (KA) nM	35.66 (1.42) [C]	33.11 (1.32) [C]	24.72 (1.56) [A,B]	16.00	<0.001	0.156
Anthranilic acid (AA) nM	14.84 (1.56) [C]	17.65 (1.45) [C]	23.36 (1.71) [A,B]	5.73	0.004	0.062
3-OH-AA (3HAA) nM	21.75 (1.24) [C]	21.59 (1.16) [C]	15.650(1.37) [A,B]	7.718	0.001	0.082
Quinolinic acid (QA) nM	273.82 (21.38) [C]	324.16 (19.9[illegible]) [C]	447.83 (23.53) [A,B]	13.50	<0.001	0.135
TRYCAT pathway (z score)	0.716 (2.122) [C]	0.100 (3.122)	-0.957 (2.734) [A]	4.544	0.012	0.050
Z IDO (z score)	-0.089 (1.067)	[illegible] (1.001)	0.101 (0.924)	0.77	0.470	0.009
Z KAT (z score)	0.013 (1.142)	[illegible]134 (1.043)	-0.190 (0.713)	2.04	0.130	0.023
Z KMO (z score)	0.030 (0.890)	-0.001 (1.046)	-0.033 (1.074)	0.14	0.872	0.002
Z QA/KA (z score)	-0.454 (0.880) [B,C]	-0.180 (0.958) [A,C]	0.759 (0.730) [A,B]	28.74	<0.001	0.249
Z HAAO (z score)	-0.360 (0.728) [C]	-0.210 (0.945) [C]	0.690 (1.013) [A,B]	21.67	<0.001	0.200

All results are shown as marginal estimated means (SE) after covarying for age, sex, body mass index and smoking. All results of analysis of variance. z IDO: index of indoleamine 2,3-dioxygenase (KYN/tryptophan), z KMO: index of kynurenine 3-monooxygenase (3HK/KYN), z KAT: index of kynurenine aminotransferases (KA/KYN), z HAAO: index of hydroxyanthranilate 3,4-dioxygenase (QA/3HAA).

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Table 3. Results of binary logistic regression analyses with schizophrenia (SCZ) as dependent variable and healthy controls (HC) as reference group.

Dichotomies	Explanatory variables	B	SE	Wald	df	p	OR	95% CI
SCZ *vs.* HC	Tryptophan	-0.603	0.182	10.97	1	0.001	0.55	0.383-0.782
	3-OH-kynurenine	-0.735	0.204	13.01	1	<0.001	0.45	0.32-0.715
	Anthranilic acid	0.525	0.216	5.93	1	0.015	1.69	1.11-2.58
	Quinolinic acid	0.584	0.203	8.29	1	0.004	1.79	1.21-2.670
SCZ *vs.* HC	z IDO	0.397	0.164	5.90	1	0.015	1.49	1.08-2.05
	z KMO	0.610	0.182	11.28	1	0.001	1.84	1.29-2.63
	z QA/KA	0.800	0.163	24.05	1	<0.001	2.23	1.62-3.07
MNP *vs.* SNP	Tryptophan	-0.676	0.299	5.11	1	0.024	0.51	0.28-0.91
	Kynurenic acid (KA)	-1.395	0.434	13.52	1	<0.001	0.20	0.09-0.48
	3-hydroxyanthranilic acid	-0.538	0.224	5.78	1	0.016	0.58	0.38-0.91
	Quinolinic acid	0.558	0.217	6.59	1	0.010	1.75	1.14-2.68
MNP *vs.* SNP	z QA/KA	0.833	0.179	21.78	1	<0.001	2.30	1.62-3.27

z IDO: index of indoleamine 2,3-dioxygenase (KYN/tryptophan), z KMO: index of kynurenine 3-monooxygenase (3HK/KYN), z QA/KA: index of quinolinic acid / kynurenic acid, indicating neurotoxicity / neuroprotection potential

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Table 4. Results of multiple regression with the overall severity of schizophrenia (OSOS) as dependent variable, and serum tryptophan catabolite biomarkers as explanatory variables.

Dependent Variables	Explanatory Variables	β	t	p	F model	df	p	R^2
#1. OSOS in all subjects	**Model**				16.53	6/173	<0.001	0.365
	Tryptophan	-0.234	-3.71	<0.001				
	Kynurenic acid	-0.203	-3.22	0.002				
	Quinolinic acid	0.205	3.31	0.001				
	3-OH-kynurenine	-0.224	-3.49	0.001				
	Anthranilic acid	0.204	3.26	0.001				
	Kynurenine	-0.150	-2.39	0.018				
#2. OSOS in all subjects	**Model**				18.58	3/176	<0.001	0.240
	z QA/KA	0.571	7.36	<0.001				
	z KMO	0.322	3.61	<0.001				
	z IDO	0.241	2.70	0.008				
#3. OSOS in schizophrenia	**Model**				15.63	2/117	<0.001	0.211
	Kynurenic acid	-0.384	-4.63	<0.001				
	Tryptophan	-0.200	-2.41	0.018				
#4. OSOS in schizophrenia	**Model**				23.17	1/118	<0.001	0.164
	z QA/KA	0.405	4.81	<0.001				

z IDO: index of indoleamine 2,3-dioxygenase (KYN/tryptophan), z KMO: index of kynurenine 3-monooxygenase (3HK/KYN), z QA/KA: index of quinolinic acid / kynurenic acid, indicating neurotoxicity / neuroprotection potential

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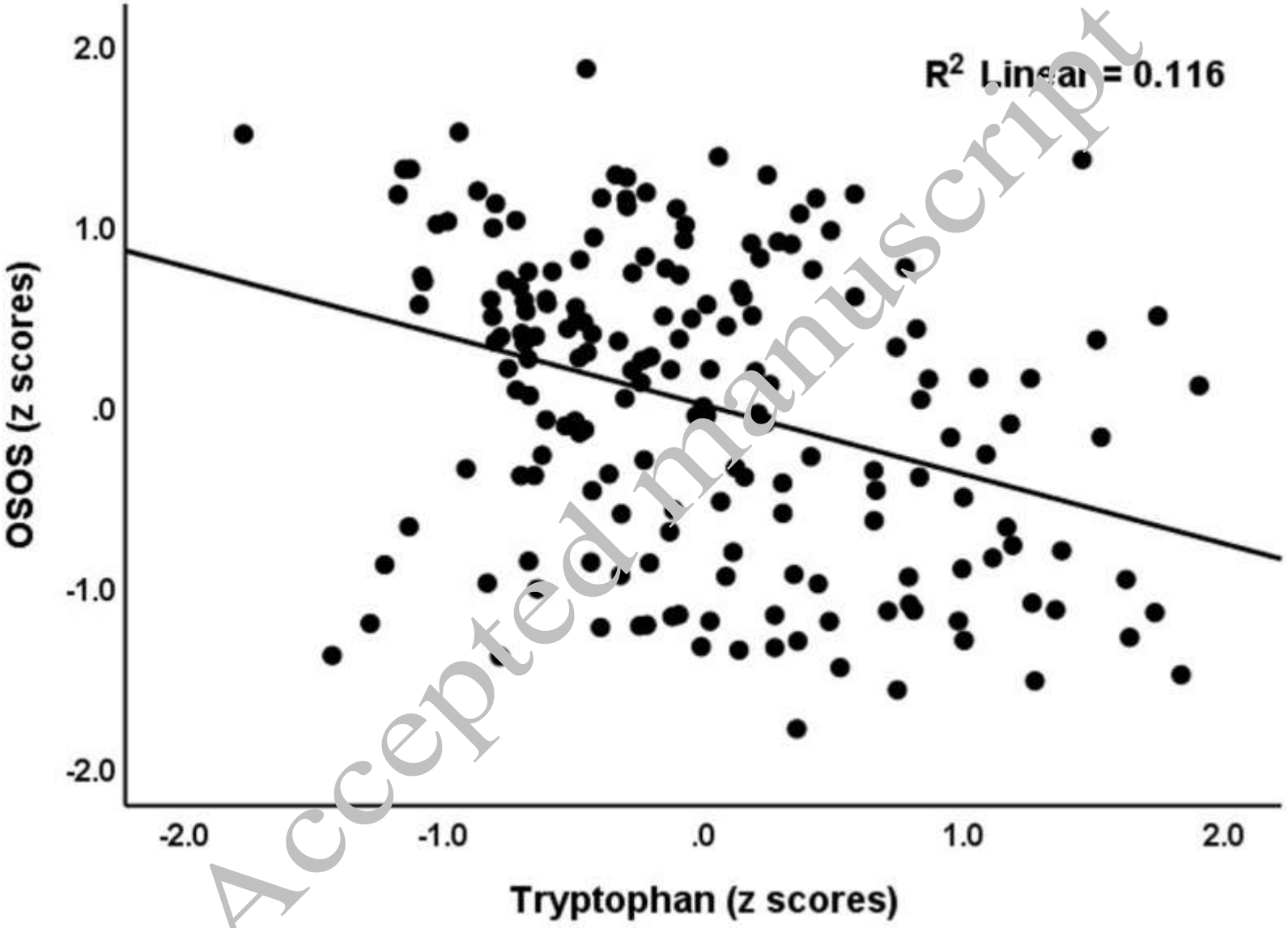

Figure 1 Partial regression of overall severity of schizophrenia (OSOS) on serum tryptophan ($p<0.01$).

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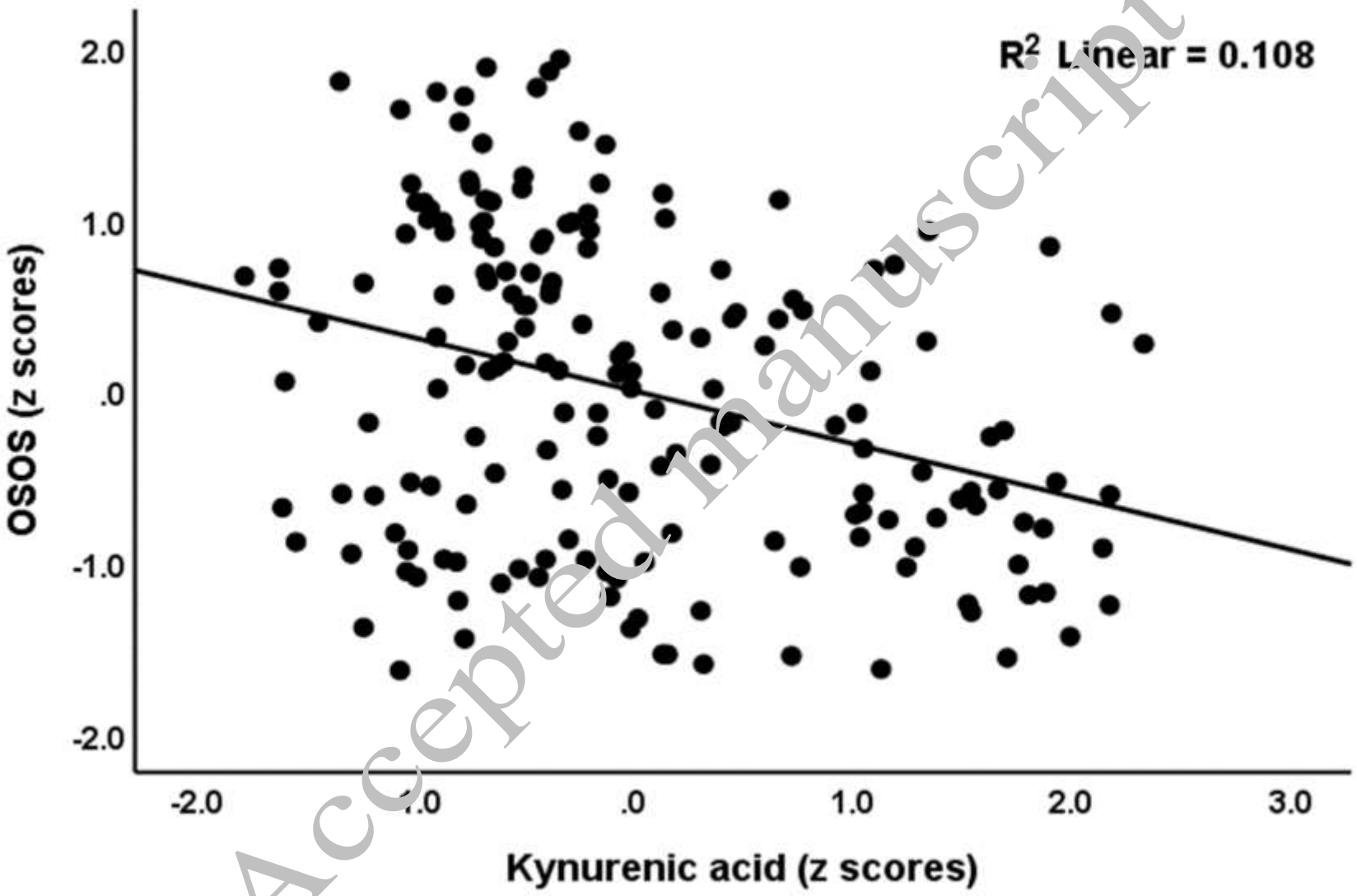

Figure 2 Partial regression of overall severity of schizophrenia (OSOS) on serum kynurenic acid ($p<0.01$).

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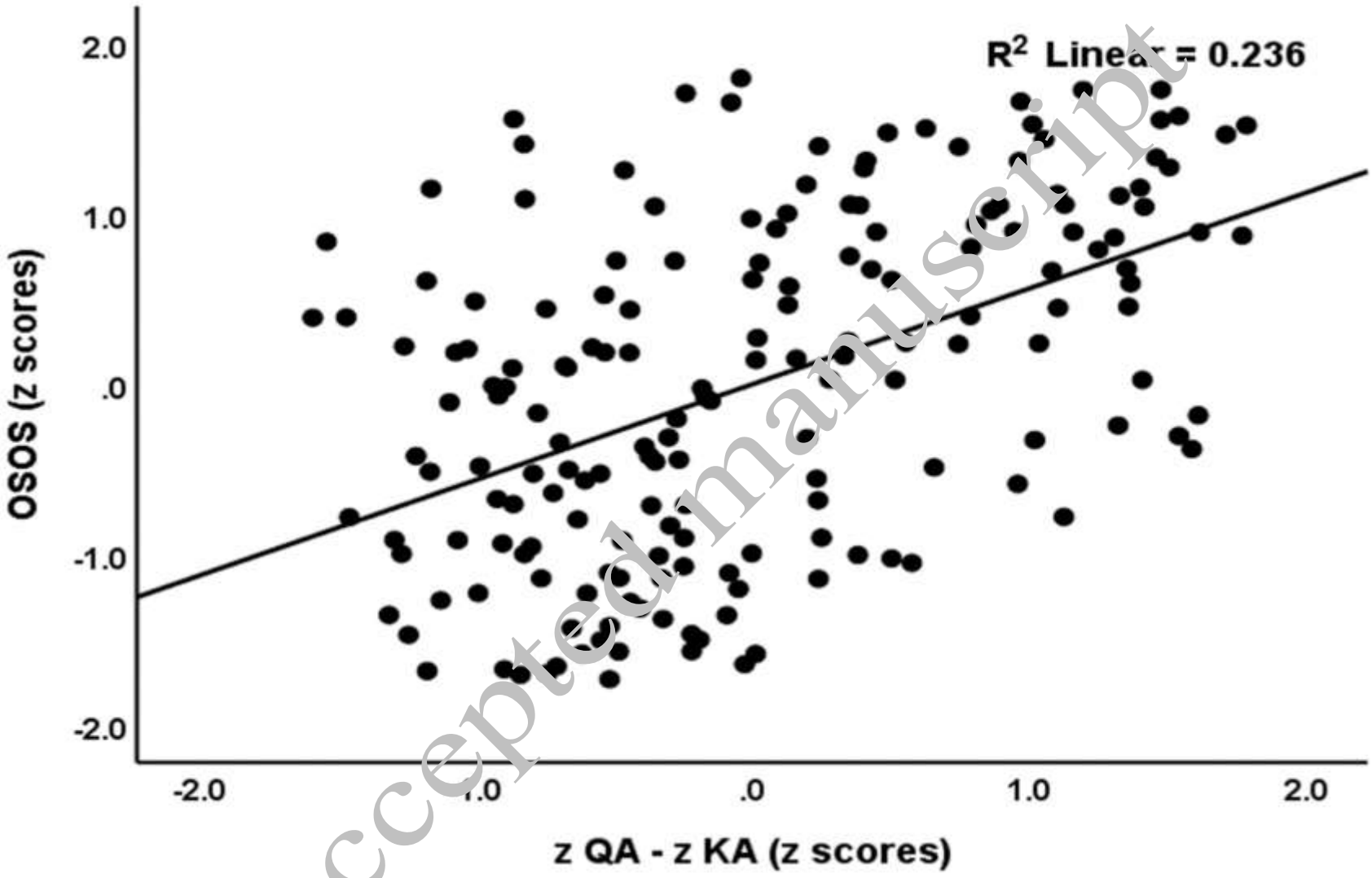

Figure 3 Partial regression of overall severity of schizophrenia (OSOS) on the ratio of quinolinic acid (QA) on kynurenic acid (KA) ($p<0.01$).

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