Original Research Article

Relationship between iron saturation indices and psychiatric disorders among persons seeking care at selected psychiatry health facilities in Ghana

ABSTRACT

Background: Iron saturation indices are associated with psychiatric disorders and disease severity. This study investigated the relationship between iron metabolism and psychiatric disorder and whether iron saturation indices could predict disease severity.

Method: The design of study was an unmatched case-control study conducted between December 2020 to March 2022 in some selected psychiatric facilities in Ghana. Venous blood was collected and serum iron, TIBC, ferritin, transferrin and full blood count were quantified to calculate intraindividual variation and to assess the relationships of these iron saturation indices to severity of psychiatric disorders.

Results: Serum iron (38.98±14.55 µmol/L), ferritin (100.23±84.98 ng/mL) and transferrin saturation (44.35±14.6%) were significantly ($p<0.05$) higher in group with psychiatric disorders compared with the controls (29.25±8.0 µmol/L; 75.25±42.71 ng/mL and 28.66±7.1%). However, total iron binding capacity (TIBC) (102.47±15.01 µmol/L), UIBC (73.22±13.12 µmol/L) and transferrin (4.08±0.6 g/L) concentrations were considerably greater in control group than in the case subjects (88.95±19.73 µmol/L; 49.97±18.32 µmol/L and 3.54±0.79 g/L). One unit increase in BMI is associated with 1.27 (aOR=1.27, $p<0.001$) times risk of psychiatric disorders and males are 6 (aOR=5.87, $p<0.005$) times at risk of disorders. At a cut off of ≤65.79 µmol/L, UIBC can distinguish psychiatric disorders from controls.

Conclusion: Serum iron and transferrin saturation appears to be good prognostic markers of diseases severity but serum iron at cut off of >35.23 µmol/L better classified individuals of severe form of psychiatric disorder.

Keyword: Iron saturation indices, psychiatric disorders, iron metabolism, prognostic marker, Ghana

INTRODUCTION

Psychiatric disorders, as defined by Solmi et al. (2023), encompass conditions affecting temperament, emotions, and cognitive processes, posing significant challenges to individuals' learning capabilities and roles within families, careers, and society. Globally, psychiatric disorders are a significant public health concern. According to the World Health Organization (WHO), approximately 1 in 4 people worldwide will experience a mental or neurological disorder at some point in their lives. Depression, anxiety disorders, schizophrenia, bipolar disorder, and substance use disorders are among common types of psychiatric disorders(WHO, 2022). According to the Ghana Health Service, mental disorders are estimated to affect about 10% of the population(Michael & Emmanuel, 2020). In Ghana, like many low- and middle-income countries, psychiatric disorders pose a considerable and the record of persons affected may not capture the full extent of mental health challenges in Ghana, as many cases may go undiagnosed or untreated. Various challenges including limited resources, inadequate mental health infrastructure, and social stigma have been identified causes of this problem. Significant gaps remain in the provision of mental health care, exacerbating the impact of psychiatric disorders on individuals, families, and communities in the country(Meghrajani et al., 2023; WHO, 2022).

Psychiatric disorders involving iron metabolism are complex conditions with multifaceted pathophysiological mechanisms. Research suggests that iron dysregulation may play a significant role in the development and progression of these disorders(David, Jhelum, Ryan, Jeong, & Kroner, 2022). While past studies focused on brain region abnormalities, contemporary research links psychiatric disorders to deficiencies in synaptic plasticity and neural connectivity. Notably, investigations over the past decade underscore the role of myelin dysfunction and corresponding white matter alterations in impeding neuronal communication, leading to a spectrum of sensory, motor, cognitive, and affective symptoms(Stephan, Baldeweg, & Friston, 2006). Furthermore, alterations in serotonin, dopamine, and glutamatergic neurotransmission have been identified as pivotal factors in schizophrenia, depression, and cognitive disorders(Pehrson & Sanchez, 2014).

Iron is essential for various neurobiological processes, including neurotransmitter synthesis, myelination, and mitochondrial function. Serum iron imbalance has emerged as a significant factor in the pathophysiology of various psychiatric disorders, potentially exacerbating symptoms and complicating treatment strategies(Rossetti, Paladini, Riva, & Molteni, 2020). While the focus on serum iron profile levels have traditionally been in contexts such as anemia or hemochromatosis, emerging research suggests its role in psychiatric health cannot be overlooked. Disturbances in iron homeostasis have been implicated in conditions like depression, schizophrenia, and bipolar disorder impacting neurotransmitter function. Iron deficiency or excess has can disrupt these crucial processes such neurotransmitter synthesis, myelination, and mitochondrial function, leading to neuronal damage, oxidative stress pathways, and neurotransmitter imbalances, contributing to the manifestation of psychiatric symptoms. (Mandal et al., 2022). Furthermore, emerging evidence suggests a bidirectional relationship between iron dysregulation and psychiatric symptoms, where psychiatric disorders may exacerbate iron abnormalities, and vice versa(Levi, Ripamonti, Moro, & Cozzi, 2024). Understanding the intricate interplay between iron metabolism and psychiatric pathology holds promise for developing novel therapeutic strategies targeting this pathway. Moreover, disparities in healthcare access and resources, may contribute to underdiagnosis and undertreatment of iron-related psychiatric manifestations, particularly in low and middle-income countries where comprehensive healthcare infrastructure may be lacking. Understanding and addressing serum iron imbalances within the context of psychiatric disorders hold promise for improving clinical outcomes and reducing the global burden of mental illness.

Globally and in Ghana, mental health disorders like anxiety, schizophrenia and depression among others pose a significant burden, sparking interest in exploring modifiable factors such as iron metabolism to enhance patient outcomes. Research is needed to understand the precise link between iron saturation indices and mental health symptoms. Valid iron-related biomarkers could improve diagnosis accuracy and treatment monitoring, particularly in the context of personalized treatment plans considering individual characteristics like gender, age, and genetic susceptibility. Additionally, the complex relationship between alcohol consumption, psychiatric disorders, and iron metabolism warrants further investigation for the development of targeted therapies. Addressing these research gaps not only advances understanding but also holds the potential to improve diagnostic tools, treatment options, and preventative measures for individuals struggling with mental illness in Ghana and globally. Hence, this study aims to determine the relationships between iron metabolism and psychiatric disorder and whether iron saturation indices could predict disease severity.

MATERIALS AND METHODS

Study design

This was an unmatched case-control study design conducted between December 2020 to March 2022. The study was a multi-centre study conducted at the Ankaful Psychiatric

Hospital in Cape Coast, Central Region and the Psychiatric Unit of the Korle Bu Teaching Hospital, Greater Accra Region, Ghana.

Ethics and human subject issues

This study was approved by the Institutional Ethics and Review Board of University for Development Studies (Number: UDS/RB/008/20). The study was thus performed following the standards laid down protocol in the 1964 Helsinki Declaration. Informed consent was obtained from all apparently healthy participants and caregivers of those with psychiatric disorders. Participation was voluntary, information obtained was strictly confidential to the researchers only and participants were kept anonymous.

Study participants and sample size

Using the Kelsey's formula (Kelsey, 1996), the minimum number of participants required for establishing desired statistical power (alpha < 0.05) was 25 for the case-control study. However, the study employed 180 with a ratio of 1:3. The total study participants comprised of 137 psychiatric disorder cases and 43 apparently healthy controls. The controls, 50 apparently healthy blood donors, were selected from Korle-Bu Teaching Hospital Central Laboratory and Blood Donor Unit were recruited as contols, however, 7 refused to consent, hence were excluded, reducing the number to 43 participants.

Psychiatric disorder was defined as a psychosocial disorder of the brain due to dysfunctional feelings, thoughts, and behaviour in a person that is not a part or normal development or culture but a disability or distress (WHO, 2022).

Data collection

Information on the demographic characteristics (such as; sex, age, material status, medication uses, etc) and clinical history of psychiatric patients were retrieved from patients' folders. Staging the severity psychiatric disorder into mild and severe was done by a qualified psychiatrist. A semi-structured self-designed questionnaire were administered to cases and controls to collect the demographic characteristics.

Serum separator and EDTA anticoagulated vacutainers were both labelled with participants' unique identifying code, and about 6 ml of venous blood sample was drawn from the antecubital fossa; 3 ml of the blood sample was dispensed in the EDTA tube and 3 ml into the serum separator tube. The blood samples in the Serum separator tube were allowed to clot before centrifugation. Serum was aliquoted in duplicates and stored at -20^{o}C until analysis.

A complete blood count (CBC) analysis was performed on blood samples in the EDTA tube within an hour of sample collection using a 5-part automated haematology analyzer (Sysmex America, Inc, 577 Aptakisic Road, Lincolnshire, IL 60069).

Biochemical assays such as lipid profile, renal function test (RFT), and liver function test (LFT) was carried out on the serum samples. Serum iron was measured on VITROS 5,1 FS analyzer, clinical chemistry system that combines dry and wet methods on one platform.

Serum ferritin was measured on the VITROS 5,1 FS analyzer based on the sandwich principle with a total duration time of 18 minutes. The assay uses a ferritin-specific antibody and a labelled ferritin-specific antibody to form a sandwich complex with the sample.

Serum TIBC (total iron-binding capacity) was measured on the VITROS 5,1 FS analyzer which assess the blood's ability to bind iron with transferrin. The principle of the serum TIBC measurement is based on the Unsaturated Iron Binding Capacity (UIBC) method, which involves saturating the available binding sites on serum transferrin with a known ferrous iron standard and measuring the excess iron by a colorimetric reaction.

The levels of transferrin were estimation using Vernet and Doyen (2000) and Gambino et al. (1997) formulae. This was calculated from serum total iron binding capacity by a factor of 25.1.

Transferrin (g/L) = $\frac{1}{25.1}\,Total\ Iron\ Binding\ Capacity\ (\frac{\mu mol}{L})$

Statistical analysis

Data was entered into Microsoft excel worksheet version 2019 (www.microsoft.com). Data were analysed using SPSS version 25 (www.ibm.com) and graphs were presented using GraphPad prism version 6.0 (www.graphpad.com). The Kolmogorov-Smirnov test was performed to check for normality and outliers. Categorical data was presented as frequency, percent and charts and compared using Chi-square test and/or Fischer's exact test. Quantitative data was presented as mean and standard deviations for normally distributed data, and median and interquartile ranges for data that was not normally distributed. Independent sample t-test was used to compare means between parametric data while Kruskal-Wallis statistics was used to compare non-parametric data. One-way analysis of variance (ANOVA) and Turkey post hoc test was used to compare three or more means. Receiver operating characteristics (ROC) curves was performed to determine sensitivity and specificity of various diagnostic markers. Statistical significance was considered at $p < 0.05$ at 95% confidence interval of the difference

RESULTS

Socio-demographic characteristic of respondents

One hundred and eighty (180) participants took part in this study which comprised 137 (76.1%) with psychiatric disorder cases and 43 (23.9%) apparently healthy controls. The mean age of subjects in the case group was 36.63 ± 12.30 years while that of the control group was 40.42 ± 10.09 years. More of the study participants were females; 51.8% vrs 51.2% for cases verses controls. A higher proportion of the study participants in the case group (23.4%) consumed alcoholic beverages compared with the controls (7.0%) with those who self-reported alcohol intake within the last 7 days (16.1%) being significantly higher (p = 0.005) in the case group than the controls (0.0%) (Table 1).

Table.1: Comparison of sociodemographic characteristics of study groups (*N* = 180)

Variable	Control (n=43)	Cases (n=137)	p-value
Age (years)	40.42±10.09	36.63±12.30	0.118
Gender			
Female	22(51.2%)	71(51.8%)	0.940
Male	21(48.8%)	66(48.2%)	
Sickling Status			
Negative	39(90.7%)	110(80.3%)	0.115
Positive	4(9.3%)	27(19.7%)	
Alcoholic Intake			
No	40(93.0%)	105(76.6%)	0.018
Yes	3(7.0%)	32(23.4%)	
Alcohol intake (last 7 days)			
No	43(100%)	115(83.9%)	0.005
Yes	0(0%)	22(16.1%)	
Regular Alcohol (last 6 months)			
No	41(95.3%)	118(86.1%)	0.100
Yes	2(4.7%)	19(13.9%)	

Data is presented as proportions and percent. Categorial variables were compared using Chi-square test or Fisher's exact test where frequencies were < 5. P-value < 0.05 considered statistically significant

Anthropometric measurements, iron status and liver enzymes among study participants

Iron status, liver enzymes and anthropometric indices of study participants stratified by psychiatric disorders are summarized in Table 2. Serum iron, ferritin and transferrin saturation were significantly higher among subjects with psychiatric disorders (cases) (38.98±14.55 µmol/L, p <0.001; 100.23±84.98 ng/mL, p = 0.041 and 44.35±14.6 %, p <0.001) compared with the controls (29.25±8.0 µmol/L; 75.25±42.71 ng/mL and 28.66±7.1 %). However, as indicated in Table 2, total iron binding capacity (TIBC), UIBC and transferrin levels were considerably greater in control group (102.47±15.01 µmol/L, p = 0.037; 73.22±13.12 µmol/L, p <0.001 and 4.08±0.6 g/L, p = 0.037) than in the case subjects (88.95±19.73 µmol/L; 49.97±18.32 µmol/L and 3.54±0.79 g/L) respectively.

MCHC levels was higher in the case group (35.18±1.09 g/dL) compared with the control group (34.07±1.55 g/dL) while Mean platelets volume (MPV) was significantly raised in the control group (9.55±0.58 fL, p <0.001) compared with the cases (7.59±3.4 fL) (Table 2).

Table 2. Comparison of Anthropometric indices, Iron status and liver enzymes among study group

Variable	Control (n=43)	Cases (n=137)	p-value
Weight (Kg)	73.34±12.21	63.87±13	0.678
Height (m)	1.65±0.09	1.66±0.1	0.387
WC (cm)	83.91±8.21	82.05±11.05	0.068
BMI (kg/m^2)	27.29±5.26	23.08±4.4	0.166
IRON (µmol/L)	29.25±8.0	38.98±14.55	<0.001
TIBC (µmol/L)	102.47±15.01	88.95±19.73	0.037
UIBC (µmol/L)	73.22±13.12	49.97±18.32	<0.001
Ferritin (ng/mL)	75.25±42.71	100.23±84.98	0.041
Transferrin (g/L)	4.08±0.6	3.54±0.79	0.037
Transferrin saturation (%)	28.66±7.1	44.35±14.6	<0.001
WBC (109/L)	6.29±1.52	5.82±1.52	0.847
RBC (1012/L)	4.74±0.51	4.63±0.65	0.115
Hb (g/dL)	14.15±1.88	14.09±1.9	0.550
HCT (%)	41.56±4.65	40.55±4.91	0.585
MCV (fL)	88.72±5.65	88.46±4.7	0.394
MCH (pg)	30.14±2.36	31.09±2.2	0.681
MCHC (g/dL)	34.07±1.55	35.18±1.09	0.008
Platelets (109/L)	229.05±62.09	214.38±72.64	0.652
MPV (fL)	9.55±0.58	7.59±3.4	<0.001
AST (IU/L)	20.23±6.67	26.26±13.45	0.087
ALT (IU/L)	17.33±9.37	17.96±8.26	0.988

Data presented as mean ± standard deviation. Continuous variables compared using unpaired student T-test and *P-value < 0.05 considered statistically significant.*

Distribution of anthropometric measurement and iron indices among study participants

The proportions of anthropometric measurements, red cell indices and iron profile stratified by psychiatric disorder are shown in Table 3. The proportion of subjects in the case group who were underweight (12.4%, $p < 0.001$) were considerably more than the proportions in the control group (0%). However, the proportions of obese and/or overweight were more in the controls (27.9% and 32.6%) compared with case group (8.8% and 19.0%).

For the iron studies, the proportion of subjects with increased serum iron and TSAT were significantly higher in group with psychiatric disorder (70.1%, $p < 0.001$ and 32.8%, $p < 0.001$) compared with normal controls (34.9% and 0%). However, the proportion of subjects withincreasedmean values of TIBC, UIBC and serum transferrin were significantly higher in the control group (90.7%, $p = 0.002$; 79.1%, $p < 0.001$ and 86.0%, $p < 0.001$) compared with case group (65.7%, 23.4%, 51.1% respectively) (Table 3).

Table 3: Distribution of anthropometric measurement, red cell indices and iron profile stratified by psychiatric disorder

Variable	Control (n=43)	Cases (n=137)	p-value
Waist circumference			
Normal	26(60.5%)	96(70.1%)	0.240
Obese	17(39.5%)	41(29.9%)	
BMI			
Normal	17(39.5%)	82(59.9%)	<0.001
Obese	12(27.9%)	12(8.8%)	
Overweight	14(32.6%)	26(19.0%)	
Underweight	0(0%)	17(12.4%)	
Serum Iron			
High	15(34.9%)	96(70.1%)	<0.001
Normal	28(65.1%)	41(29.9%)	
TIBC			
High	39(90.7%)	90(65.7%)	0.002
Normal	4(9.3%)	47(34.3%)	
UIBC			
High	34(79.1%)	32(23.4%)	<0.001
Normal	9(20.9%)	105(76.6%)	
Serum Ferritin			
High	0(0%)	9(6.6%)	0.085
Normal	43(100%)	128(93.4%)	
Serum Transferrin			
High	37(86.0%)	70(51.1%)	<0.001
Normal	6(14.0%)	67(48.9%)	
TSAT			
High	0(0%)	45(32.8%)	<0.001
Normal	43(100%)	92(67.2%)	
Hb			
Low	10(23.3%)	27(19.7%)	0.615
Normal	33(76.7%)	110(80.3%)	
MCV			
Low	2(4.7%)	3(2.2%)	0.392
Normal	41(95.3%)	134(97.8%)	

Data is presented as proportions and percent. Categorial variables were compared using Chi-square test or Fisher's exact test where frequencies were < 5. P-value < 0.05 considered statistically significant

Determinants of psychiatric disorders

The impact of various parameters on the occurrence of psychiatric disorders are shown in table 4. Being male (OR=3.23, p<0.001), lower BMI (OR=0.84, p<0.001), high levels of serum Iron (OR=1.08, p<0.001) and TSAT (OR=1.16, p<0.001) and low levels of TIBC (OR=0.96, p<0.001), UIBC (OR=0.92, p<0.001) and transferrin (OR=0.37, p<0.001) as well as alcohol intake (OR=4.06, p=0.026) were found to be significantly associated with the occurrence of psychiatric disorders. After adjusting for confounding factors however, being male was associated with a 6 times risk (aOR=5.87, p<0.005) of having a mental disorder whiles a unit increase in BMI (aOR=1.27, p<0.001) was associated with an increased risk of psychiatric disorder.

Table 4: Association between selected variables and the occurrence of mental health disorders

Variable	OR (CI)	P value	aOR (CI)	p-value
Sex				
Female	Ref.	-	-	-
Male	3.23 (0.49-1.93)	<0.001	5.87(1.72-20.04)	0.005
Age (Years)	0.97 (0.95-1.00)	0.070	1.00(0.95-1.04)	0.806
BMI (Kg/m^2)	0.84 (0.78-0.91)	<0.001	1.27(1.12-1.43)	<0.001
Iron (µmol/L)	1.08 (1.04-1.12)	<0.001	0.73(0.52-1.03)	0.072
TIBC (µmol/L)	0.96 (0.94-0.98)	<0.001	2.36(0.00-28.00)	0.857
UIBC (µmol/L)	0.92 (0.89-0.94)	<0.001	-	-
Ferritin (ng/mL)	1.01 (1.00-1.01)	0.065	0.99(0.98-1.001)	0.073
Transferrin (g/L)	0.37 (0.22-0.62)	<0.001	-	-
TSAT (%)	1.16 (1.09-1.22)	<0.001	1.15(0.85-1.57)	0.363
Alcohol Intake				
No	Ref.	-	-	-
Yes	4.06 (1.18-14.02)	0.026	0.26(0.04-1.57)	0.143

Receiver operator characteristics (ROC) for iron parameters in predicting mental health disorders

The ROC curves and the Area Under the Curves (AUC) showing the predictive abilities of the various iron metabolism indices in predicting psychiatric disorders are shown in figure 1 whiles their respective cut offs for classification of mental health disorders are shown in table 5. With the exception of ferritin levels, all other parameters significantly classified subjects as either having psychiatric disorders or not. However, at a cut off of ≤65.79 µmol/L (AUC=0.844, p<0.001), UIBC better classified individuals as having psychiatric disorders.

Table 5: Cutoffs, Sensitivities and specificities of Iron parameters in predicting mental health disorders

Variable	Youden Index	Cut off	Sensitivity	Specificity
Iron (µmol/L)	0.42	>33.87	58.39	83.72
TIBC (µmol/L)	0.36	≤91.26	51.82	83.72
UIBC (µmol/L)	0.58	≤65.79	76.64	81.40
Ferritin (ng/mL)	0.21	>78.30	53.28	67.44
Transferrin (g/L)	0.36	≤3.64	51.82	83.72

TSAT (%)	0.52	>38.39	59.12	93.02

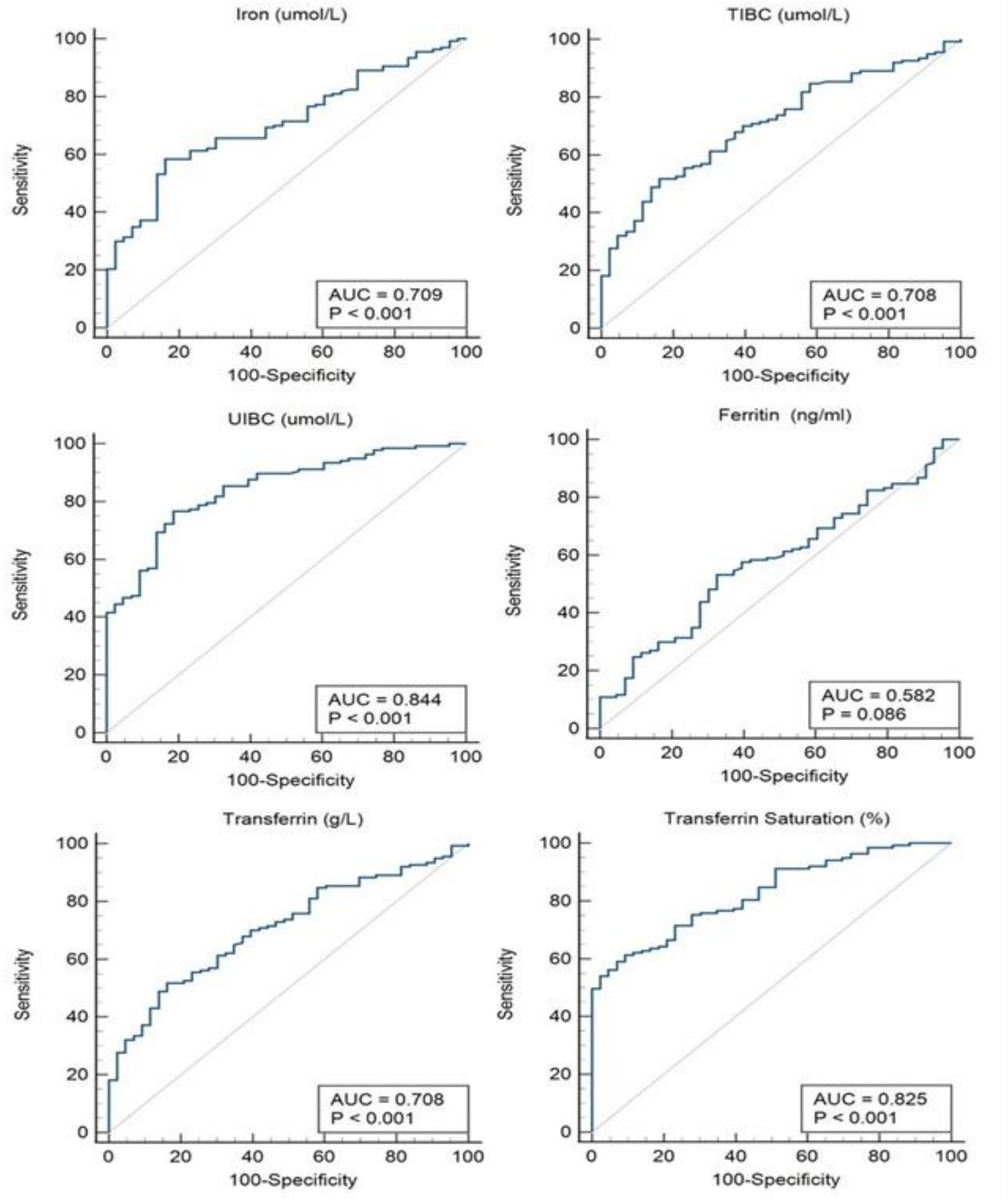

Figure 1: ROC curves for Iron parameters for predicting mental health disorders

Distribution of sociodemographic characteristics stratified by severity of psychiatric disorder

Table 6 shows the proportions of sociodemographic characteristics of respondents stratified by severity of psychiatric disorder. The majority of the subjects with severe form of psychiatric disorders were on alcohol within the last 7 days (20.5%) of data collection compared with 14 percent of mild cases and this was statistically significant (p = 0.011) (Table 4.7).

Table 6: Sociodemographic characteristics of respondents stratified by severity of psychiatric disorder

Variable	Control (n=43)	Mild (n=93)	Severe (n=44)	p-value
Gender				
Female	22(51.2%)	53(57%)	18(40.9%)	0.212
Male	21(48.8%)	40(43%)	26(59.1%)	
Alcoholic Intake				
No	40(93.0%)	72(77.4%)	33(75%)	0.057
Yes	3(7.0%)	21(22.6%)	11(25%)	
Alcohol intake (last 7 days)				
No	43(100%)	80(86%)	35(79.5%)	0.011
Yes	0(0%)	13(14%)	9(20.5%)	
Regular Alcohol (last 6 months)				
No	41(95.3%)	80(86%)	38(86.4%)	0.259
Yes	2(4.7%)	13(14%)	6(13.6%)	

Data is presented as proportions and percent. Categorial variables were compared using Chi-square for trend. P-value < 0.05 considered statistically significant

Demographics, iron indices, liver enzymes stratified by severity of psychiatric disorder

One-way Analysis of Variance (ANOVA) was run with severity scored as the independent variable and participants demographics, iron studies and liver enzymes as dependent variable. Results from the ANOVA with a Greenhouse-Geisser correction showed that the means for age, BMI, serum iron, TIBC, UIBC, transferrin, transferrin saturation and AST were significantly different (p <0.05) between the severity stratification. The Turkey HSD Post hoc analysis shows that the mean concentration of serum iron and transferrin saturation differ significantly across the stratifications with increased levels in severe psychiatric disorders (44.89±15.69 µmol/L vrs 49.65±15.23%) compared with mild (36.19±13.16 µmol/L vrs 41.85±13.6%) and the apparently healthy controls (29.25±8 µmol/L vrs 28.66±7.05%). Further, the mean concentrations of BMI, TIBC, UIBC and transferrin differ significantly between controls verses mild and controls verses severe with increased levels in the control group compared with the other strata. Again, the mean concentrations of AST are significantly raised in severe psychiatric disorder (27.57±16.1, p = 0.017) compared with the controls (20.23±6.67) as shown in Table 7.

Table 7: ANOVA and post-hoc comparison of participant demographics, iron studies and liver enzymes stratified by severity of psychiatric disorders

Variable	Control[a]	Mild[b]	Severe[c]	ANOVA	aVb	aVc	bVc
Age (Years)	40.42±10.09	37.78±12.36	34.18±11.92	0.047	0.678	0.043	0.287
Weight (Kg)	73.34±12.21	64.42±13.44	62.73±12.07	<0.001	<0.001	<0.001	0.93
Height (m)	1.65±0.09	1.66±0.08	1.68±0.12	0.252	0.953	0.315	0.661
WC (cm)	83.91±8.21	83.01±11.84	80.01±8.94	0.175	0.861	0.248	0.350
BMI (kg/m^2)	27.29±5.26	23.46±4.6	22.29±3.77	<0.001	<0.00	<0.00	0.495

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Iron (µmol/L)	29.25±8	36.19±13.16	44.89±15.69	<0.001	0.012	<0.001	<0.001
TIBC (µmol/L)	102.47±15.01	87.54±19.07	91.93±20.96	<0.001	<0.001	0.028	0.604
UIBC (µmol/L)	73.22±13.12	51.36±17.44	47.04±19.95	<0.001	<0.001	<0.001	0.515
Ferritin (ng/mL)	75.25±42.71	94.97±68.53	111.35±102.28	0.094	0.501	0.091	0.741
Transferrin (g/L)	4.08±0.6	3.49±0.76	3.66±0.83	<0.001	<0.001	0.028	0.600
TSAT (%)	28.66±7.05	41.85±13.6	49.65±15.23	<0.001	<0.001	<0.001	0.003
AST (IU/L)	20.23±6.67	25.65±12.04	27.57±16.1	0.014	0.052	0.017	0.925
ALT (IU/L)	17.33±9.37	17.91±8.55	18.05±7.71	0.912	0.955	0.936	0.904

The mean difference is significant at <0.05 level

Receiver operator characteristics (ROC) for iron parameters in predicting severity of psychiatric disorders

The ROC curves and the Area Under the Curves (AUC) showing the predictive abilities of the various iron metabolism indices in differentiating mild from severe mental health disorders are shown in figure 2 whiles their respective cut offs for classification of severity of mental health disorders are shown in table 8. Only serum iron concentration and TSAT levels significantly classified subjects as either having severe mental health disorders or not. However, at a cut off of >35.23 µmol/L (AUC=0.677, p<0.001), serum iron better classified individuals as having severe mental disorders.

Table 8: Cutoffs, Sensitivities and specificities of Iron parameters in predicting severity mental health disorders.

Variable	Youden Index	Cut off	Sensitivity	Specificity
Iron (µmol/L)	0.31	>35.23	75.00	55.91
TIBC (µmol/L)	0.22	>95.98	50.00	72.04
UIBC (µmol/L)	0.26	≤40.78	56.82	68.82
Ferritin (ng/mL)	0.13	>83.20	59.09	53.76
Transferrin (g/L)	0.22	>3.82	50.00	72.04
TSAT (%)	0.26	>36.57	79.55	46.24

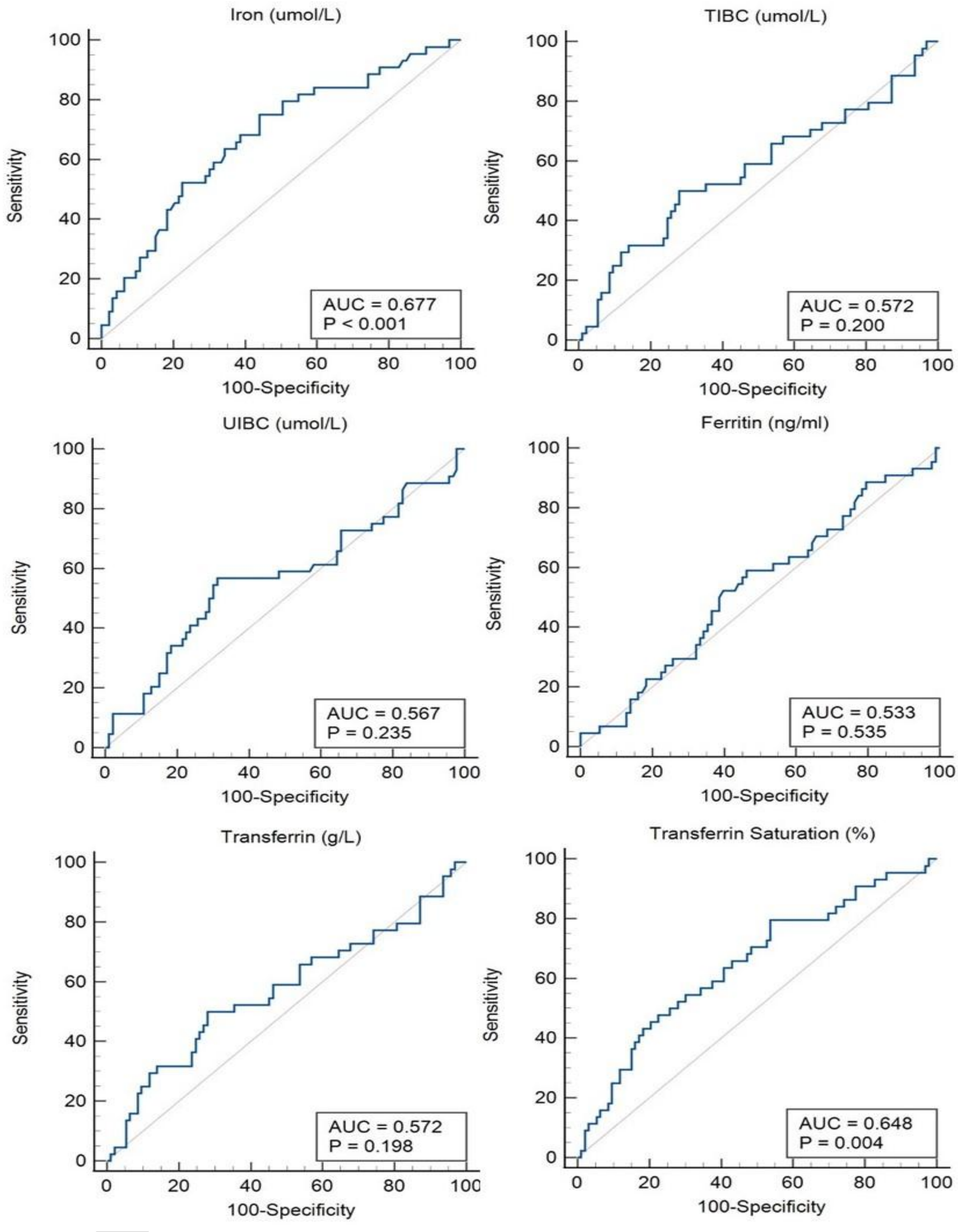

Figure 2: ROC curves for Iron parameters for predicting severity of mental health disorders

DISCUSSION

The physiology of the brain depends to some extent on iron, which is involved in the transport of oxygen, the creation of myelin, DNA, and neurotransmitters, as well as energy production. The hypothesis was to determine whether iron saturation indices play a role in the pathophysiology of psychiatric disorders or was just a marker that increases psychiatric disorder compared to non-psychiatric disorders. The findings of this present study revealed a higher concentration of serum iron, TSAT as well as serum ferritin levels among those with psychiatric disorders compared with the controls. This agrees with findings by Owiredu et al. (2019) who conducted a similar study among schizophrenia patients in Kumasi, Ghana. In addition, a significantly lower TIBC and UIBC was observed among cases compared to controls and this was consistent with finding of Ikeda (2001) who also observed a similar trend among epileptics compared to controls. The above marker/findings are pointers to iron overload,although ferro-differentiation requires a certain amount of iron, iron overload in the brain aggravates neurological disease by producing reactive oxygen species (ROS) and destroying brain cells, which results in a variety of mental health disorders (Gao, You, Zhang, Chang, & Yu, 2023).

Psychotropic medication use can further raise the risk of physical problems or consequences, even though people with mental illnesses typically have worse physical health outcomes. Individuals with psychiatric or mental illnesses are more likely to be overweight or obese than the general population. Obesity and mental health conditions have a reciprocal association. A study by Correll, Detraux, De Lepeleire, and De Hert (2015) indicated that people with schizophrenia have a 2.8–4.4 times increased risk of obesity, while those with major depression or bipolar disease have a 1.2–1.7fold increased risk. In contrast, prior research by Correll et al. (2015) has identified weight gain and increased BMI as a well-known side effect of antipsychotics used in the acute and maintenance treatment of patients with schizophrenia and other psychiatric illnesses. The outcome of this present study revealed that one unit increase in BMI is associated with 1.27 times risk of developing psychiatric disorders; therefore, higher BMI is associated with higher risk of developing psychiatric disorders. The findings of clinical and animal trials point to increased food intake and appetite as well as delayed satiety signaling as important behavioral changes that underlie antipsychotic-induced weight gain and obesity. Also, it seems that weight gain brought on by antipsychotics is related to antagonistic interactions at 5-HT2C and H1 receptors.

Clinical observations and biological pathways have linked obesity to psychiatric disorders. It was reported that patients who are diagnosed with obesity may exhibit a persistent increase in the likelihood of receiving a psychiatric co-diagnosis; a study by Leutner et al. (2023) identified obesity as a relevant risk factor for receiving additional psychiatric diagnoses. Increased neuroinflammation resulting from cytokine production in adipocytes was found to be one of the biological pathways linking obesity to psychiatric disorders, according to a study by (Karczewski et al., 2018). High fat content was also shown to increase inflammation and have a negative impact on neurotrophic factors and the gut microbiome, both of which are linked to obesity and psychiatric issues. In addition to the previously listed factors, Darwish, Beroncal, Sison, and Swardfager (2018) suggested that the disease load of chronic metabolic disorders may act as a mediator in the transition from obesity to psychiatric disorders.

When it comes to explaining the variations in psychiatric risk susceptibility, gender is a major factor. Women are more likely than men to develop psychiatric issues, with young women particularly at risk (Gulland, 2016). A different study by Pedersen et al. (2014) revealed that women have a significantly higher lifetime risk of most mood disorders and all anxiety disorders than men, despite the fact that men are three times more likely than women to depend on alcohol and report drug use.

The current study found that serum iron, TIBC, UIBC, transferrin and transferrin saturation can be used to predict psychiatric disorder but UIBC with a cut-off of ≤65.79 μmol/L can better distinguish psychiatric disorders from non-psychiatric disorders. This shows that UIBC could be used as a diagnostic marker for psychiatric disorders. However, a study by Munkholm, Jacoby, Vinberg, and Kessing (2023) found ferritin as a diagnostic disease marker for bipolar disorder, it was found that elevated ferritin levels were found in depressed states. Again, iron metabolism linked to inflammation and oxidative stress through a previous study by Rowland et al (2015a) found that elevated levels of markers of inflammation was associated with elevated ferritin levels.

Furthermore, the study also determined the relationship between iron saturation indices and the severity of psychiatric disorders. Iron metabolism has been hypothesized to play an important role in neurologic development and function. According to Kim and Wessling-Resnick (2014), changes in brain iron metabolism affect behavior, learning/memory capacity, emotional and psychological problems. Although the mechanism involved between iron metabolism and emotional behavior are multifactorial; regulation of mood (Youdim & Green, 1978), anxiety (Hill, 1985) and neuronal activity (Batra & Seth, 2002) are controlled by neurotransmitters homeostasis (that is; GABA and monoamines). Thus, severity of a psychiatric disorder maybe strongly affected by brain iron levels.

In this study, serum iron and transferrin saturation increased with severity of psychiatric disorder. Studies have shown that the pathogenesis of neurodegenerative disorder is due to excess iron in the brain (Bartzokis et al., 1999; Connor & Lee, 2006; Nandar & Connor, 2011; Rouault & Cooperman, 2006). Increase iron levels implies increased ROS which attack and damage cells and tissues (Tuomainen et al., 2007). In animal models, a study conducted by Maaroufi et al. (2009) showed that anxious and aggressive response were observed when adult rats were administered with iron through daily intraperitoneal injection over the study period. Thus, iron overload alters mood and anxiety-like behaviors (Maaroufi et al., 2009). This may imply that increased iron levels in the brain can result in increased severity of psychiatric disorder. Remember that ferrtin is used as the proxy for tissue levels of iron.

Alcohol abuse was found to be associated with increased severity of psychiatric disorder as it was indicated by high proportion (20.5%) of those who were recently (last 7 days) on alcohol had severe form of psychiatric disorder. This finding agrees with Berglund and Ojehagen (1998) who reported that psychiatric disorders worsens with alcohol abuse. Heavy drinking coexists with several different forms of psychiatric disorders and when they co-occur, maintaining abstinence becomes more difficult among patient (Kessler et al., 1997; Modesto-Lowe & Kranzler, 1999; Shivani, Goldsmith, & Anthenelli, 2002). This can lead to alcohol abuse which increases the severity of the condition and/or verse vice.

Chronic alcoholism impaired brain function by altering hormonal and various neurotransmitters involved in mood and anxiety disorders (Koob, 2000). Thus, alcohol abuse is common among patients with severe form of mental disorders. Severity of disorder may vary depending on the how recently alcohol was consumed, the amount consumed, how long it was used, or the vulnerability of the individual experiencing the psychiatric disorder (Anthenelli, 1997).

Clinical staging is a form of diagnosis that defines the extent of progression of a disease. In psychotic disorders, a common model used in staging is based on duration and relapse criteria rather than the impact or the anatomical extent (Drożdżowicz, 2020). McGorry and colleagues proposed clinical features such as sign and symptoms, and objective measure that joins them to psychopathology (P. McGorry & Van Os, 2013; P. D. McGorry, Hickie, Yung, Pantelis, & Jackson, 2006; P. D. McGorry, Nelson, Goldstone, & Yung, 2010). On staging of psychiatric disorder as mild and/or severe, the study found that serum iron and transferrin saturation (TSAT) were good prognostic markers for severity of psychiatric disorders and at a cut off of >35.23 µmol/L, serum iron better classified individuals as having severe psychiatric disorders. This shows that, serum iron can be used as a prognostic marker to classify severe psychiatric disorders in addition to the aforementioned clinical sign and symptoms.

CONCLUSION

The study sheds light on the relationship between iron saturation indices and psychiatric disorders. Iron overload was found to be associated with psychiatric disorders. Risk factors include persons born males and increase body mass index. Serum iron, TIBC, UIBC, transferrin and transferrin saturation are diagnostic markersof psychiatric disorders but at a cut off of ≤65.79 µmol/L, UIBC can distinguish psychiatric disorders from healthy individuals. Alcohol abuse and iron overload were associated with severity of psychiatric disorders. Serum iron and transferrin saturation were good prognostic markers for severity of psychiatric disorders and at cut off of >35.23 µmol/L, serum iron better classified individuals as having severe psychiatric disorders.

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