ANTHROPOMETRIC MEASUREMENTS PREDICT LIVER STEATOSIS IN SCHIZOPHRENIC PATIENTS.

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Abstract

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Objectives
Schizophrenic patients present higher all-cause mortality when compared to the general population, which could be associated with an unhealthy lifestyle resulting in a high prevalence of metabolic syndrome in these patients. Noteworthy, the metabolic effects of an unhealthy lifestyle associated with antipsychotic drugs are risk factors for non-alcoholic fatty liver disease development. Hence, the objective of this study was to investigate the presence of steatosis in schizophrenic patients under psychiatric treatment and its possible predictors.

Method
Observational study of 30 institutionalized schizophrenic patients. Confirmation of steatosis was obtained by abdominal ultrasound evaluation. Body composition and phase angle were obtained by bioelectrical impedance. Anthropometric assessment and hand-grip strength tests were also performed.

Results
A total of eleven patients (36.7 %) had diagnostic of steatosis. Most of the patients (56.6%) were treated using between three to five drugs, and predominantly were using anti-psychotics (100%). The association between body mass index and the presence of steatosis was significant. Steatosis patients had significantly higher body mass index (p = 0.006), abdominal perimeter (p = 0.012), arm perimeter (p = 0.006), and adductor pollicis muscle (p = 0.014). No differences in hand grip strength and other anthropometric characteristics were found.

Conclusion
This study shows a prevalence of hepatic steatosis of 36.7% in patients with schizophrenia which was associated with body mass index. In addition, abdominal perimeter, arm perimeter, adductor pollicis muscle, and BMI were significant predictors for the presence of steatosis. Future multicentric studies could expand our results, which are important especially for the south american population, where data is still scarce.

Keywords: hepatic diseases; non-alcoholic fatty liver disease, mental health; malnutrition..

Palavras-Chave: Hepatopatias; Hepatopatia Gordurosa não Alcoólica; Saúde Mental; Desnutrição

Resumo

MEDIDAS ANTROPOMÉTRICAS PREDIZEM ESTEATOSE HEPÁTICA EM PACIENTES ESQUIZOFRÊNICOS

Objetivo
Pacientes esquizofrênicos apresentam maior mortalidade por todas as causas quando comparados à população geral, o que pode estar associado a um estilo de vida pouco saudável, resultando em uma alta prevalência de síndrome metabólica nesses pacientes. Digno de nota, os efeitos metabólicos de um estilo de vida pouco saudável associado a drogas antipsicóticas são fatores de risco para o desenvolvimento de doença hepática gordurosa não alcoólica. Assim, o objetivo deste estudo foi investigar a presença de esteatose em pacientes esquizofrênicos sob tratamento psiquiátrico e seus possíveis preditores.

Métodos
Estudo observacional de 30 pacientes esquizofrênicos institucionalizados. A confirmação da esteatose foi obtida pela avaliação ultrassonográfica abdominal. A composição corporal e o ângulo de fase foram obtidos por impedância bioelétrica. Também foram realizados testes antropométricos e de força de preensão manual.

Resultados
Um total de onze pacientes (36,7%) apresentaram diagnóstico de esteatose. A maioria dos pacientes (56,6%) foi tratada usando entre três a cinco drogas, e predominantemente estavam em uso de antipsicóticos (100%). A associação entre o índice de massa corporal e a presença de esteatose foi significativa. Os pacientes com esteatose apresentaram índice de massa corporal significativamente maior (p = 0,006), perímetro abdominal (p = 0,012), perímetro do braço (p = 0,006) e músculo adutor do polegar (p = 0,014). Não foram encontradas diferenças na força de preensão manual e outras características antropométricas.

Conclusão
Este estudo mostra uma prevalência de esteatose hepática de 36,7% em pacientes com esquizofrenia que foi associada ao índice de massa corporal. Além disso, o perímetro abdominal, o perímetro do braço, o músculo adutor do polegar e o IMC foram preditores significativos para a presença de esteatose. Futuros estudos multicêntricos poderiam ampliar nossos resultados, que são importantes especialmente para a população sul-americana, onde os dados ainda são escassos.

INTRODUCTION

Schizophrenia (SZ) is characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction. For a diagnosis, symptoms must have been present for six months and include at least one month of active symptoms [1]. The World Health Organization (WHO) highlights the recent global increase in the prevalence of mental disorders, including schizophrenia due to population growth and aging, leading to a special initiative to advance in policies and interventions to ensure quality of care for patients with impaired mental health conditions [2]. This epidemiologic approach aims to avoid the occurrence of these disorders, whilst reducing disease impacts, and mitigating further associated comorbidities [2].

Nevertheless, the considerable discrepancy of all-cause mortality between schizophrenic patients compared to the general population has worsened in recent decades. Hence, it is important to investigate all aspects of metabolic health, avoiding several associated comorbidities which could be related to behavioral changes of patients with mental disorders [3]. Furthermore, the associated behavioral disturbances in schizophrenia are associated with an unhealthy lifestyle due to inappropriate dietary intake and decreased physical activity levels resulting in a high prevalence of metabolic syndrome in these patients [4]. Also, the use of antipsychotic drugs is also associated with the development of several comorbidities such as obesity, hypertension, hyperlipidemia, and insulin resistance [5]. Noteworthy, the metabolic effects of an unhealthy lifestyle associated with antipsychotic drugs are risk factors for non-alcoholic fatty liver disease development [6].

Among liver diseases, Non-Alcoholic Fatty liver disease (NAFLD) is the second most common, characterized by the accumulation of triglycerides (TG) in liver cells, when this is not caused by alcohol consumption, hepatitis C infection, hereditary liver disease, or drug-induced liver disease [7]. Notably, NAFLD presents a wide spectrum, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) which can culminate in cirrhosis. Hepatic steatosis initially occurs when the liver metabolizes the excess of free fatty acids which leads to several mechanisms associated with hepatocyte damage and fibrosis such as oxidative stress, increased inflammatory mediators, and dysregulated apoptosis [8]. Hence, early detection of steatosis is pivotal to ensure appropriate treatment and improve the associated outcomes in schizophrenic patients, considering the increased risk and pharmacological treatments [9]. Nevertheless, to the best of our knowledge, only a few studies have aimed to analyze the prevalence of NAFLD in schizophrenic patients. The prevalence of NAFLD in young schizophrenic patients is higher than in the general population [10]. A recent robust observational study conducted in Chinese schizophrenic patients showed a prevalence of 22%, which is similar to the prevalence reported in a study in veterans with schizophrenia [11, 12]. Given together the links between schizophrenia, unhealthy lifestyle habits, metabolic risk, and NAFLD development, we aimed to investigate the presence of steatosis in schizophrenic patients under psychiatric treatment and its possible predictors.

METHODS

Population

This is an observational study, comprising a non-probabilistic sample of patients diagnosed with schizophrenia from AGAFAPE (Associação Gaúcha de Familiares de Pacientes Esquizofrênicos), located at Porto Alegre, Brazil. The sample was composed by convenience, including patients diagnosed with schizophrenia, with no sex or age restrictions, whose alcohol intake was limited to 40g/day, and which family signed an informed consent form allowing participation. Following the clinical evaluation, patients were divided in two groups: control (n = 19) and steatosis (n = 11).

Clinical Evaluation

All patients underwent the evaluation of steatosis performed by a qualified physician, using a standardized abdominal ultrasound [13]. Body composition (fat-free mas an fat max percentage) and phase angle (AF) were obtained by bioelectrical impedance (BIA), placing electrodes on the extremities of the body (hand, wrist, foot and ankle), using the Biodynamics® device, model 450 [14]. Using a plicometer (Cerscorf®) and anthropometric tape, the triceps skinfold thickness (TST), arm perimeter (AP), abdomen perimeter (ABP) and calf perimeter (CP) were obtained. Adductor pollicis muscle thickness was obtained with the Cerscorf® brand plicometer, exerting continuous pressure to pinch the adductor muscle at the apex of an imaginary triangle formed by the extension of the thumb and index finger of the patient's dominant hand, with three repetitions, using the average of measurements [15]. Also, the hand-grip strength was obtained with a mechanical grip dynamometer with an adjustable handle (Baseline® brand, model Smedley Spring) after three measurements separated by 30-second intervals. The result was the highest registered value [15].

Statistical analysis

Quantitative variables were described by the mean ± SD, and categorical variables by absolute and relative frequencies. Associations of categorical variables were assessed with the Chi-square test and intergroup comparisons were performed with the independent samples t-test. Also, logistic regressions were performed to evaluate the relationship of presence of steatosis with several predictive variables. The significance level adopted was 5% ($p \leq 0.05$) and the analyses were performed using the SPSS program version 22.0.

Ethical aspects

This study was approved by a local research ethics committee and registered at Plataforma Brasil (Registered Protocol number: 76641317.6.0000.5308) and was performed in accordance with the ethical standards of the 2000 Declaration of Helsinki and followed the guidelines for the publication of observational studies [16].

RESULTS

A total of thirty patients participated in the study, with a mean age of 43.13 and with a mean of 20 year of diagnostic confirmation of schizophrenia. A total of eleven patients (36.7 %) had diagnostic of steatosis. Most of the patients (56.6%) were treated using between 3 to 5 drugs, and all patients were using anti-psychotics

(100%). The association between the use of antipsychotics and the presence of steatosis tended towards significance (x2 = 5.562, p = 0.06; Likelihood Ratio = 6.481, p = 0.03; Cramer's V = 0.43, p = 0.62).

Table 1. Sample characteristics (n = 30)

		n	%
Sex	**Male**	21	70.0
	Female	9	30.0
Steatosis diagnostic	0	19	63.3
	1	11	36.7
Number of medications	1	3	10.0
	2	5	16.7
	3	7	23.3
	4	4	13.3
	5	6	20.0
	6	2	6.7
	7	2	6.7
	8	1	3.3
Antipsychotics	1	20	66.7
	2	8	26.7
	3	2	6.7
Antidepressants	0	17	56.7
	1	11	36.7
	2	2	6.7
Anticonvulsants	0	19	63.3
	1	9	30.0
	2	2	6.7
Anxiolytics	0	20	66.7
	1	9	30.0
	2	1	3.3
Other medications	0	12	40.0
	1	9	30.0
	2	3	10.0
	3	6	20.0

Source: Authors

The evaluated variables are shown in **Table 2**. Steatosis patients had significantly higher body mass index (p = 0.006), abdominal perimeter (p = 0.012), arm perimeter (p = 0.006), and adductor pollicis muscle (p = 0.014). No differences in hand grip strength and other anthropometric characteristics were found.

Regarding the relationship of the selected variables with the presence of steatosis, the logistic regression results is showed in **Table 3**. The odds ratio indicated that each unitary gain in abdominal perimeter, arm perimeter, adductor pollicis muscle, and BMI increases the chances of the presence of steatosis in schizophrenic patients.

DISCUSSION

The main objective of the present study was to investigate the presence of hepatic steatosis in schizophrenic patients undergoing treatment. The results indicate a prevalence of hepatic steatosis in 36.7% of the evaluated patients. In addition, the association of antipsychotic drug use with the presence of hepatic steatosis tended to be significant. Also, each unitary gain in the abdominal perimeter, arm perimeter, adductor pollicis muscle, and BMI increases the chances of the presence of steatosis in schizophrenic patients.

The nonalcoholic fatty liver disease (NAFLD) represents the most common chronic liver disease in the world, it is a complex metabolic-inflammatory disease associated with poor health outcomes and decreased quality of life [17, 18]. Further, NAFLD represents the hepatic manifestation of metabolic syndrome – a group of cardiometabolic components present in an important portion of patients with NAFLD [18]. Moreover, recent evidence suggests that patients with psychiatric disorders have some predisposition to the development of NAFLD, among the mechanisms implicated in the development of the disease we can indicate: dysregulation of the hypothalamic-pituitary-adrenal axis, metabolic syndrome, as well as metabolic side effects of antipsychotic medication - hyperglycemia and dyslipidemia – components of metabolic syndrome, especially with clozapine and olanzapine [17, 19].

Importantly, the prevalence of diagnosed mental disorders is 13% of the estimated world population, and Brazil is the second country with the highest prevalence of mental disorders [20]. In addition, mental disorders account for 21% of all disability-adjusted life years in Brazil [21], and recent epidemiological analysis indicates a higher occurrence of schizophrenia compared to other mental disorders in the whole population, and more specifically in male patients [22]. Similarly, epidemiological data indicate that NAFLD affects about 25% of the world's population, and is more prevalent in Western countries; however, a significant increase in prevalence is observed among countries in other parts of the world, such as the Asian continent [12].

Nevertheless, the present study showed a prevalence of 36.7% of hepatic steatosis in schizophrenic patients. Considering data from different studies, only a few studies evaluated

Table 2. Evaluated variables comparison between groups

	Total (n = 30)	Control (n = 19)	Steatosis (n = 11)	p value
Age	43.13 ± 10.7	41.53 ± 11.4	45.91 ± 9.1	0.286
Time since SZ diagnostic (years)	20.79 ± 12.4	18.56 ± 12.2	24.64 ± 12.3	0.199
Height (cm)	167.83 ± 9.4	169.05 ± 9.6	165.73 ± 9.0	0.359
Weight (kg)	75.22 ± 14.2	71.45 ± 14.0	81.75 ± 12.8	0.055
Abdominal perimeter	97.08 ± 12.0	93.00 ± 11.9	104.14 ± 8.8	0.012*
Triceps Skinfold thickness	16.63 ± 5.9	15.37 ± 5.5	18.82 ± 6.2	0.126
Arm perimeter	30.47 ±4.3	28.92 ± 4.1	33.14 ± 3.1	0.006*
Hand Grip Strength	61.33 ± 27.6	62.63 ± 29.1	59.09 ± 26.0	0.741
Adductor Pollicis Muscle	12.0 ± 3.1	10.97 ± 2.9	13.77 ± 2.7	0.014*
Fat-free mass (%)	67.58 ± 7.6	68.04 ± 8.5	66.80 ± 6.0	0.674
Fat mass (%)	32.4 ± 7.6	31.96 ± 8.5	33.15 ± 5.9	0.685
Body Mass index	26.75 ± 5.0	24.93 ± 4.1	29.90 ± 4.9	0.006*
Phase Angle	5.98 ± 1.2	5.68 ± 1.3	6.50 ± 0.9	0.079

Data are represented as Mean ± Standard Deviation; * Significant difference comparing control to steatosis (independent-samples t-test, p ≤ 0.05).

Source: Authors

Table 3. Logistic Regression regarding variables and the presence of steatosis

	p value	95% C.I. for EXP(B)	Odds (%)	Ratio
Abdominal perimeter	0,023*	1,014	1,201	10,4
Triceps Skinfold thickness	0,129	0,97	1,268	10,9
Arm perimeter	0,022*	1,053	1,923	42,3
Hand Grip Strength	0,731	0,968	1,023	-0,5
Adductor Pollicis Muscle	0,025*	1,046	1,946	42,7
Fat-free mass (%)	0,662	0,885	1,081	-2,2
Fat mass (%)	0,673	0,924	1,13	2,2
Body Mass index	0,017*	1,044	1,546	27
Phase Angle	0,089	0,907	3,995	90,3

C.I. = Confidence Interval; p value of Wald test

Source: Authors

hepatic health in schizophrenic patients, focusing on NAFLD. For example, an observational study including patients with schizophrenia and other common mental disorders showed an overall NAFLD prevalence of 17.63%, which was higher in schizophrenic patients (22.44%) when compared to other disorders, indicating that schizophrenia is a risk factor for NAFLD, alongside antipsychotics use, hypertension, diabetes, and dyslipidemia [12]. Likewise, a study with 145 patients diagnosed with schizophrenia, presenting mean age of 42.2 years and 14.8 years since diagnostic confirmation reported a prevalence of 21.4%, and the association between the steatosis with the presence of metabolic syndrome, albeit it was not associated with BMI or other variables [23].

Furthermore, in the present study the association between body mass index and the presence of steatosis was significant, and steatosis patients had significantly higher body mass index, abdominal perimeter, arm perimeter, and adductor pollicis muscle. Notably, simple anthropometric parameters, such as BMI and waist circumference, are useful for predicting

NAFLD in adults from different countries [24-26], and the present results indicated that not only body mass index predicts steatosis, but also abdominal perimeter, arm perimeter, and adductor Pollicis Muscle showed a significant relationship with the presence of steatosis. Correspondingly, the importance of BMI in the prediction of metabolic disturbances led to its inclusion in the National Cholesterol Education Program Adult Treatment Panel III criteria for diagnosis of metabolic syndrome [27]. Even when considering multiple factors and using advanced methodologies, BMI still prevails as the most important predictor of steatosis and NAFLD [28]. Importantly, NAFLD is associated with insulin resistance, hypertension, and dyslipidemia, and is currently considered the hepatic manifestation of the metabolic syndrome [29], triggering a proposal for a new nomenclature of the disease, changing it from NAFLD to MAFLD - Metabolic Associated Fatty Liver Disease [30]. Strikingly, the aforementioned metabolic impairments associated with NAFLD explain the increased risks of cancer, cardiovascular and cerebrovascular events, reinforcing the need to evaluate hepatic health in schizophrenic patients.

Although the association between the use of antipsychotics and the presence of steatosis only tended to be significant, it is important to access schizophrenic patients for the development of this condition. Notwithstanding, the use of medication is associated with increased risk for NAFLD, as demonstrated in a study of 191 subjects showing a 25.1% prevalence of NAFLD at the third-year follow-up. In this study, there were associations of the fibrosis score with body mass index, waist circumference, and other biochemical parameters [9].

Similarly, a cross-sectional study with 253 patients diagnosed with schizophrenia showed a prevalence of NAFLD of 42.7%. Of the 108 patients diagnosed with NAFLD, 13 had signs of fibrosis on ultrasound. Also, in the univariate analysis, the total dose of antipsychotic drugs was significantly associated with the presence of steatosis, whereas in the multivariate analysis, the dose of drugs with a known risk of metabolic syndrome and hyperprolactinemia was significantly associated with NAFLD [31].

Some limitations of our findings should be addressed. The sample size was limited to a single institution and needs reevaluation in future multicentric studies. Also, we used ultrasonography to diagnose liver steatosis, and although ultrasonography is accurate when compared with nuclear magnetic resonance spectroscopy and liver biopsy, the identification of fatty infiltration of the liver occurs above a threshold of 30%, which could have gendered our final analysis and underestimated the prevalence of steatosis [32]. Additionally, the present study lacks blood biomarker data. For instance, a cohort of Chinese cases and controls indicated a prevalence comparatively higher, where the authors compared 202 men aged 18-5 years diagnosed with schizophrenia in treatment of at least one month with antipsychotics with 149 healthy controls. The clinical evaluation included the Positive and Negative Syndrome Scale (PANSS), disease-related information, and laboratory tests: fasting blood glucose, total cholesterol, triglyceride, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The authors showed that the prevalence of NAFLD in the study group was 50% when compared to 20% in the control group. In the univariate analysis, NAFLD correlated significantly with BMI, triglycerides, medications, and dose as well as with the PANSS score.[33]. Moreover, a prospective Spanish study with a 3-year follow-up [9] included 191 patients with a recent diagnosis of schizophrenia – first event – (94% of patients were naïve for psychiatric treatment and none of them had a diagnosis of steatosis evaluated by NAFLD fibrosis score or FIB-4 score). On admission, at 3 months and annually until 3 years the NAFLD fibrosis score, FIB-4 score, and fatty liver index (FLI) were calculated. At the end of the follow-up period, 25% of the patients had an FLI score ≥ 60, a good predictor of steatosis. When comparing patients with FLI ≥ 60 with patients with FLI ≤ 60 the authors found that patients with FLI ≥ 60 had statistically higher values of triglycerides (≥ 150 P 0.000), waist circumference (≥ 102 men and ≥88 women P 0.000) and presence of the metabolic syndrome.

CONCLUSION

This study shows a prevalence of hepatic steatosis of 36.7% in patients with schizophrenia which was associated with body mass index. In addition, abdominal perimeter, arm perimeter, adductor pollicis muscle, and BMI were significant predictors for the presence of steatosis. Future multicentric studies could expand our results, which are important, especially for the south american population, where data is still scarce.

Referencias

1 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders 5th ed. Arlington, VA: American Psychiatric Association; 2013.

2 Organization WH. The WHO special initiative for mental health (2019-2023): universal health coverage for mental health. . World Health Organization. : 2019.

3 Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007 Oct;64(10):1123-31. doi: 10.1001/archpsyc.64.10.1123.

4 Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry. 2015 Oct;14(3):339-47. doi: 10.1002/wps.20252.

5 Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020 Jan;7(1):64-77. doi: 10.1016/S2215-0366(19)30416-X.

6 Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. Diabet Med. 2007 Jan;24(1):1-6. doi: 10.1111/j.1464-5491.2007.02025.x.

7 Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016 Aug;65(8):1038-48. doi: 10.1016/j.metabol.2015.12.012.

8 Geier A, Tiniakos D, Denk H, Trauner M. From the origin of NASH to the future of metabolic fatty liver disease. Gut. 2021 Feb 25;70(8):1570–9. doi: 10.1136/gutjnl-2020-323202.

9 Morlán-Coarasa MJ, Arias-Loste MT, Ortiz-García de la Foz V, Martínez-García O, Alonso-Martín C, Crespo J, et al. Incidence of non-alcoholic fatty liver disease and metabolic dysfunction in first episode schizophrenia and related psychotic disorders: a 3-year prospective randomized interventional study. Psychopharmacology (Berl). 2016 Dec;233(23-24):3947-3952. doi: 10.1007/s00213-016-4422-7.

10 Yan J, Hou C, Liang Y. The prevalence and risk factors of young male schizophrenics with non-alcoholic fatty liver disease. Neuropsychiatr Dis Treat. 2017 Jun 12;13:1493-1498. doi: 10.2147/NDT.S137183.

11 Fuller BE, Rodriguez VL, Linke A, Sikirica M, Dirani R, Hauser P. Prevalence of liver disease in veterans with bipolar disorder or schizophrenia. Gen Hosp Psychiatry. 2011 May-Jun;33(3):232-7. doi: 10.1016/j.genhosppsych.2011.03.006.

12 Ma Q, Yang F, Ma B, Jing W, Liu J, Guo M, et al. Prevalence of nonalcoholic fatty liver disease in mental disorder inpatients in China: an observational study. Hepatol Int. 2021 Feb;15(1):127-136. doi: 10.1007/s12072-020-10132-z.

13 Lee SM, Lee JM, Kang H-J, Yang HK, Yoon JH, Chang W, et al. Liver fibrosis staging with a new 2D-shear wave elastography using comb-push technique: Applicability, reproducibility, and diagnostic performance. PLoS One. 2017 May 16;12(5):e0177264. doi: 10.1371/journal.pone.0177264.

14 Marroni CA, Miranda D, Boemeke L, Fernandes SA. Phase Angle Bioelectrical Impedance Analysis (BIA) as a Biomarker Tool for Liver Disease. In: Preedy VR, editor. Biomarkers in Liver Disease. Dordrecht: Springer Netherlands; 2016. p. 1-18.

15 Lameu EB, Gerude MF, Campos AC, Luiz RR. The thickness of the adductor pollicis muscle reflects the muscle compartment and may be used as a new anthropometric parameter for nutritional assessment. Curr Opin Clin Nutr Metab Care. 2004 May;7(3):293-301. doi: 10.1097/00075197-200405000-00009.

16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014 Dec;12(12):1495-9. doi: 10.1016/j.ijsu.2014.07.013. PMID: 25046131.

17 Jawad MY, Meshkat S, Tabassum A, McKenzie A, Di Vincenzo JD, Guo Z, et al. The bidirectional association of nonalcoholic fatty liver disease with depression, bipolar disorder, and schizophrenia. CNS Spectr. 2022 Oct 21:1-20. doi: 10.1017/S1092852922001043.

18 Shea S, Lionis C, Kite C, Atkinson L, Chaggar SS, Randeva HS, et al. Non-Alcoholic Fatty Liver Disease (NAFLD) and Potential Links to Depression, Anxiety, and Chronic Stress. Biomedicines. 2021 Nov 16;9(11):1697. doi: 10.3390/biomedicines9111697.

19 Grant RK, Brindle WM, Donnelly MC, McConville PM, Stroud TG, Bandieri L, et al. Gastrointestinal and liver disease in patients with schizophrenia: A narrative review. World J Gastroenterol. 2022 Oct 14;28(38):5515-5529. doi: 10.3748/wjg.v28.i38.5515.

20 (IHME). IfHMaE. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States: 2017.

21 Schramm JMdA, Oliveira AFd, Leite IdC, Valente JG, Gadelha ÂMJ, Portela MC, Campos MR. Transição epidemiológica e o estudo de carga de doença no Brasil. Ciência & Saúde Coletiva. 2004: 897

22 Carteri RB, Oses JP, Cardoso TdA, Moreira FP, Jansen K, Silva RAd. A closer look at the epidemiology of schizophrenia and common mental disorders in Brazil. Dement Neuropsychol. 2020 Jul-Sep;14(3):283-289. doi: 10.1590/1980-57642020dn14-030009.

23 Aarøe ASK, Odgaard Maeng K, Leifsdottir Jacobsen R, Eggert Jensen S, Graff C, Polcwiartek C, et al. Hepatic steatosis in patients with schizophrenia: a clinical cross-sectional study. Nord J Psychiatry. 2022 Feb;76(2):114-119. doi: 10.1080/08039488.2021.1939779.

24 Singh A, Parida S, Narayan J, Nath P, Padhi PK, Pati GK, et al. Simple Anthropometric Indices are Useful for Predicting Non-alcoholic Fatty Liver Disease [NAFLD] in Asian Indians. J Clin Exp Hepatol. 2017 Dec;7(4):310-315. doi: 10.1016/j.jceh.2017.05.005.

25 Yoo HJ, Park MS, Lee CH, Yang SJ, Kim TN, Lim KI, et al. Cutoff points of abdominal obesity indices in screening for non-alcoholic fatty liver disease in Asians. Liver Int. 2010 Sep;30(8):1189-96. doi: 10.1111/j.1478-3231.2010.02300.x.

26 Zheng RD, Chen ZR, Chen JN, Lu YH, Chen J. Role of Body Mass Index, Waist-to-Height and Waist-to-Hip Ratio in Prediction of Nonalcoholic Fatty Liver Disease. Gastroenterol Res Pract. 2012;2012:362147. doi: 10.1155/2012/362147.

27 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec 17;106(25):3143-421.

28 Liu Y-X, Liu X, Cen C, Li X, Liu J-M, Ming Z-Y, et al. Comparison and development of advanced machine learning tools to predict nonalcoholic fatty liver disease: An extended study. Hepatobiliary Pancreat Dis Int. 2021 Oct;20(5):409-415. doi: 10.1016/j.hbpd.2021.08.004.

29 Kuchay MS, Misra A. From non-alcoholic fatty liver disease (NAFLD) to metabolic-associated fatty liver disease (MAFLD): A journey over 40 years. Diabetes Metab Syndr. 2020 Jul-Aug;14(4):695-696. doi: 10.1016/j.dsx.2020.05.019.

30 Eslam M, Sanyal AJ, George J. MAFLD: MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020 May;158(7):1999-2014.e1. doi: 10.1053/j.gastro.2019.11.312.

31 Koreki A, Mori H, Nozaki S, Koizumi T, Suzuki H, Onaya M. Risk of Nonalcoholic Fatty Liver Disease in Patients With Schizophrenia Treated With Antipsychotic Drugs: A Cross-sectional Study. J Clin Psychopharmacol. 2021 Jul-Aug 01;41(4):474-477. doi: 10.1097/JCP.0000000000001421.

32 Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002 Sep;123(3):745-50. doi: 10.1053/gast.2002.35354.

33 Yan J, Hou C, Liang Y. The prevalence and risk factors of young male schizophrenics with non-alcoholic fatty liver disease. Neuropsychiatr Dis Treat. 2017 Jun 12;13:1493-1498. doi: 10.2147/NDT.S137183.