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The bidirectional association of nonalcoholic fatty liver disease with depression, bipolar disorder, and schizophrenia

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a complex metabolic-inflammatory disease associated with poor outcomes and decreased quality of life. NAFLD is overrepresented in patients with psychiatric disorders like depression, bipolar disorder, and schizophrenia; however, a comprehensive review on NAFLD and psychiatric disorders remains to be delineated. This review endeavors to investigate the association of NAFLD with psychiatric disorders, including shared pathogenesis and future clinical derivatives. Extant literature suggests that patients with psychiatric disorders (in particular, mood disorders) are more susceptible to the development of NAFLD due to multiple reasons, including but not limited to hypothalamic–pituitary–adrenal axis dysregulation, metabolic syndrome, and chronic perceived stress. Moreover, the clinical manifestations of mood disorders (e.g., anhedonia, psychomotor retardation, lifestyle modification, etc.), and potentially long-term treatment with weight-gaining agents, differentially affect these patients, making them more prone to NAFLD. Considering the increased morbidity associated with both mood disorders and NAFLD, our review recommends regular screenings for NAFLD in select patients with mood disorders exhibiting signs of increased risk (i.e., obesity, metabolic syndrome, diabetes, or family history of NAFLD) for better diagnosis and holistic care of both potentially interrelated conditions.

Review

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease with a spectrum of clinicopathological presentations. The clinical course and progression of NAFLD often begins with the accumulation of triglycerides in hepatocytes which predisposes these cells to inflammation and necrosis resulting in nonalcoholic steatohepatitis (NASH).[1,2] The progression of the disease can lead to eventual cirrhosis and possibly hepatocellular carcinoma.[1] Although several histopathological features of NAFLD and NASH are similar to what are observed in alcoholic fatty liver disease (eg. steatosis, inflammation, hepatocyte ballooning, Mallory–Denk bodies, and fibrosis within the lobules), NAFLD/NASH occurs in the absence of excess alcohol use.[3]

The pathology of NAFLD is conceptualized as a complex multifactorial disease state involving metabolic-inflammatory effectors often observed across disparate disorders (eg. diabetes, mood disorders, obesity, and cardiovascular disease).[3,4] It is currently estimated that approximately 25% of the world's population meet or exhibit histopathological evidence of NAFLD.[5] The rising prevalence of obesity and associated metabolic syndrome in both middle- and high-income countries is predicted to result in a higher number of NAFLD cases globally over the coming years.[6] Overarchingly, the highly comorbid, insidious, and prevalent nature of NAFLD makes it a significant healthcare concern.[1]

It is posited that the pathogenesis of mood disorders includes, but is not limited to, disturbances across metabolic and inflammatory systems.[7] Although the association between

the metabolic-inflammatory pathways and mood disorders is robust, the exact causal direction and longitudinal presentations remain incompletely understood. Therefore, it is postulated that a bidirectional link exists between metabolic-inflammatory syndromes and mood disorders.[7–9] A separate line of evidence unequivocally demonstrates that persons with mood disorders are differentially affected by obesity, diabetes, and metabolic syndrome.[10,11] A derivative of the foregoing observation is that persons with mood disorders would be predicted to be at greater risk for NAFLD and NASH.[3,11]

This narrative review aims to summarize the extant literature pertaining to the association of NAFLD and NASH with psychiatric disorders, the shared pathophysiological nexus, and potential therapeutic and research vistas.

Association of NAFLD with psychiatric disorders

To better understand the association of NAFLD with psychiatric disorders, we subdivided the available literature across the following major psychiatric disorders: major depressive disorder (MDD), bipolar disorder (BD), schizophrenia, and cognitive dysfunction.

Major depressive disorder

MDD is a chronic illness associated with affective, somatic, and cognitive alterations.[10] The global disease burden of MDD has increased, with an annual >50 million years lived with disability.[12] Many recent cross-sectional studies have established a significant association of MDD with co-occurrence of NAFLD (Table 1). Furthermore, a recent meta-analysis synthesizing cross-sectional studies has shown that depression increases the odds of developing NAFLD by up to 42% (pooled OR = 1.46, 95% CI: 1.15, 1.85, p = 0.002).[13] The foregoing meta-analysis also reported that patients with NAFLD were more likely to report depressive symptoms when compared with their non-NAFLD counterparts in general (pooled OR = 1.13, 95% CI: 1.03, 1.24, p = 0.007).[13]

To our knowledge, two recently published cohort studies have established the risk of developing NAFLD in individuals diagnosed with depression, and vice versa. Cho et al. followed Korean adults (n = 142 005) with no NAFLD and no excessive alcohol consumption at baseline for a median of 4 years. Overall, depression modestly increased the risk for developing NAFLD (aHR = 1.07, 95% CI: 1.03–1.11, p < 0.001). However, when stratified by BMI category, the risk increased significantly for overweight (BMI ⩾ 25 kg/m^2) individuals (aHR = 1.25, 95% CI: 1.16–1.35, p < 0.001) in comparison to normal weight individuals (BMI ≤ 25 kg/m^2; aHR = 1.02, 95% CI: 0.98–1.07, p = 0.072).[14]

Another longitudinal study that followed adolescents (n = 160) with NAFLD for a mean duration of 3.8 years reported a steady increase in the incidence of depression among participants over time from baseline (i.e., 8.1% had depression initially).[15] During the follow-up period, an additional 9.5% (95% CI = 4.7%–14.3%) of the adolescents with NAFLD developed depression. However, the study by Noon et al. was limited due to the lack of control group (i.e., adolescents without NAFLD) and relatively small number of participants.[15] Further information regarding important diagnostic definitions, patient characteristics, and relevant findings of these two cohorts is delineated in Table 1.

Multiple cross-sectional and cohort studies have also described a positive bidirectional association between the severity of depression and the degree of NAFLD fibrosis. In the cohort by Cho et al., obese people with greater severity of depression exhibited an increased risk of having NASH with greater degrees of fibrosis when compared to obese people having lesser to no depression (aHR = 3.55, 95% CI: 1.38–9.13, p < 0.005).[14] Similarly, in the second longitudinal study, adolescents who developed depression reported worse outcomes based on alanine transferase liver enzyme serology (indicator of liver injury) when compared with those who did not develop depression (i.e., improved 21%, stable 36%, worse 43% versus improved 42%, stable 35%, worse 23%; p < 0.01, respectively).[15]

Moreover, in the majority of cross-sectional studies, a dose-dependent correlation was found between severity of depression and the histological stage of NAFLD even after adjustment for confounding factors (ie. diabetes, gender, age, obesity, hypertension, etc.).[16–23] Further relevant details are described in Table 1.

Bipolar disorder

BD is a serious and debilitating illness formally differentiated from MDD by the presence of hypomania or mania.[9] Accumulating research has shown that patients with BD are more likely to develop insulin resistance, obesity, and other metabolic disruptions when compared with patients with MDD.[9] Notwithstanding, studies investigating the association of BD with NAFLD are limited. A retrospective cross-sectional electronic chart review of veterans (n = 10638) reported that patients with BD (both I and II) had significantly increased odds of developing NAFLD when compared with healthy controls (aOR = 2.57, SE = 0.316, p = 0.03).[24]

In another recently published study, Godin et al. analyzed the data of 1969 BD (both I and II) patients to ascertain the association with NAFLD. The prevalence of NAFLD was found to be 28.4%, with a higher rate in males compared to females (OR = 3.5; 95% CI = 2.54–4.72; p = N/A). When compared with the prevalence of NAFLD in the general population, which is estimated to be at 17%, the likelihood of presenting with NAFLD was significantly greater in patients with BD.[25,26] The prevalence increases further when comorbid diabetes, metabolic dysfunction, and obesity are present, along with BD.[25] An important consideration is that a significant proportion of patients with BD are prescribed antipsychotic agents for maintenance treatment, and many of these agents (eg. risperidone, olanzapine, or quetiapine) are associated with significant metabolic alterations and could play a part in overall pathogenesis of NAFLD.[9,27–29] Parenthetically, the relationship between valproate use and risk of NAFLD is not established, although several studies report such an association.[30,31] Moreover, the included studies remained limited in discerning the difference between the association of BD-I and BD-II with NAFLD, respectively.

Schizophrenia

Schizophrenia is a chronic psychotic illness that often requires lifelong management with antipsychotic agents.[32] Long-term exposure to antipsychotic agents is associated with progressive disruption of glucose-insulin homeostasis, dyslipidemia, and weight gain.[27,28] As such, NAFLD is more prevalent among patients with schizophrenia as compared to general population.[3] Like MDD and BD, multiple cross-sectional studies have shown a strong association between schizophrenia and NAFLD. For pertinent details of key cross-sectional studies, refer to Table 2.[24,33–37]

In a prospective interventional study, patients with schizophrenia (N = 191, with 180 being antipsychotic-naive) were maintained

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Table 1. Characteristics of Key Studies Ascertaining NAFLD Across Patients with Depression

Lead Author	Year	Study type	Patient characteristics and number	Diagnostic criteria for depression	Diagnostic criteria for NAFLD	Primary objective of study	Association between depression and NAFLD	Association between obesity with depression and NAFLD	Association between severity of depression and histological features of liver	Limitations
Elwing JE	2006	Retrospective, case-controlled study	36 subjects with NASH and 36 control subjects (age, BMI, waist-hip ratio, and gender matched)	MDD and GAD diagnosed using diagnostic interview schedule (DIS) and according to criteria in DSM-IV; life-time history of MDD/GAD considered if subjects had any history of MDD/GAD at any point in life; depression questions from PHQ-9 to corroborate findings	Liver biopsy	To compare the rates of criteria-defined major depressive disorder (MDD) and generalized anxiety disorder (GAD) in NASH subjects to those in a comparison group and determine the relationship of antecedent psychiatric illness to liver biopsy findings	Significantly increased rates of MDD in NASH subjects (OR, 3.8; 95% CI, 1.4–10.2; $p = .018$)	N/A	N/A	Possible medication effects, small sample size, and the potential for ascertainment bias; method of excluding NASH in controls (ultrasound) was imperfect
Lee K	2013	Cross-sectional/ population-based study	10231 NHANES participants; 18+ years; (50% were male, 71% were non-Hispanic Whites, 11% non-Hispanic Blacks, 8% Mexican Americans, and 10% others including Asians)	PHQ-9; A PHQ-9 score of at least 10 had a sensitivity and specificity of 88% for a clinical diagnosis of major depression	NAFLD was defined by the absence of any other causes of CLD [e.g., negative HCV RNA, negative hepatitis B virus surface antigen, less than excessive alcohol consumption] as well as by the presence of elevated liver enzymes (alanine aminotransferase [ALT] 40 U/L and aspartate aminotransferase [AST] 37 U/L in men and ALT, AST 31 U/L in women)	To assess the association of four common causes of CLD (CH-C, CH-B, NAFLD, and ALD) with depression utilizing a commonly used scale, the Patient Health Questionnaire (PHQ-9)	Depression was not associated with NAFLD	Participants with NAFLD were more likely to be Mexican American, had higher BMI and waist circumference and more commonly had all the components of metabolic syndrome.	N/A	Cross-sectional and therefore, only associations/no causal links; may have underestimated the true prevalence of NAFLD; PHQ-9 has not been validated for screening depression in this patient population; possibility of confounders such as the use of antidepressants and excessive alcohol use, which may have impacted the true prevalence of depression

Table 1. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Diagnostic criteria for depression	Diagnostic criteria for NAFLD	Primary objective of study	Association between depression and NAFLD	Association between obesity with depression and NAFLD	Association between severity of depression and histological features of liver	Limitations
Youssef NA	2013	Cross-sectional study	567 patients with NAFLD enrolled in the Duke NAFLD clinical database	HADS questionnaire	Liver biopsy	To examine the association between depression, anxiety and antidepressant pharmacotherapy with severity of histological features in patients with NAFLD	Subclinical and clinical depression was noted in 53% and 14% of patients respectively; significantly associated with more severe ballooning in a dose-dependant manner $p = 0.0201$; in patients with NAFLD, depression was associated with more sever hepatocyte ballooning	N/A	Depression categories associated with portal fibrosis grades ($p = 0.038$) and tended to be associated with hepatocyte ballooning grades ($p = 0.085$)	Analysis limited by cross-sectional study designs and inability to control potential confounding factors; may have inherent sampling and reporting biases; small sample size
Tomeno W	2015	Retrospective cross-sectional study	258 patients with biopsy-proven NAFLD were included	MDD was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR)	Biopsy; presence of macrovesicular fatty changes in the hepatocytes, with displacement of the nuclei to the edges of the cells	To identify the clinical features of non-alcoholic fatty liver disease (NAFLD) patients comorbid with MDD, and to investigate the influence of MDD on the effect of treatment in patients with NAFLD	Serum AST, ALT, GGT, Cholinesterase, Ferritin, and hs-CRP were significantly higher in the NAFLD patients comorbid with MDD as compared with those without MDD	N/A	The comorbid state of MDD was associated with more severe histological liver steatosis and worse treatment outcomes in patients with NAFLD	Relatively small sample size
Jung J	2019	Cohort study	112797 general Korean population	Center for Epidemiological Studies-Depression (CES-D) questionnaire	Abdominal Ultrasound was performed by standard criteria for diagnosing fatty liver based on parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, and bright vessel walls	To ascertain the association between NAFLD and depression in Korean population	The univariate ORs indicated the negative association of depression with the degree of ultrasonographically detected fatty liver, FLI and FIB-4 score. However, adjustment for covariates patterned the dose-dependent relationship between depression and ultrasonographically detected fatty liver,	N/A	N/A	NAFLD was assessed only by non-invasive modalities; data is not enough to investigate the history of anti-depressant medication and diagnosed MDD; results cannot suggest the potential mechanism for our findings. In particular, we

Table 1. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Diagnostic criteria for depression	Diagnostic criteria for NAFLD	Primary objective of study	Association between depression and NAFLD	Association between obesity with depression and NAFLD	Association between severity of depression and histological features of liver	Limitations
							FLI and FIB-4 score, despite the statistical insignificance in some cases. Statistical significance was identified only in group stratified by FLI even after adjustment for covariates, and groups with ultrasonographically detected fatty liver and FIB-4 did not show the statistical significance.			could not provide any evidence for the role of insulin resistance mediating the association between depression and fatty liver
Lee JW	2020	Cross-sectional/ population-based study	4688 participants; 19+ years; Korean nationality	PHQ-9 questionnaire Korean version; self-administered; a score ≥ 10 indicates a clinical diagnosis of major depression with a sensitivity and specificity of 88%.	NAFLD was defined using a validated hepatic steatosis index that was calculated as 8 × ALT/AST ratio + body mass index (+2, if diabetes; +2, if female); optimal cut-off value for NAFLD was set at >36	To examine the relationship between depression and NAFLD in a representative Korean adult population from the Korea National Health and Nutrition Examination Survey (KNHANES)	NAFLD more prevalent in depressed (33.7%; 95% CI, 28.4–39.5%) versus non-depressed participants (23.8%; 95% CI, 22.2–25.5%); without adjustments: participants with depression had 63% increase in OR of NAFLD (95% CI, 1.26–2.10; $p < 0.001$); with sociodemographic adjustments: depressed participants had a 16% increase in the OR of NAFLD; final fully adjusted model (age, sex, alcohol consumption, diabetes, cardiovascular disease, and waist circumference), the OR of NAFLD was 54% higher in participants with	N/A	N/A	Survey design of study - could not use structured diagnostic interviews and therefore, no info on major depressive disorder or on duration, severity, or type of treatment of past depression; NAFLD diagnosis not done through imaging or biopsies but rather through an operational criteria for defining NAFLD based on a predicting model that has been widely validated; cross-sectional and therefore, only associations/ no causal links;

Table 1. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Diagnostic criteria for depression	Diagnostic criteria for NAFLD	Primary objective of study	Association between depression and NAFLD	Association between obesity with depression and NAFLD	Association between severity of depression and histological features of liver	Limitations
							depression (95% CI,1.00–2.37; $p = 0.053$) compared with those without depression.			prevalence of depression may have been underestimated since only non institutionalized Koreans who were able to attend the mobile examination center were included
Choi JM	2021	Retrospective cross-sectional study	25333 Korean subjects (56.2% male); subjects included those with depression or anxiety (as assessed by the Beck Depression Inventory or State–Trait Anxiety Inventory) and NAFLD diagnosed through abdominal ultrasound; mean age 47 years; NAFLD prevalence 30.9%	Beck Depression Inventory	Abdominal/hepatic ultrasound; criteria included "bright liver" and evident contrast between hepatic and renal parenchyma, focal sparing, vessel blurring, and narrowing of the lumen of the hepatic veins	To investigate the relationship between NAFLD and anxiety or depression in Korean subjects who participated in health check-ups	Univariate analysis: no association between NAFLD and depression; stratified analysis (by gender): NAFLD significantly associated with 44% increase in depression in women (OR 1.44, 95% CI 1.17–1.76); association remained significant after adjusting for age, BMI, alcohol, diabetes, and smoking (OR 1.43, 95% CI, 1.14–1.80); also an insignificant trend of increasing risk of depression according to the stage of steatosis in a dose-dependent manner (OR 1.35, 95% CI, 1.00–1.78; OR 1.52, 95% CI, 1.12–2.03; and OR 1.75, 95% CI, 0.76–3.56, mild, moderate, and severe, respectively)	N/A	N/A	Observational study design; association between NAFLD and mood disorder does not imply causality; over- or underreporting of symptoms due to self-reporting depression questionnaire; recommended cut-off points for BDI are not consistent among specific disease or population -- therefore, they used cutoff values based on a previous study in a Korean population; NAFLD only assessed by ultrasound (gold standard is liver biopsy); lack in accurate diagnosis of mild steatosis; fibrosis critical factor in

Table 1. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Diagnostic criteria for depression	Diagnostic criteria for NAFLD	Primary objective of study	Association between depression and NAFLD	Association between obesity with depression and NAFLD	Association between severity of depression and histological features of liver	Limitations
										mental health of NAFLD patients but they could not assess fibrosis stage; could not assess influence of history of antidepressants; no information on the history of hypertension but systolic and diastolic blood pressure adjusted for in the multivariate analysis; could not exclude all patients who had a drinking habit
Cho IY	2021	Longitudinal cohort study (follow up of up to 8.9 years)	142005 Korean adults with neither hepatic steatosis nor excessive alcohol consumption at baseline were followed for up to 8.9 years	20-item Korean version of the Center for Epidemiological Studies-Depression (CES-D); clinically significant depressive symptoms at baseline = CES-D score ⩾16	Abdominal ultrasounds (blinded radiologists); diagnostic criteria included diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma, deep beam attenuation and bright vessel walls	To examine whether depression, in obese and non-obese subjects, is associated with: (a) an increased risk of incident HS and (b) HS plus high probability of advanced fibrosis	Depression weakly but positively associated with hepatic steatosis	Association between depression and HS was stronger in obese versus non obese participants; adjusted HR (95% CI) for incident HS comparing CES-D ⩾ 16 to CES-D < 8 was 1.24 (1.15–1.34), among obese subjects, whereas the corresponding adjusted HR (95% CI) was 1.00 (0.95–1.05) among those without obesity	N/A	Ultrasound for diagnosis instead of the gold-standard liver biopsy; missing intra- and inter-observer agreement tests between the radiologists and different radiologists were involved over the study; depressive symptoms measured using a self-administered questionnaire --> possible over/underreporting of symptoms; health history also collected through self-administered questionnaires --> measurement

Table 1. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Diagnostic criteria for depression	Diagnostic criteria for NAFLD	Primary objective of study	Association between depression and NAFLD	Association between obesity with depression and NAFLD	Association between severity of depression and histological features of liver	Limitations
										error -- > residual confounding most likely affects the association observed; findings may not be generalizable because sample consisted of a single ethnicity and only young/ middle-aged healthy subjects with good access to health care
Noon S	2021	Prospective, longitudinal cohort study	160 adolescents with NAFLD	DSM-5 criteria; diagnosed by psychologists/ psychiatrists	Liver biopsy	To determine the incidence of clinically diagnosed depression and anxiety in adolescents with NAFLD.	In adolescents with NAFLD, 8.1% (13/160) were diagnosed with depression prior to being diagnosed with NAFLD; Adolescents with NAFLD ages 15 to 17 were at greater risk for development of depression when compared to those ages 12 to 14 (adjusted odds ratio [aOR] = 1.60, 95% confidence interval [CI] = 1.11, 2.52); The cumulative incidence of depression in adolescents with NAFLD was 9.5% (95% CI, 4.7%–14.3%); The cumulative prevalence of depression in adolescents with NAFLD was 16.9% (95% CI, 11.0%–22.7%)	N/A	Distribution of liver histology severity did not significantly differ between those with and without depression	Lack of a control group, in particular for obesity; possibly underestimated the rates of depression due to issues of access to mental health care; cohort largely male and predominantly Hispanic (sex differences in depression and rates of depression may be higher in a non-Hispanic population

Table 1. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Diagnostic criteria for depression	Diagnostic criteria for NAFLD	Primary objective of study	Association between depression and NAFLD	Association between obesity with depression and NAFLD	Association between severity of depression and histological features of liver	Limitations
Shaheen AA	2021	Retrospective cohort study	19053 UK adults	The Health Improvement Network Data	The Health Improvement Network Data	To evaluate the impact of major depressive disorder and antidepressants on survival among patients with alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD).	MDD occurred less frequently among incident NAFLD patients (16.1%), compared to ALD (22.8%) patients	N/A	N/A	Due to the retrospective nature of the study, our NAFLD and ALD cohort definitions may have been subject to misclassification;
Yang S	2021	Cross-sectional/ population-based study	1186 US middle aged adults	N/A	Nonalcoholic fatty liver disease was diagnosed if participants had liver steatosis in the absence of any of the possible secondary causes of fatty liver	To determine the nationwide prevalence of and associated factors for NAFLD and fibrosis in adults aged 45–79 years from the United States	Depression was associated with an increased risk of NAFLD, but was not associated with NAFLD-related advanced fibrosis in a general population of US adults aged 20 years or older	As expected, the presence of metabolic-related disorders including overweight/ obesity, abdominal obesity, hypertension, and diabetes, which are common contributors to NAFLD, also predicted a high risk of NAFLD	The presence of depression potentially increases the risk of NAFLD	The cross sectional nature of the study is appropriate to evaluate the prevalence of disease in a certain period but weakens the evidence of risk factor identification due to residual confounders and unclear causal direction

Abbreviations: ALD, Adrenoleukodystrophy; BDI, Beck Depression Inventory; BMI, Body mass index; CH-B, Chronic hepatitis B; CH-C, Chronic hepatitis C; CI, Confidence interval; CLD, Chronic liver disease; CT, Computerized tomography; DM type 2, Type 2 diabetes mellitus; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; DSM-IV, The Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; FIB-4, Fibrosis-4; FLI, Fatty liver index; GAD, Generalized anxiety disorder; GGT, Gamma-glutamyl transferase; HADS, Hospital Anxiety and Depression Scale; HCV, Hepatitis C virus; HS, Health Subjects; hs-CR*P*, High-sensitivity C-reactive protein; ICD-109, International Classification of Diseases; MDD, Major Depressive disorder; MRI, Magnetic Resonance Imaging; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic Steatohepatitis; NHANES, The National Health and Nutrition Examination Survey; OR, Odd ratio; PHQ-9, Patient Health Questionnaire; RNA, Ribonucleic acid; WPAI, Work Productivity and Activity Impairment.

Table 2. Characteristics of Key Studies Ascertaining NAFLD Across Patients with Cognitive Deficits, Bipolar Disorder and Schizophrenia

Lead Author	Year	Study type	Patient characteristics and number	Psychiatric illness/domain under study	Diagnostic criteria for psychiatric domain/illness	Diagnostic criteria for NAFLD	Primary objective of study	Association between illness/ domain and NAFLD	Association between obesity with domain/ illness and NAFLD	Association between severity of domain/ illness and histological features of liver	Limitations
Fuller	2011	Retrospective study	Schizophrenia (n = 6521), bipolar disorder (n = 5319) and matched controls (Schizophrenia (n = 6521), bipolar disorder (n = 5319))	Bipolar disorder or schizophrenia	International Classification of Diseases, 9th Revision	N/A	Prevalence of liver disease in veterans with bipolar disorder or schizophrenia	Patients with schizophrenia and bipolar disorder had a higher prevalence of liver disease and alcohol-related cirrhosis than matched controls.	N/A	N/A	Atypical antipsychotic medication or inpatient hospital admissions were not measured.
Hsu.	2014	Cross-sectional study	661266 subjects aged ≥18	Schizophrenia	The International Classification of Diseases, Ninth Revision,	N/A	Prevalence and incidence of NAFLD in schizophrenia.	The prevalence of chronic liver disease in patients with schizophrenia (7.0%) was 1.27 times as high as that of the general population (6.1%).	N/A	N/A	Several factors that are associated with chronic liver disease, such as body weight, laboratory data, substance use history, and occupation, were not available.
Morlán-Coarasa	2016	Prospective randomized interventional study	191 psychosis (83 were initially randomized to aripiprazole, 12 risperidone, 46 quetiapine, 50 ziprasidone.)	Psychosis	DSM-IV criteria for brief psychotic disorder	NAFLD fibrosis score, FIB-4 score, and the fatty liver index (FLI)	Incidence of NAFLD in first episode schizophrenia and related psychotic disorders.	None of the patients showed significant liver fibrosis according to the mentioned scores at baseline, prior to randomization. At 3 years follow-up, 25.1% of individuals showed a FLI score ≥60, which is a predictor of steatosis.	N/A	N/A	No histologic diagnosis of NAFLD and lack of placebo group.
Yan	2017	Cross-sectional study	Schizophrenia (N = 202), healthy controls (n = 149)	Schizophrenia	ICD-109	Abdominal ultrasonography findings	The prevalence and risk factors of young male with schizophrenia and NAFLD.	The prevalence of NAFLD was 49.5% in the study group, and 20.1% in the control group.	Significantly higher in obese subjects	N/A	Cross-sectional nature of study design.
Celikbilek A.	2018	Cross-sectional study	NAFLD (n = 70) healthy participants (n = 73)	Cognitive function	Montreal Cognitive Assessment (MoCA)	Abdominal ultrasonography findings	Cognitive performance	Lower MoCA score in participants with NAFLD than in the healthy group (P < 0.05) / NAFLD	Not significant	N/A	Small sample size. Study design. No histology report. Potential selection bias

Table 2. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Psychiatric illness/domain under study	Diagnostic criteria for psychiatric domain/illness	Diagnostic criteria for NAFLD	Primary objective of study	Association between illness/ domain and NAFLD	Association between obesity with domain/ illness and NAFLD	Association between severity of domain/ illness and histological features of liver	Limitations
								patients had deficits in the visuospatial and executive function domains.			
Filipović	2018	Case controlled study	Patients with NAFLD (n = 40) Patients without NAFLD (n = 36)	Cognitive function	Montreal Cognitive Assessment (MoCA)	Abdominal ultrasonography findings	Cognitive performance	NAFLD led to lower cognitive potentials: odds ratio 0.096; 95% CI:0.032–0.289; p < 0.001. Patients with NAFLD suffered more with cognitive impairment and depression: RR = 3.9; 95% CI 1.815–8.381; p = 0.0005 and RR = 1.65; 95% CI 1.16–2.36; p = 0.006.	N/A	N/A	Small sample size. Diagnosis of NAFLD was operator dependent
Balp	2019	Cross-sectional study	NASH (n = 184), general population (n = 79 267), DM type 2 cohort (n = 4783).	Anxiety, depression, sleep difficulties	Short-Form (SF)-36v2, WPAI scores, self-reported physician diagnosis	N/A	Assessed the comparative burden of NASH, relative to a representative sample from the general population and DM type 2, in terms of health-related quality of life, work productivity and activity impairment (WPAI), and healthcare resource use.	NASH patients had significantly worse health-related quality of life, worse WPAI scores, and more healthcare resource use than the general population. But did not differ from DM type 2 patients.	N/A	N/A	No confirmation of NASH diagnosis via liver biopsy. All measures and outcomes assessed were patient-reported data. Study design.

Table 2. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Psychiatric illness/domain under study	Diagnostic criteria for psychiatric domain/illness	Diagnostic criteria for NAFLD	Primary objective of study	Association between illness/ domain and NAFLD	Association between obesity with domain/ illness and NAFLD	Association between severity of domain/ illness and histological features of liver	Limitations
Kang	2020	Cross-sectional study	171321 adults who underwent health screening examination	Perceived stress	Short version of the Perceived Stress Inventory (PSI)	Abdominal ultrasonography findings	Association between perceived stress and the prevalence of NAFLD. The positive association between PSI score and NAFLD was observed	The prevalence of NAFLD was 27.8%.	The positive association between PSI score and NAFLD was observed more in obese compared to non-obese.	N/A	Study design. Stress assessment was based on self-report. Test–retest reliability of PSI score is not available.
Ma	2021	Observational study	Mental disorder inpatients (n = 66 273 (schizophrenia = 25 503, bipolar disorder = 14 377, Depressive disorder = 11 406, Other = 14 987)	Depression, schizophrenia, bipolar disorder	10th revision of the International Classification of Diseases (ICD-10)	Abdominal ultrasonography findings, Disease history	Prevalence of nonalcoholic fatty liver disease in mental disorder inpatients	11 681 inpatients had NAFLD, the prevalence was 17.63%.	N/A	N/A	All participants from inpatients from specialized psychiatric hospitals.
Huang	2021	Cross-sectional study	NAFLD (n = 5181)	Health Related Quality of Life (HRQL)	Chronic Liver Disease Questionnaire (CLDQ)-NAFLD	Ultrasound, CT, MRI 24 months or liver biopsies in 36 months.	Health-related quality of life in patients with NAFLD	The overall CLDQ score was 5.66 $\pm$ 0.89. NAFLD had impaired HRQL in all the six domains of CLDQ (abdominal symptoms, activity, emotional function, fatigue,systemic symptoms.	Significantly associated with overall CLDQ score.	N/A	CLDQ-NAFLD used in this study has not been well verified in China. Large sample size limits the performance of longitudinal follow-up.
Godin	2021	Cross-sectional study	Bipolar disorder (n = 1969)	Bipolar disorder	Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)	Fatty Liver Index (FLI) and the Forns Index (FI)	Prevalence of NAFLD and to identify the potential associated risk factors in bipolar disorder.	Prevalence of NAFLD in this sample was estimated at 28.4%.	Significantly higher in obese.	N/A	No histologic diagnosis of NAFLD. Study design.

Table 2. *Continued*

Lead Author	Year	Study type	Patient characteristics and number	Psychiatric illness/domain under study	Diagnostic criteria for psychiatric domain/illness	Diagnostic criteria for NAFLD	Primary objective of study	Association between illness/ domain and NAFLD	Association between obesity with domain/ illness and NAFLD	Association between severity of domain/ illness and histological features of liver	Limitations
Koreki	2021	Cross-sectional study	Schizophrenia/ schizoaffective disorder (N = 253)	Schizophrenia/ schizoaffective disorder	NA	Abdominal ultrasonography findings	Risk of NAFLD in Patients With Schizophrenia.	108 patients (42.7%) showed NAFLD. NAFLD was more prevalent in younger patients, particularly in females. The total dose of antipsychotic drugs that carry a risk of metabolic syndrome, and the total dose of antipsychotic drugs that carry a risk of hyperprolactinemia were significantly associated with NAFLD.	Significantly higher in obese.	N/A	Study design. Lack of data for actual prolactin levels or states of menstruation.

Abbreviations: ALD, Adrenoleukodystrophy; BDI, Beck Depression Inventory; BMI, Body mass index; CH-B, Chronic hepatitis B; CH-C, Chronic hepatitis C; CI, Confidence interval; CLD, Chronic liver disease; CT, Computerized tomography; DM type 2, Type 2 diabetes mellitus; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; DSM-IV, The Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; FIB-4, Fibrosis-4; FLI, Fatty liver index; GAD, Generalized anxiety disorder; GGT, Gamma-glutamyl transferase; HADS, Hospital Anxiety and Depression Scale; HCV, Hepatitis C virus; HS, Health Subjects; hs-CR*P*, High-sensitivity C-reactive protein; ICD-109, International Classification of Diseases; MDD, Major Depressive disorder; MRI, Magnetic Resonance Imaging; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic Steatohepatitis; NHANES, The National Health and Nutrition Examination Survey; OR, Odd ratio; PHQ-9, Patient Health Questionnaire; RNA, Ribonucleic acid; WPAI, Work Productivity and Activity Impairment.

on antipsychotic agents (i.e., aripiprazole, risperidone, quetiapine, or ziprasidone), and followed for three years.[38] At the end of the follow-up period, 25.1% (n = 48/191) developed liver steatosis, and 19.4% (n = 37/191) were determined to have indeterminate steatosis (i.e., at high future risk). No statistical difference was found between the incidence of NAFLD and the initial choice of antipsychotic agent.[38] Results from this study emphasize the hidden burden of NAFLD among patients with schizophrenia.

Cognitive dysfunction

Extensive research in the last decade has ascertained that cognition is paramount when patient-reported functionality and well-being are considered.[39] The residual cognitive deficits following remission of an MDD or BD episode hamper the recovery of an individual to premorbid functionality.[40] Even in the absence of a mood episode, patients suffering from metabolic syndrome (i.e., obesity, insulin resistance, diabetes mellitus, or hypertriglyceridemia) perform worse on standardized cognitive tests compared with healthy controls.[41,42]

A relatively small number of studies have studied the association between cognitive deficits and NAFLD. A cross-sectional study by Celikbilek et al.[43] reported lower Montreal Cognitive Assessment (MoCA) scores in NAFLD patients when compared with healthy controls (18.17 $\pm$ 5.20 versus 21.08 $\pm$ 3.93; $p < 0.001$, respectively). On further sub-domain analysis, patients with NAFLD did significantly worse on visuospatial and executive items in comparison to healthy controls. Moreover, a negative correlation between liver fibrosis and cognitive measures was observed (i.e., $r = -0.359$; $P < 0.05$).[43]

Similarly, another study reported that patients with NAFLD were at a significantly higher risk for cognitive impairment than healthy individuals (RR = 3.9, 95%, CI = 1.815–8.381, and $p = 0.0005$) when assessed through MoCA.[44] Furthermore, patients with NAFLD performed poorly in the work environment relative to healthy individuals when measured through Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH). These patients reported more absenteeism (28.5% versus 12.4%, p = 0.003), presenteeism (33.7% versus 23.0%, p = 0.006), overall work impairment (49.2% versus 30.8%, $p < 0.001$), and activity impairment (48.0% versus 32.6%, $p < 0.001$) compared to healthy controls.[45] The same study attributed these deficits in work efficiency to compromised mental component scores relative to healthy individuals (39.2 versus 45.2, $p < 0.001$).[45] Further important details of these studies are presented in Table 2.

Pathophysiological nexus between NAFLD and psychiatric disorders

Shared pathophysiological domains of NAFLD and psychiatric illnesses are multifold, complex, and likely to follow a multiple-hit model (i.e., cumulative effect of physical and psychological stress over time in presence of a baseline vulnerability).[3,46]

Hypothalamic–pituitary–adrenal axis dysregulation and subsyndromal inflammation

The human brain is one of the main centers that mounts homeostatic responses to internal and external changes. The main loop that handles both internal and external stressors is the hypothalamic–pituitary–adrenal (HPA) axis.[47] The detailed description of the HPA axis is beyond the scope of this review; however, a brief overview is provided herein. As the name suggests, this feedback loop comprises three major components: hypothalamus, pituitary gland, and the adrenal glands.[47] The hypothalamic component comprises chiefly the paraventricular nucleus (PVN), which has neuroconnections with all brain regions but primarily with the amygdala, hippocampus, and forebrain.[48] These afferent projections provide the hypothalamus with input regarding psychological, humoral, endocrine, and visceral information. The hypothalamus connects to the pituitary gland through corticotropin-releasing hormone, which further exerts its action on adrenal secretion of glucocorticoids (namely cortisol) through adrenocorticotropic hormone.[48] The hormone cortisol modulates the stress response, immune function, glucose metabolism, and executive cognitive functions.[49,50] Because of this complex interconnected nature of the HPA axis, any dysregulation across it can affect psychological, humoral, endocrine, and visceral domains of the human body.[48,51].

The HPA axis is also described as a resilience network against routine stressors[52]. The axis is also malleable and keeps on transforming across one's lifespan. The highest malleability is during the initial years of life (including the prenatal life).[53] Any early life adverse event (either physical in the form of an illness or psychological in the form of abuse, etc.) can trigger a series of events both in the brain and the body that can lead to a dysfunctional HPA axis later on in life.[53,54] This dysfunctional HPA axis can often lead to mounting excessive responses to a threat (that might be just a perceived one at times). The dysregulated HPA response leads to an increased release of cortisol hormone that can lead to further manifestations down the line (e.g., mood alterations, obesity, inflammation, metabolic syndrome, NAFLD, etc.).[55] Interestingly, early-life adverse effects and malnourishment are positively associated with NAFLD occurrences later in life, providing further support to this proposition.[56,57] In accordance with multiple hit theory of pathogenesis, it is important to understand that this whole pathophysiology depends on the genetic vulnerability and persistent surrounding stressors gradually accumulating overtime. Moreover, significant chronic unpredictable stress may also offset the HPA axis later in adulthood.[51,58]

We hypothesize that dysregulation in the HPA axis drives the link between NAFLD and psychiatric disorders. It has been observed repeatedly that psychiatric disorders (i.e., schizophrenia, MDD, or BD) often lead to an overly responsive HPA axis resulting in elevated/dysregulated cortisol release.[51,52,59,60] Not only can an overly active HPA axis cause some symptoms of mood/psychotic disorders, it also leads to significant endocrine and visceral adverse effects. Dysregulated cortisol release has been associated with obesity, inflammation, insulin resistance, and fat dysmetabolism.[51] It is also associated with an increased risk of stroke and cardiovascular disease.[61] All these endocrine effects are closely related to the pathogenesis of NAFLD and its progression to NASH and liver cirrhosis.[1,3,4] This hypothesis is also in line with multiple clinical and bench studies that have found increased cortisol levels among patients with NAFLD repeatedly.[62–64]

As previously mentioned, NAFLD is triggered by the build-up of triglycerides in hepatocytes. These triglycerides are often cleared by kupffer cells (resident macrophages in the liver); however, in presence of fat dysmetabolism the triglyceride load exceeds the clearance capacity of kupffer cells. This leads to build up of triglycerides within the hepatocytes and with time, creates a pro-inflammatory environment that can lead to steatohepatitis (i.e., NASH) and cell necrosis (that furthers the inflammation).[1,3] Usually the balance between

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pro-inflammatory and anti-inflammatory factors is also maintained by the HPA axis.[61] It has been found that persistently elevated or dysregulated cortisol secretion can lead to subsyndromal inflammation in the body.[65] This subsyndromal inflammation can exacerbate the local inflammation within the hepatocytes, catalyzing the whole pathogenetic cycle. This hypothesis predicts that psychiatric disorders might affect a person long before they develop NAFLD or NASH. Moreover, in presence of a psychiatric disorder and related HPA axis dysregulation, the longitudinal risk of developing NAFLD can get significantly higher than in the general population.[66] This also suggests that a psychiatric disorder might not be a co-morbidity in select patients of NAFLD, rather both the psychiatric disorder and the NAFLD might be components of a broader HPA-metabolic syndrome.[7]

Metabolic syndrome and obesity

Metabolic syndrome is a complex phenomenon with polygenic inheritance and multiple causal links. It is strongly associated with NAFLD as well as mood disorders.[11,47,67] Although there are multiple working definitions, metabolic syndrome is usually diagnosed with ≥3 abnormalities in the glucose, high-density lipoproteins, cholesterol, triglycerides, obesity, and blood pressure measurements.[68] During the past decade, multiple landmark studies have shown that insulin resistance (as a part of metabolic syndrome) is associated with mood disorders and cognitive dysfunctions.[7,39,69] Moreover, metabolic syndrome (in particular insulin resistance) has shown the strongest association with NAFLD.[70] This could be predictive of insulin resistance as a downstream common pathway to both mood disorders and NAFLD in select number of patients. This pathway makes more sense if we involve the obesity component of metabolic syndrome. In the previous section, we have delineated that obesity plus depression was significantly more associated with NAFLD when compared to depression or obesity alone. This can be explained further with one of our group's previous work where we suggested the presence of a metabolic-mood syndrome.[7] In that review, we suggested that patients with mood disorders and obesity are harder to treat, and have more severe symptoms and cognitive deficits. The paradigmatic component behind mood-metabolic syndrome remains dysregulated inflammation.[11]

Similar to our explanation of the HPA axis that gradually favored pro-inflammatory cytokines (e.g. interleukin (IL)-1ß, IL-6) over anti-inflammatory cytokines, we believe that added obesity acts in a very similar fashion.[71,72] Furthermore, inflammatory markers including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), IL-6, adiponectin, and leptin, which are present in visceral fat potentially aggravate the whole pathogenetic picture (including insulin resistance).[73] Insulin resistance is also associated with less glucose uptake and more lipolysis across peripheral tissues of the body. This leads to excessive circulating free fatty acids (FFA) both within and outside the peripheral adipocytes.[74] In particular, within adipose cells FFA binds to toll-like receptors (similar receptors that bind to microbial antigens) which triggers the inflammatory cascade. Interestingly, this inflammation further increases insulin resistance which in turn increases inflammation leading to a vicious self-sustaining cycle.[75] Obesity either due to metabolic, physical, or psychological causes leads to further availability of FFA that catalyzes the whole pathogenetic cycle. This proinflammatory environment leads to the progression of NAFLD to NASH and possibly liver cirrhosis. Moreover, the inflammatory hypothesis for depression has been well described in the literature with a significant positive association between the severity of depression and inflammatory markers.[11] The potentiating inflammatory phenomenon provides an explanatory framework linking the observation that depression and obesity might be greater risk factors for NAFLD as compared to either of these pathologies alone.

As such, the elevated risk of NAFLD in patients with psychiatric disorders is hypothesized to be due to well-established risk factors that are overrepresented in this population. For example, obesity, diabetes, along with metabolic syndrome differentially affect patients with psychiatric disorders. Factors more specific to the mood disorder population that possibly mediate risk are the higher rate of inflammatory alterations in the mood disorder population and possibly exposure to psychotropic agents that affect weight and/or metabolism.[76–79]

Chronic psychosocial stress and personal factors

It is important to note that the pathogenesis of psychiatric illnesses is very often tightly linked with the environment one lives in.[10] Only recently have we started to take the concept of psychache (i.e., perceived mental pain, unease, or stress due to emotional, personal or social unmet needs) seriously into consideration.[80] It is important to understand the word 'perceived' here making stress a subjective experience completely.[54] Although perceived stress is important to adapt and grow as a person in life, chronic unpredictable stress is almost always detrimental to pertinent health quality measures.[81] A previous animal study revealed that chronic unpredictable stress led to obesity due to leptin resistance.[82] Furthermore, the combination of a high-fat diet and stress-induced depression in a similar study was associated with abnormal serum lipid levels and increased inflammatory cytokines in the brain that were possibly mediated by Toll-like receptors - Nuclear factor kappa B (NF-κB) signaling.[82] This animal study can predict the direction of stress, obesity, and possibly obesity-related disorders (including NAFLD).[82]

Amongst people who were apparently healthy, higher perceived stress was significantly associated with the presence of NAFLD (OR = 1.17, 95% CI = 1.11–1.22, $p < 0.001$). The association became stronger when obesity and perceived stress were taken together (OR = 1.26, 95% CI = 1.19–1.33, $p = 0.01$).[58] It has been already known that chronic stress is an independent risk factor for cardiovascular and diabetic morbidity which often overlaps with the pathogenesis of NAFLD.[61,83–85] Hence, although the direct cross-sectional studies investigating the association of perceived stress with NAFLD are limited, we can extend the hypothesis of the association of stress with NAFLD in the presence of evidence supporting its significant shared links with cardiovascular and endocrinal pathogenesis.[56]

The foregoing possibly connects to our recurring hypothesis of HPA dysregulation among patients with NAFLD. Even in the absence of a formal diagnosis of a psychiatric ailment, HPA axis is involved in the analysis and diffusion of stress on a daily basis.[54] A dysregulated HPA axis would point towards a higher degree of perceived stress with apparently normal daily cues.[51] It also leads to compromised resilience at a personal level.[52] The positive associations of chronic stress with NAFLD in one large cross-sectional study and with related metabolic and cardiovascular diseases in a multitude of other studies signify the potential relation of environmental factors, perception of those factors, and resultant morbidities.[58,61,83–85]

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Other personal factors that can play shared roles are the levels of physical activity, dietary intake, and long-term medications. More often than not, patients with depression are more likely to eat unhealthy food and have a sedentary lifestyle.[86,87] Moreover, patients with mood disorders are also more related to consumption of junk foods that can drive obesity and obesity-related disorders (e.g., NAFLD, insulin resistance, cardiovascular disorders, etc.).[88] This pattern closely relates to the psychomotor retardation, anhedonia, and fatigue that are very common findings with depression.[86] Along with dietary habits, this lack of physical activity raises the risk of further metabolic disturbances that may later be predictive of NAFLD.[89] In addition to dietary and activity parameters, patients with schizophrenia face significant morbidity due to persistent negative symptoms (i.e., avolition, anhedonia, flat affect or alogia, etc.) and recurrent positive symptoms (i.e., hallucinations, disordered speech, delusions or disorganized behavior, etc.).[90] To manage the symptoms, patients with schizophrenia often have to take antipsychotics throughout their lives, with some of them significantly associated with metabolic disruption and metabolic syndrome (i.e., olanzapine, clozapine, or quetiapine, etc.).[29,91] The same case can be made for patients with BD who have to take maintenance treatment throughout their lives, often with weight-causing agents.[9] Furthermore, reward pathway deficits are often observed in patients with psychiatric ailments that remain even after the remission of their symptoms. These alterations in reward pathways are predictive of greater substance use (e.g., alcohol, cocaine, and other illicit substances, etc.) that can lead to liver injury and exacerbation of any existing liver inflammation.[88] Hence, on a personal level, psychiatric ailments increase the propensity of an individual toward the aforementioned behavioral risk factors that have been strongly associated with the development of NAFLD.[92]

Discussion

Our review underlies the clinical burden of NAFLD among patients with psychiatric disorders. Moreover, the present literature suggests that patients with obesity and a psychiatric disorder (i.e., MDD, BD, or schizophrenia) are significantly further associated with NAFLD compared with either of the conditions alone. We also hypothesize that a dysregulated HPA axis and downstream insulin resistance could be a shared pathophysiological link in a select number of patients presenting with a phenotype comprising both mood disorders and NAFLD (Figure 1).

Patient-specific care

It is important to manage patients with mood or psychotic disorders holistically (i.e., pertaining to physical, metabolic, and emotional parameters) to reach optimum patient-reported clinical endpoints.[86] Multiple internal (e.g., vulnerability to metabolic dysregulation) and

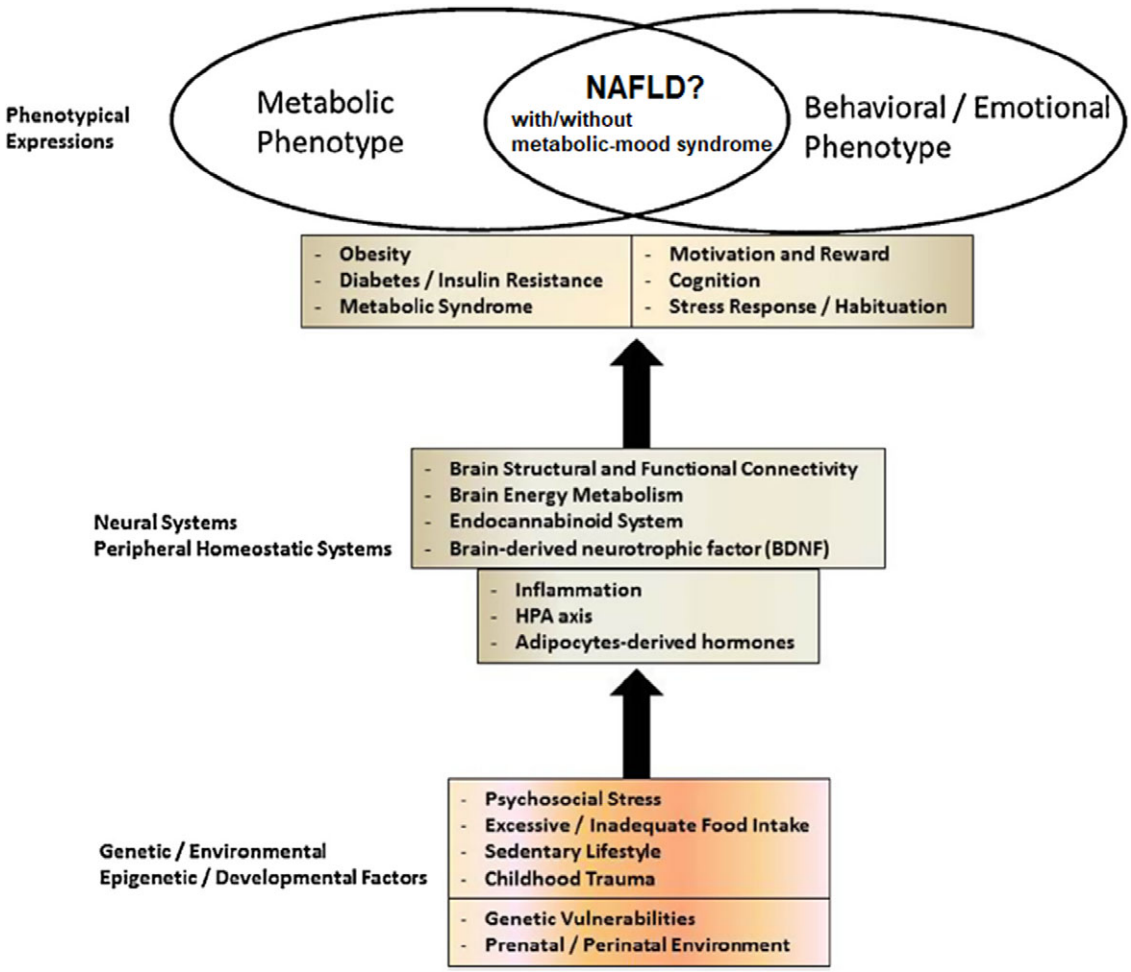

Figure 1. Pathophysiological flow of shared pathogenesis of mood disorders and NAFLD. (Shared and adapted with the permission of Mansur et al.[7])

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external (e.g., long-term treatment with metabolically disruptive agents) factors require patients with psychiatric illnesses to undergo strict observation and follow-up for their weight and metabolic parameters.[9,11] Herein, it is important to select treatments that are safer to use metabolically over a long period of time whenever it is therapeutically possible.

Although many antidepressants (i.e., selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors) have been marketed as weight-neutral agents, they appear to cause weight gain in real-world data in subsets of patients.[93,94] However, these data have been criticized to be associative and not causal in nature.[93] Nevertheless, with the usual presence of metabolic disruption among patients with mood and psychotic disorders, it is essential to include metabolic parameters (i.e., cholesterol level, hemoglobin A1c level, fasting glucose, waist and body mass index measurements) in our treatment targets even with weight neutral antidepressants and other therapeutic agents.[86,93] Not only do these metabolic parameters predict morbidity across various physical organs but they also ascertain the response and remission rates of mood or psychotic disorders, respectively.[95,96] The strong association of NAFLD with psychiatric disorders urges us to take metabolic disruption more seriously and to tailor patient-specific treatments that can lead to maximum benefit with minimum to no harm whatsoever.[56]

Screening for NAFLD

Currently, there is no screening protocol for NAFLD and most of the time, the diagnosis of NAFLD follows the incidental discovery of deranged liver function tests (i.e., increased aspartate aminotransferase or alanine aminotransferase) in primary care settings. The stage of incidental discovery is often associated with a progressive stage of disease with limited treatments at hand.[97] Although there is a debate about which patient population might benefit the most from standardized screening guidelines, it remains a unified perspective that screening will help in managing this disease better.[97] Although the diagnostic criteria for NAFLD is liver biopsy, the screening can be reliably done with a liver ultrasound and measurement of liver function tests taken together.[98] Our review highlights patients with psychiatric illnesses to be at high risk for NAFLD and calls for including them in the patient population who can benefit the most from regular screenings for NAFLD.

Moreover, in the presence of obesity, longer duration of psychiatric illness, higher severity, and family history of NAFLD, ultrasound screening becomes an unmet clinical need rather than a preventive measure.[97] Further work remains to be done to narrow down patients within the psychiatric cohort who would benefit the most from any standardized screening guidelines.

Future research vistas and potential therapeutics

A few questions still remain unanswered in the current literature. Due to the limited number of longitudinal studies, it is hard to determine a causal link, the duration it takes for NAFLD to develop, and any concomitant aggravating or relieving factors within patients with psychiatric disorders. Moreover, literature is limited with respect to the exact role of medications that are being administered. Furthermore, the specific patient characteristics with metabolic disorders and psychiatric illnesses who might be disproportionately more prone to the development of NAFLD still remain to be determined. Future researchers should design longitudinal studies for a sufficient duration of time to answer these key questions, and further elaborate on the association we strongly discern between NAFLD and psychiatric disorders, especially domains of psychopathology such as anhedonia and cognitive impairment.[40,99] Furthermore, future studies should compare treatment-naive and under treatment patients to see if there is any pattern associated with strict management of affective or psychotic symptoms, choice of medication, and development of NAFLD.

As far as potential therapeutics are concerned, no medication has been approved by the United States Food and Drug Administration to treat NAFLD.[1] The first line of treatment for NAFLD remains weight loss and multimodal lifestyle modification to decrease insulin resistance (e.g., avoidance of red meat, trans-fat, or highly refined carbohydrates, etc.).[100] Quite interestingly the drugs that are being used off-label to treat metabolic syndrome and insulin resistance (such as glucagon-like peptide-1 receptor agonists, metformin, and thiazolidinediones) have also shown some efficacy in ameliorating cognitive symptoms and depressive features.[99,100] Further research is required to assess the effects of select psychotropic medications that demonstrate anti-inflammatory effects (e.g., fluoxetine or fluvoxamine), as well as anti-cytokine agents, and potential therapeutic effects on reducing the severity of NAFLD.[101,102]

Furthermore, it will be beneficial to the field to investigate predictive genetic biomarkers that can aid in identifying subsets of psychiatric patients who are at an increased risk of developing NAFLD. Currently, there is a scarcity of research dedicated to identifying shared genetic pathways between psychiatric disorders and NAFLD.[66] One study in patients with BD reported that a recessive variant genotype (MM versus II/IM) patatin-like phospholipase domain-containing protein 3 (PNPLA3), which is involved in triglyceride metabolism, could increase the odds of developing NAFLD (OR = 4.579; CI = 1.607–13.043; p = 0.0044) in patients with BD.[103] MicroRNA (miRNAs) and altered mitochondrial metabolic genes are two other promising shared genetic components that have shown to play a role in energy metabolism perturbations in patients with NAFLD and psychiatric disorders (ie. depression, BD, and schizophrenia) and hence, need to be studied further.[66]

Limitations

Our review remains limited despite the strong association between NAFLD and psychiatric disorders due to the cross-sectional nature of most of the studies. Although a few included longitudinal studies strengthened the propensity of a mood or psychotic disorder to have a bidirectional pathogenetic link with NAFLD, further research is needed to test the hypothesis behind the potential cause and effect in disparate psychiatric disorders.

Conclusion

NAFLD disproportionately affects individuals with psychiatric disorders, with risk factors for NAFLD being primarily overrepresented in people with mood disorders. The concurrent diagnosis of NAFLD and a mood disorder predisposes to increased morbidity and significantly decreased quality of life. Future research should attempt to parse mechanistic substrates that underlie NAFLD and mood disorders. In the meantime, clinicians should be vigilant in their assessment, psychoeducation, and treatment of patients with mood disorders and/or NAFLD.

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